Verbal and nonverbal communication in schizophrenia – New insights from uni- and multimodal brain imaging

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INHALT

„Glaube denen, die die Wahrheit suchen,

und zweifle an denen, die sie gefunden haben.“

(André Gide)

Abstract

Socio-cognitive symptoms represent prominent and often strongly impairing deficits in patients with schizophrenia and they are tightly intertwined with dysfunctional communicative representations or systems. In particular, deficient verbal and nonverbal social information processing is associated with decreased functional outcome and prominent difficulties in everyday social interactions. Some specific aspects of verbal and nonverbal communication in schizophrenia have been thoroughly assessed by previous studies, particularly semantic priming at word level (verbal-cognitive domain) as well as face and facial emotion recognition (nonverbal-affective domain) and rather broad socio-cognitive functions including Theory of Mind (ToM). However, only very little is known about disease-related alterations in more complex language functions, such as pragmatic (e.g. non-literal) language comprehension, or emotion processing from social cues other than the face, such as human body language.

To this end, the present dissertation intended to investigate neurophysiological correlates of verbal and nonverbal socio-communicative (dys)functions in schizophrenia that have so far been rarely investigated using functional imaging, namely pragmatic language (verbal-cognitive domain, part 1) and emotional body language (nonverbal-affective domain, part 2) processing. Neurophysiological activity was assessed by means of functional near-infrared spectroscopy (fNIRS) measurements, either applied alone (unimodal imaging) or combined with electroencephalography (EEG; multimodal imaging). These specific neuroimaging methods have been chosen because they are characterised by high ecological validity and a relatively high flexibility regarding their applicability in varying contexts, implying a great potential of these techniques to assess social communicative functions in schizophrenia that are highly relevant for everyday social interactions.

For the **first part** of this work, **verbal-cognitive communication functions** in schizophrenia were assessed using a pragmatic language comprehension paradigm and simultaneously applied EEG-fNIRS measurements. **Study 1** investigated whether combined EEG-fNIRS measurements are useful to elucidate the linkage of neural and haemodynamic substrates underlying pragmatic language comprehension. To this end, 20 healthy subjects judged literal, non-literal (metaphoric), and meaningless sentences with respect to their meaningfulness, while simultaneous EEG-fNIRS data were acquired. Both neural markers in terms of event-related potentials (ERPs, particularly the P200 and the

N400 potentials) and haemodynamic markers of cortical activity within the language network (reflected by the fNIRS data obtained over inferior frontal and posterior temporal/parietal cortices) were modulated by different sentence types in healthy participants. Moreover, ERP amplitudes and cortical haemodynamic responses were significantly correlated during non-literal language processing. Therefore, study 1 underlines the usefulness of simultaneous EEG-fNIRS measurements to investigate neural and haemodynamic markers of pragmatic verbal-cognitive functions.

The paradigm and neuroimaging methods introduced in study 1 were adopted by **study 2** which sought to elucidate neurophysiological correlates of verbal-cognitive processes (i.e. pragmatic language comprehension) in patients with schizophrenia. 22 healthy subjects and 22 patients with schizophrenia performed the meaningfulness judgement task while EEG-fNIRS measurements were applied. Schizophrenia patients showed decreased task performance and altered ERP (N400) modulations as well as decreased left-cortical haemodynamic responses during language comprehension. Correlation analyses showed that, as in study 1, ERPs were strongly linked to haemodynamic cortical activity in healthy subjects, but not in patients. Thus, study 2 elucidates distinct neurophysiological anomalies of pragmatic language processing in patients with schizophrenia using combined EEG-fNIRS.

For the **second part** of this dissertation, **nonverbal-affective communication functions** were investigated by means of an emotion labelling paradigm involving dynamic human body movements, while fNIRS measurements were carried out. In **Study 3**, 33 healthy participants were assessed by means of fNIRS measurements while they labelled emotional states from walking patterns, whereby a non-affective control task (walking speed recognition) was also included. The results of study 3 showed increased haemodynamic responses to negative body movements (independent of task type) within a distributed cortical network, comprising visual association areas as well as body/movement perception-specific cortical regions. In sum, study 3 revealed that fNIRS is suitable to depict cortical activation associated with emotion perception from body language, providing a new and innovative approach to assess so far rarely investigated socio-affective functions within naturalistic settings.

In **study 4**, haemodynamic response patterns of two core areas of the network that had been identified in study 3 (lateral occipital cortex/extrastriate body area [EBA] and superior temporal sulcus [STS]) were assessed in a sample of schizophrenia patients

(N=20). Again, the paradigm and neurophysiological measurement setup were adopted from the preceding study. A clinical (patients with major depression) and a healthy control group (each N=20) were used to interpret respective results in terms of diagnostic specificity. Only schizophrenia patients showed impaired emotion recognition from body movements. Moreover, they revealed altered haemodynamic responses to emotional body movements in the EBA and STS, along with decreased functional connectivity of the STS with other cortical regions. This hyperconnectivity of the STS was correlated with positive symptom severity in schizophrenia.

Taken together, the results obtained in the four studies revealed 1) that fNIRS measurements – either unimodally applied or combined with EEG – are useful to detect cortical activation associated with verbal-cognitive and nonverbal-affective information processing. 2) Patients with schizophrenia show significant alterations in these neurophysiological processes along with impaired recognition of pragmatic language (verbal-cognitive domain) and emotional body language (nonverbal-affective domain). The findings complement previous studies on more commonly assessed socio-communicative dysfunctions in schizophrenia (altered semantic priming and facial expression perception). The present work provides a holistic overview over different social communication dysfunctions that may be apparent in patients suffering from schizophrenia and their accessibility via fNIRS and EEG-fNIRS measurements, respectively. Hereby, all project parts focused on an innovative implementation of neuroimaging methods that may be particularly promising for future directions in neuropsychiatric research. The findings are discussed in the light of contemporary models of pragmatic language comprehension as well as nonverbal social information processing. Moreover, they are integrated into current concepts of schizophrenia, particularly with respect to etiological models and neurocognitive frameworks as well as the endophenotype concept.

Future studies will have to investigate (1) in which way verbal and nonverbal communication anomalies co-occur (i.e. how they are related within the same patient sample) and (2) how these findings, which are thus far limited to the *perception* of social signals, are related to *expressive* deficits of schizophrenia patients during social communication. Moreover, future studies should clarify how the present findings can be usefully integrated to potentially support diagnostic and therapeutic processes in order to improve psycho-social outcome for patients with schizophrenia.

Zusammenfassung

Sozial-kognitive Symptome stellen ein markantes und häufig stark beeinträchtigendes Defizit von Patienten mit schizophrener Erkrankung dar, welches eng mit Dysfunktionen in Kommunikation und Interaktion verknüpft ist. Hierbei sind insbesondere Einschränkungen in der Verarbeitung verbal und nonverbal dargebotener sozialer Information mit einem verminderten generellen Funktionsniveau sowie deutlichen Schwierigkeiten bei alltäglichen sozialen Interaktionen assoziiert. Einige spezifische Teilbereiche verbaler und nonverbaler Kommunikation bei Schizophrenie wurden bereits in früheren Studien zum Teil ausführlich untersucht, wie beispielsweise semantische Bahnung (Priming) auf Wortebene (verbal-kognitive Ebene), (emotionale) Gesichtsverarbeitung (nonverbal-affektive Ebene) sowie weniger scharf umgrenzte sozial-kognitive Funktionen einschließlich Theory of Mind (ToM). Bislang ist jedoch wenig bekannt über störungsbezogene Veränderungen komplexer Sprachverarbeitung, wie pragmatisches (z. B. nicht-wörtlich gemeintes) Sprachverstehen, oder der Verarbeitung von Emotionen auf Basis sozialer Reize, die nicht auf Gesichter beschränkt sind, wie beispielsweise menschliche Körpersprache.

Die vorliegende Dissertation befasst sich daher mit der Untersuchung neurophysiologischer Korrelate solcher verbaler und nonverbaler kommunikativer (Dys-)Funktionen bei Schizophrenie, die bislang nur wenig mittels funktioneller Bildgebung untersucht worden sind. Hierbei werden zum einen pragmatische Sprache (verbal-kognitive Ebene) und zum anderen emotionale Körpersprache (nonverbal-affektive Ebene) fokussiert. Die Erfassung neurophysiologischer Aktivität erfolgt mithilfe der Methode der funktionellen Nahinfrarot-Spektroskopie (fNIRS), welche hierbei entweder allein (unimodale Messungen) oder in Kombination mit Elektroenzephalographie (EEG, multimodale Messungen) zum Einsatz kommt. Diese bildgebenden Verfahren wurden insbesondere aufgrund ihrer hohen ökologischen Validität und flexiblen Anwendbarkeit in verschiedensten Untersuchungs-Situationen ausgewählt, welche ein hohes Potential beider Methoden zur validen und ökonomischen Untersuchung alltagsrelevanter kommunikativer Funktionen bei Schizophrenie nahe legen.

Der **erste Teil** dieser Arbeit befasst sich mit der Erforschung von Funktionen zur **verbal-kognitiven Kommunikation** bei Schizophrenie, welche mithilfe eines Paradigmas zum pragmatischen Sprachverstehen sowie simultaner EEG-fNIRS-Messungen untersucht werden. **Studie 1** untersucht hierbei, inwiefern kombinierte EEG-fNIRS-Messungen helfen können, die neuronalen und hämodynamischen Prozesse, die dem pragmatischen Sprachverstehen zu Grunde liegen, zu untersuchen und besser zu verstehen. Hierfür beurteilten 20 gesunde Probanden wörtliche, nicht-wörtliche (metaphorische) und bedeutungslose Sätze bezüglich ihrer Sinnhaftigkeit, während EEG-fNIRS-Messungen durchgeführt wurden. Die Befunde von Studie 1 legen nahe, dass sowohl neuronale Marker im Sinne ereigniskorrelierter Potentiale (EKPs, insbesondere P200- und N400-Amplituden) als auch hämodynamische Marker kortikaler Aktivität innerhalb des Sprachverarbeitungs-Netzwerks (fNIRS-Aktivierungsmuster innerhalb inferior-frontaler und temporo-parietaler Kortizes) bei gesunden Probanden durch unterschiedliche Satzbedeutungen moduliert werden. Darüber hinaus zeigten sich signifikante Zusammenhänge zwischen ERP-Amplituden und kortikalen hämodynamischen Antworten während der Verarbeitung nicht-wörtlicher Sprache. Damit unterstreicht Studie 1 den Nutzen kombinierter EEG-fNIRS-Messungen zur Untersuchung neurophysiologischer Marker pragmatischer, verbal-kognitiver Funktionen.

Die in Studie 1 eingeführten Methoden (Sprachverstehen-Paradigma und EEG-fNIRS-Messungen) werden in **Studie 2** aufgegriffen. In dieser Studie sollen die neurophysiologischen Korrelate verbal-kognitiver Prozesse bei Patienten mit Schizophrenie untersucht werden. 22 gesunde Probanden und 22 Schizophrenie-Patienten durchliefen die in Studie 1 erprobte Sprachverständnisaufgabe, während EEG-fNIRS-Messungen der kortikalen Aktivität simultan durchgeführt wurden. Schizophrenie-Patienten zeigten hierbei ein verringertes Sprachverstehen sowie signifikante Veränderungen der N400-ERP-Modulierung sowie verringerte links-kortikale hämodynamische Antworten während der Sprachverarbeitung. Während der in Studie 1 gefundene Zusammenhang zwischen neuronaler (ERPs) und hämodynamischer (fNIRS) Aktivierungsmuster für die gesunde Probandengruppe repliziert werden konnte, ergab sich keine solche Korrelation für die Schizophreniepatienten. Somit konnten in Studie 2 distinkte Veränderungen der neurophysiologischen Verarbeitung pragmatischer Sprache bei Patienten mit Schizophrenie mithilfe kombinierter EEG-NIRS-Untersuchungen aufgedeckt werden.

Der **zweite Teil** dieser Dissertation befasst sich mit Funktionen **nonverbal-affektiver Kommunikation**, welche mithilfe einer Emotionsidentifikations-Aufgabe auf Basis von Körperbewegungen sowie fNIRS-Messungen untersucht werden. In **Studie 3** wurden zunächst 33 gesunde Probanden mittels fNIRS untersucht, während diese emotionale Zustände aus Gehbewegungen identifizierten, wobei auch eine neutrale Kontrollaufgabe (Einschätzung der Geh-Geschwindigkeit) durchgeführt wurde. Es ergaben sich erhöhte hämodynamische Antworten auf negative Bewegungsmuster (unabhängig von der

Aufgabenstellung) innerhalb eines verzweigten kortikalen Netzwerkes, welches visuelle Assoziationsareale ebenso einschloss wie Regionen, die mit der Verarbeitung von statischen Körpern und/oder biologischer Bewegung assoziiert sind. Die Befunde aus Studie 3 legen nahe, dass fNIRS eine angemessene Methode zur Erfassung kortikaler Aktivierungsmuster darstellt, die mit der Verarbeitung emotionaler Körpersprache assoziiert sind. Die Methode bietet damit einen neuen und innovativen Ansatz, bisher noch wenig erforschte sozio-affektive Prozesse eingehend und in naturalistischen Umgebungen zu untersuchen.

Im Rahmen von **Studie 4** wurden anschließend hämodynamische Antwortmuster zweier Zielregionen des in Studie 3 identifizierten kortikalen Netzwerkes (lateraler okzipitaler Kortex/extrastriates „Body Areal" [EBA] und superiorer temporaler Sulcus [STS]) bei einer Gruppe schizophrener Patienten (N=20) untersucht. Auch hier wurden die in der vorangegangen Studie erprobten Methoden (Paradigma und neurophysiologische Messung) wieder aufgenommen. Eine klinische (Patienten mit Majorer Depression) sowie eine gesunde Kontrollgruppe (jeweils N=20) wurden zusätzlich untersucht um entsprechende Ergebnisse auch in Hinsicht auf ihre diagnostische Spezifität interpretieren zu können. Einzig für die Gruppe der Schizophreniepatienten ergaben sich Einschränkungen im Emotionserkennen aus Körperbewegungen. Diese Patientengruppe zeigte darüber hinaus veränderte hämodynamische Antworten auf emotionale Bewegungsmuster innerhalb der EBA und des STS, sowie eine verminderte funktionelle Konnektivität des STS mit anderen kortikalen Regionen. Diese funktionelle Hypokonnektion des STS korrelierte außerdem mit der Schwere der Positivsymptomatik bei Schizophreniepatienten.

Zusammengefasst ergaben die in den vier Studien erbrachten Ergebnisse folgendes Bild: (1) fNIRS Messungen, sowohl uni- als auch multimodal (hier: in Kombination mit EEG) angewendet, bilden eine nützliche Methode zur realitätsnahen Erfassung kortikaler Aktivierung, die mit verbal-kognitiver und nonverbal-affektiver Informationsverarbeitung in Zusammenhang stehen. (2) Patienten mit Schizophrenie zeigen signifikante Veränderungen dieser neurophysiologischen Prozesse, welche behavioral mit einem verminderten pragmatischem Sprachverstehen (verbal-kognitive Ebene) sowie Einschränkungen im Erkennen emotionaler Körpersprache (nonverbal-affektive Ebene) einhergehen. Diese Befunde ergänzen frühere Studien zu weniger komplexen, aber bislang häufiger untersuchten sozio-kommunikativen Dysfunktionen bei Schizophrenie (z. B. verändertes semantisches Priming sowie beeinträchtigte Verarbeitung von Gesichtsausdrücken). Die aktuelle Arbeit liefert dabei einen ausführlichen Überblick über verschiedene kommunikative Dysfunktionen, die bei Patienten mit einer schizophrenen Erkrankung auftreten können und

beleuchtet zugleich deren Zugänglichkeit mittels fNIRS bzw. kombinierter EEG-fNIRS-Messungen. In den einzelnen Projektteilen wurde dabei auf den Einsatz innovativer Untersuchungsmethoden wertgelegt, die für die neuropsychiatrische Forschung in Zukunft von besonderer Bedeutung sein könnten. Die Befunde werden vor dem Hintergrund theoretischer Modelle zum pragmatischen Sprachverstehen sowie der Verarbeitung nonverbaler sozialer Information diskutiert. Darüber hinaus werden die Ergebnisse in aktuelle Konzepte der Schizophrenie integriert, insbesondere im Hinblick auf äthiologische Modelle und neurokognitive Erklärungsansätze der Erkrankung. Zudem wird eine Einordnung der hier untersuchten kommunikativen Funktionen in das Endophänotypenkonzept versucht.

Zukünftige Studien sollten weiter untersuchen in wie fern (1): Veränderungen der verbalen und nonverbalen Kommunikation gemeinsam auftreten (d.h. wie sie innerhalb ein und der selben Patientengruppe auftreten und zusammenhängen, bzw. interagieren) und (2): wie die Befunde dieser Arbeit, die sich auf die rein *perzeptuelle* Komponente sozialer Signale beschränken, mit möglichen Defiziten im *Ausdruck* sozialer Informationen zusammenhängen. Darüber hinaus könnten zukünftige Untersuchungen klären, wie sich die aktuellen Befunde in praxisrelevante klinische Bereiche, insbesondere diagnostische und therapeutische Prozesse, integrieren lassen um für Patienten mit Schizophrenie Verbesserungen hinsichtlich des psycho-sozialen Funktionsniveaus zu erreichen.

1. General Introduction

1.1 Topic overview & structure of the present work

As the title of this dissertation reveals, the present work comprises different psychological aspects that can hardly be summarised into a single term or topic. In fact, at least three research-relevant issues could be distinguished: (1) verbal and nonverbal communication processes, (2) schizophrenia as a (neuro-) psychiatric disorder, and (3) the use of brain imaging methods. In order to provide a concise overview over the current topic that further outlines its relevance, the following three main questions shall be considered:

1. What comprises **verbal and nonverbal communication** and why are these aspects so relevant for psychological research?
2. Why should particular aspects of verbal and nonverbal communication be investigated in **patients with schizophrenia**?
3. Why looking at the **brain** instead of looking at the patient?

Addressing these questions, the following section shall provide a broad framework for the present work and deduce a scientific rational for the research topic presented here. Finally, a concise overview over the structural composition of this work will be provided to guide the reader through this dissertation.

1. What comprises verbal and nonverbal communication and why are these aspects so relevant for psychological research?

Answering this question is, at the same time, fundamental and difficult. In a nutshell, one can state that our language abilities distinguish us from all other life forms, suggesting their central role in social dynamics (1953; cited byBurns, 2006). These "language abilities" are by no means limited to what we usually first imagine when thinking about language. Speech, the verbal counterpart of our communication skills, usually (in everyday social situations) occurs in concert with different forms of nonverbal information. The correct recognition and interpretation of social signals requires an intact processing of both verbal (i.e. speech/language) and nonverbal (e.g. facial expressions and body language) social cues and the embedding of both into a given context. Chance and Mead have emphasised that these verbal and nonverbal language abilities are inextricably linked to social functioning. The authors have further argued that the social dynamics, which are thought to rely on language abilities, "may be a major driving force in human brain evolution" (Burns, 2006, p. 77, right column). Hence, a holistic understanding of the psychological systems providing these extraordinarily complex functions is crucial for understanding human societies and human development in health and disease. Hereby, verbal and nonverbal language can take many different shapes, challenging the psychological sciences which try to develop adequate experimental approaches for assessing these functions. Verbal language, for example, can be regarded on a micro level - including prelexical aspects such as phoneme or syllable processing- as well as on a macro level, referring to semantic aspects, i.e. language meaning and complex language forms such as humour or non-literal language. Analogously, nonverbal communicational signals comprise a set of visually and auditory accessible stimuli. Facial and bodily expressions are the main visual stimuli providing nonverbal social information, whereby both aspects can be either regarded as a whole or further decomposed (e.g. single face or body parts versus whole faces or bodies can be regarded). Thus, when investigating verbal and nonverbal communication abilities in humans a great number of different functions and systems can be assessed experimentally, all sharing one common denominator: their fundamental significance for intact social living.

2. Why should particular aspects of verbal and nonverbal communication be investigated in patients with schizophrenia?

From a life-time perspective, schizophrenia may be the psychological syndrome with the most strongly impairing deficits in psycho-social functioning. Long term clinical and functional outcome and quality of life represent crucial variables that might constitute the most important yet most difficult to assess psychological functions in patients with schizophrenia. While these variables are influenced by a large variety of factors, they have been most strongly associated with social cognition and communication deficits (Burns, 2006), pointing towards a high relevance of these aspects for treatment research and rehabilitation. Due to the complexity of the subject matter, communication patterns and anomalies in schizophrenics are a wide field of investigation. For example, "schizophrenia" combined with either "social cognition" or "social communication" produces 1812 or 1112 hits on PUBMED (http://www.ncbi.nlm.nih.gov/pubmed/; date of research: June 1st 2014). However, comparability of studies is usually strongly limited and there is a wide range of scientific quality of published research, rarely allowing for conclusive and generalisable outcomes. Therefore, despite this merely overwhelming body of research, the background of social communication impairments in schizophrenia is still poorly understood and recent scientific findings concerning the neuropsychological basis of these impairments are rarely integrated in current diagnostic and therapeutic standards. Hence, there is need for state-of-the-art, innovative, and practically realizable psychological paradigms and studies.

3. Why looking at the brain instead of looking at the patient?

During the last century, psychology attempted to (re)define itself by conceptually linking the mind to the brain. Accordingly, the psychiatric disciplines developed medical models for the study of mental disorders that emphasise brain pathology (Malhi & Lagopoulos, 2008). To date, neuroscientific research – involving imaging of both healthy and pathological processes – is on its heyday and enormous resources are invested in solving the mystery of the human brain. To this end, two large international initiatives, the European-led human brain project (Hampton, 2014; https://www.humanbrainproject.eu/) and the US American BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative (Bargmann & Newsome, in press; http://www.nih.gov/science/brain/) have recently been brought into life. Thus far, psychological and psychiatric sciences have largely benefited from brain imaging studies, as they provided unique insights into the pathophysiology of mental disorders. As a relevant and fruitful consequence, functional imaging findings have already inspired researchers and clinicians to develop new and innovative methods that may aid therapy, such as neuromodulatory techniques (e.g. transcranial magnetic stimulation [TMS], transcranial direct/alternating current stimulation [TDCS/TACS] or functional imaging-based neurofeedback [NFB]), or modify and advance established treatments, such as pharmacological and psychotherapeutic interventions. The other way round, findings from neuroimaging studies also revealed that cerebral processes are not static and may also be modified, for example by an exposure to therapeutic interventions (Barsaglini, Sartori, Benetti, Pettersson-Yeo & Mechelli, 2014). Therefore, neuroimaging techniques further provided evidence for bidirectional interplay between biological and mental processes. For example, neuroimaging findings have substantially contributed to the today widely accepted view that schizophrenia can be seen as a neurodevelopmental disorder. Likewise, the traditional idea that schizophrenia is characterised by "breaking up or splitting of psychic functioning" (Eugen Bleuler, 1908, cited by Kuhn & Cahn, 2004) has found support from imaging studies revealing deficient connectivity between distributed cerebral networks (for example Fitzsimmons, Kubicki & Shenton, 2013; see also section 1.2). The identification of neurobiological counterparts of cognitive, affective, and psycho-social symptoms contributed to a better understanding of the disorder, especially with respect to its heterogeneous manifestations. Hence, given that brain imaging findings do not stand alone, but are linked to observable phenotypes and are reasonably integrated into disease models and therapeutic approaches, brain imaging of psychological symptoms can significantly improve our understanding of mental disorders.

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Naturally, social communication can be regarded from the two perspectives of *perception* or *expression* of social signals[1]. Because the perception of social signals can be operationalised more easily, the present work focuses on the *perception and comprehension* of verbal and nonverbal social signal processing and their neurophysiological correlates in schizophrenia. Hereby, a general introduction (chapter I), will first review how current opportunities for using neuroimaging methods aid to understand psychiatric disorders (section 1.2) and will further provide an up-to-date description of schizophrenia as a neuropsychiatric disorder (section 1.3). In order to produce testable hypotheses on social-communicative functions in schizophrenia patients, well-defined aspects of verbal and nonverbal perceptive functions needed to be picked for the current projects, derived from previous research findings and current perspectives on

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[1] At this point, please note that the perception and expression of social information can certainly not be regarded as unrelated, one hundred percent distinguishable psychological domains. There is a widely accepted agreement that perception and action and their underlying brain systems are coupled and interact on multiple levels (Prinz, 1997; Warren, 1990). While perception-action coupling has also been hypothesised to be crucial in social contexts (Preston & de Waal, 2002), here I will put emphasise on the perceptual domain for simplification.

social communication and cognition in schizophrenia (section 1.4). To this end, the present work will focus on neurophysiological and behavioural measures of two selected subtypes of verbal and nonverbal language functions in schizophrenia patients which will be introduced in Chapter II. This chapter will provide a comprehensive overview on previous findings from studies that have so far investigated specific types of verbal language comprehension (section 2.1) and nonverbal social information recognition (section 2.2) in schizophrenia patients. Subsequently, four own studies will be presented: two studies on verbal (chapter III) and on nonverbal (chapter IV) signal perception. For both topics, the respective first study assesses the usability of 1) innovative neuroimaging methods and 2) newly established paradigms for testing the corresponding verbal and nonverbal perceptual functions in a sample of psychologically healthy subjects. In a second step, two clinical studies will be presented which aim at potential alterations in behavioural and neurophysiological measures during verbal and nonverbal language recognition in schizophrenia and possible links to psychopathology. While the immediate results of each study will be discussed within each sub-section, a general discussion (chapter V) integrates the present findings into a broader framework, drawing general conclusions and further comment on future research perspectives.

1.2 Functional brain imaging in psychiatric disorders - Where are we now?

> „The Human Brain is the most complex system that we know of. We would like to develop some kind of 'Google' brain where we can zoom in and out, see it from different perspectives and understand how brain structure and function is related."
>
> Prof. Katrin Amunts
> Institute of Neuroscience and Medicine, Jülich
> (Contributor to the Human Brain Project)

The above quotation vividly highlights that we are still struggling to understand how the human brain, the most complex organ, is doing its job. Nonetheless, the introduction of brain imaging methods and their ongoing and rapid technical development have strongly contributed to the understanding of neural processes, along with the pathophysiology of mental disorders. In the past the neural bases of psychological functions had been mostly inferred from studies with neurological patients using specifically designed behavioural paradigms. The introduction of neuroimaging methods enabled a direct testing of hypotheses on neurophysiological correlates of perceptual, emotional, and higher-order cognitive processes as well as respective disturbances or impairments observed in mental illness. Against this background, there has been an exponential increase in functional neuroimaging studies assessing neurophysiological correlates of the full spectrum of psychological symptoms occurring in mental disorders.

Methods that depict the neural representation of psychological functions can bee distinguished by the type of information that is being assessed. Tomographical techniques can display the structural organisation of the brain, while functional imaging allows us to investigate changes in ongoing brain activity, for example in response to external (i.e. visual, auditory, tactile, etc.) stimulation or during cognitive operations. One of the most frequently applied techniques, magnetic resonance imaging [MRI], can provide information on both the anatomical (structural MRI [sMRI]) and the functional (functional MRI [fMRI]) level. Other techniques are restricted to either functional (e.g. electroencephalography [EEG]; magnetoencephalography [MEG]; near-infrared-spectroscopy [NIRS]; diffuse optical imaging [DOT]) or structural (e.g., x-ray based methods, such as computed tomography [CT]) assessments. With respect to purely functional methods, sophisticated approaches for a spatial registration of functional activation data to corresponding brain structures have been developed in recent years (Cutini, Scatturin & Zorzi, 2011; Grech et al., 2008; Okamoto et al., 2004; Tsuzuki et al., 2012). Such methods allow for a topological assignment of detected functional brain activation to defined cerebral structures without the need for tomographical measurements, which can be advantageous (see also below). However, spatial accuracy of these post-hoc anatomical registrations of functional activation is usually lower compared to data obtained via tomographical methods.

Apart from the structural-functional distinction, methods can be classified according to the type of biological signal that is measured. For example, EEG, MEG, and also intracranial electrophysiological recordings (which are neglected from here on due to their high invasiveness) directly assess fine-graded electrical activity released by post-synaptic potentials of pyramidal cells in the brain. Other methods (e.g. fMRI, NIRS, or DOT) indirectly access neural activity by measuring haemodynamic changes in certain brain regions. These methods exploit the principle of neuro-vascular coupling (Fox & Raichle, 1986), a phenomenon describing local adaptation of blood flow to increased neural activity within a circumscribed brain region. This increased neural activity elevates energy needs of brain cells. Other imaging techniques, such as positron-emission tomography (PET) and single-photon emission computed tomography (SPECT), target metabolism within the brain. Therefore, these techniques use radioactive tracers that, depending on the selected tracer, accompany a specific metabolic process and aggregate in an active region. These measures image neuropharmacological processes within the brain, and their sensitivity to biomarkers in tissue (e.g. enzymes, hormones, or amino acids, the basic elements of different neurotransmitters such as glutamate and gamma-aminobutyric acid [GABA]) is multiple times higher as compared to MRI. However, to date PET and SPECT studies are less frequently applied within the field of psychiatric neuroscience (as compared, for example, to fMRI or EEG assessments), due to a more restricted availability of these methods, their restricted spatial resolution, and for ethical reasons, considering that both methods constitute invasive, nuclear techniques.

The high relevance of functional imaging to psychiatric research can be illustrated by the endophenotype concept (Gottesman & Gould, 2003; Gottesman & Shields, 1973). Endophenotypes have been described as "internal phenotypes discoverable by a biochemical test or microscopic examination" (Gottesman & Gould, 2003, p. 337; left column) and therefore represent an objectively accessible marker at the interface between the neural expressions of genes and the heterogeneous phenotypes of the disorder (see Figure 1). A central assumption of the endophenotype concept states that variation in an endophenotype will depend upon fewer genetic variation than the more complex disease phenotype and therefore would be more amenable to genetic analysis (Gottesman & Gould, 2003). While a number of attempts have been made to define the optimal characteristics of an endophenotype (listed in Walters & Owen, 2007), a general agreement has been achieved concerning the following features: an endophenotype should (1) be associated with illness in the population; (2) be heritable; (3) tend to co-segregate with the illness in multiply affected families; (4) be found in unaffected relatives of cases at a higher rate than in the general population (and ideally show evidence for common genetic risk factors from twin studies; Walters & Owen, 2007). Moreover, (5) endophenotypes are assumed to be state-independent, meaning that they manifest in an individual whether or not illness is active (Gottesman & Gould, 2003). More recently, a sixth criterion has been added: “The endophenotype should be a trait that can be measured reliably, and ideally is more strongly associated with the disease of interest than with other psychiatric conditions (i.e., specificity)” (Chan & Gottesman, 2008, p. 962).

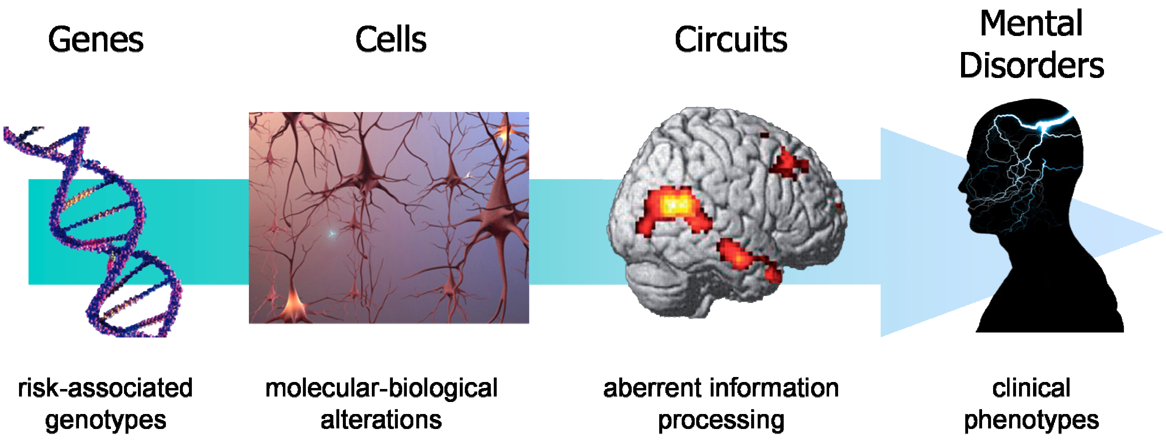

Figure 1. Exemplary illustration of the brain imaging intermediate phenotype concept.

Putative endophenotypes for schizophrenia spectrum disorders have ranged from clinical characterizations (e.g. the presence of schizotypy in patients' relatives), over neuropsychological profiles (e.g. working memory or executive function impairments) to the currently focussed neurophysiological and structural measures of specific, functionally important brain regions (e.g. abnormal P300 event-related potential, deficient P50 suppression, prefrontal hypoactivations)[2]. However, the search for endophenotypes of schizophrenia is tedious and challenging, as it is significantly hampered by the fact that the diagnosis "schizophrenia" summarises highly heterogeneous psychiatric phenotypes. In the past years, putative endophenotypes for schizophrenia, as well as for other mental disorders, have been investigated using basically all commonly applied neuro-imaging methods. Particularly regarding more recently established imaging techniques, such as fNIRS, endophenotype research is now rapidly evolving. Many researchers hope that endophenotypes can help to solve the genetic puzzle of schizophrenia and the use of functional imaging methods is a significant part of this strategy.

Another emerging trend in neuroscience constitutes investigations on the "human connectome" which is described as a network of anatomical connections linking the neuronal elements of the human brain. Using graph analyses, the neural elements and inter-connections that constitute the brain can be comprehensively mapped (Sporns, Tononi & Koetter, 2005; Van Essen, 2013). Hence, cartographic images of cerebral structural connectivity – determining the existence, strength, and/or direction of links

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[2] Lists of endophenotype candidates in schizophrenia can be found, for example, in Calkins et al. (2007) and Turetsky, Calkins, Light, Olincy, Radant and Swerdlow (2007).

between different brain parts – complement maps that refer to the spatial arrangement (instead of connections) of brain parcels (Van Essen, 2013). This research arm has strongly benefited from the development of and recent advances in diffusion tensor imaging (DTI), an advanced MRI-based method that allows measuring the coherence and direction of white-matter fiber tracts. Connectome research identified hub nodes within the brain that are densely interconnected, forming a *rich club* of different brain regions. Such rich club organizations are now intensively investigated as they are assumed to be crucial for efficient global brain communication and integration of information (van den Heuvel & Sporns, 2011). However, it has been criticised that knowledge of brain parcel connections is not necessarily informative on *how* the brain actually processes information[3]. Accordingly, the imaging of functional circuits, i.e. cerebral networks that show patterns of co-activation, has also been increasingly focussed and – analogously to its topological counterpart – termed *functional connectome* (Biswal et al., 2010). While functional connectivity analyses are mostly based on spontaneous and task-free resting-state measurements using fMRI, but also EEG, MEG or fNIRS, task-related functional connectivity of brain areas has also been demonstrated. The increasing interest in anatomical and functional network connections and the rapid advances in connectomics have paralleled a shift also in clinical neuroscience from assessing pathology within certain brain regions to characterizing disturbances of interconnected neural systems (Fornito & Bullmore, 2014). Thus, resting state connectivity anomalies have been identified in various neurological and psychiatric disorders, such as schizophrenia, anxiety, depression, autism, attention-deficit/hyperactivity disorder (ADHD), dementia, and epilepsy, with syndromes revealing partly overlapping and partly unique dysfunctions (Broyd, Demanuele, Debener, Helps, James & Sonuga-Barke, 2009; Whitfield-Gabrieli & Ford, 2012). Regarding schizophrenia in particular, frontal and temporal connectivity disturbances on a structural and functional level have recently been reviewed (Fitzsimmons et al., 2013).

The above described sophisticated approaches – mapping spatial arrangements of brain areas and their interconnections and linking them to distinct psychological functions – are extremely useful to investigate fundamental processes of information transmission as well as respective disturbances in patients suffering from mental disorders. However, their

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[3] Vice versa, one can of course also argue that knowledge about the structural organisation and topological properties of the brain is necessary in order to understand the functional properties of such a complex network (Ball et al., 2014).

implementation is less sufficient to investigate neurophysiological counterparts of particular psychological symptoms that occur rather acutely in mental disorders. To target this issue, functional brain imaging data can also be obtained while patients actually experience symptoms – either naturally or experimentally induced by disease-specific cues (Linden & Fallgatter, 2009). In the former case, the investigator is dependent on a natural symptom occurrence which cannot be guaranteed during a neurophysiological measurement session. The latter option promises higher experimental control, however, it may suffer from reduced ecological validity. The identification of symptom-related brain activation can be (and has increasingly been) used to assist therapeutic interventions. For example, findings on regional brain function abnormalities in patients can guide neuromodulatory treatments, such as TMS or NFB. Both methods can be seen as prime examples of state-of-the-art neurophysiological techniques in applied neuroscience and their practical value is currently being assessed in a number of studies (see, for example, Croarkin, Wall & Lee, 2011; Ehlis, Schneider, Dresler & Fallgatter, 2014). While TMS modulates the excitability of superficial neurons through a magnetic field that is created outside the head by moving electric charges within the TMS coil, neurofeedback is a computer-based training method in which selected brain activity parameters are processed online and made visible and fed back to the patient. Different neurofeedback protocols that are based on different imaging methods (fMRI, EEG, MEG, and fNIRS) have been established. With respect to cost-benefit deliberations, fNIRS neurofeedback might be the most advantageous, but applicability and efficacy of fNIRS neurofeedback for treating psychological symptoms in different psychiatric disorders needs to be more extensively assessed.

Another critical issue in the field of psychiatric neuroscience is ecological validity. Problems and symptoms that psychiatric patients are usually faced with typically do not occur when resting in a scanner. Moreover, the assessment of certain symptoms may be more or less suitable with certain imaging methods compared to others. For example, although repeatedly applied, online investigations on auditory hallucinations using fMRI should be interpreted with caution, as contributions of loud scanner noises to relevant activation patterns within the auditory cortex cannot be clearly determined. Therefore, psychiatric neuroscience increasingly requires methods that allow for valid and reliable assessments of neurophysiological substrates of symptoms that occur under specific conditions. For example, patients with schizophrenia frequently show impairments in social communication (Burns, 2006; Wible, 2012), a symptom most prevalent in situations that involve social interactions. For this reason, neuroimaging research of psychiatric disorders demands for – more than in most other areas of research – economically and ecologically reasonable methods that are easily applicable. Methods that are applicable in real-world contexts (such as conversations, movements, etc.) can help to translate basic neuroscientific knowledge into pragmatic contexts that are much closer to daily life situations. Especially EEG and fNIRS share such advantageous features: Both methods can be applied in upright positions, and for both techniques portable systems already exist. Due to its relative insensitivity to (particularly distal) body movements, fNIRS may be particularly suitable to assess functional activation patterns in a variety of clinical applications, such as during real-life cue exposure, online social interactions, or even during therapeutic interventions. While such applications have, up to now, been implemented rather occasionally, current trends are clearly pointing in that direction (Ehlis et al., 2014).

Although there is probably not a single psychiatric symptom that has not at least once been assessed via functional imaging methods, still many open questions remain, for example regarding the cause-effect relationships between aberrant brain structure and function and the many-faceted phenotypes of mental illnesses. Linden and Fallgatter (2009) noted that "we have to be careful with causal inferences from observations of regional brain activity during experience of specific symptoms" (p. 2, left column). Although measured brain activity may indeed reflect a consequence of a psychological symptom, it could also be explained in terms of a compensatory mechanism. Moreover, the influence of bottom-up processes on symptom experience can not be determined precisely (Linden & Fallgatter, 2009). In other words, although the use of imaging techniques brought eminent progress to the understanding of mental disorders, the utility of these studies for causal pathological models of disorders is limited. Furthermore, considering the large variety of techniques that can uncover different aspects of (abnormal) brain structure and function, the method must be appropriate for the scientific topic at hand (and may be superior over other imaging techniques). Hence, cost-benefit considerations must not be neglected to ensure a reasonable usage of imaging methods in psychiatric research. For example, because neural activity is always characterised by a spatial (topographical distribution of neural activation within the brain or specific brain areas) and a temporal (generation and changes of neural activation over time) dimension, the choice of an imaging technique will also strongly depend on the dimension of interest. While EEG and MEG accurately resolve temporal changes of brain activation, spatial resolution of these methods is limited and topographical patterns of neural activity are only accessible through probabilistic procedures. In contrast, methods that record haemodynamic measures of neural activity, such as fMRI or fNIRS, produce images of higher spatial precision, with the drawback of strongly limited temporal resolution, and should therefore be favoured when the location of brain activation is of interest. Hereby, fNIRS takes an intermediate position – regarding temporal and spatial resolution characteristics – between EEG/MEG and fMRI. On the one hand, fNIRS is characterised by a higher sampling rate and therefore better temporal resolution compared to fMRI. However, as a purely functional imaging method, fNIRS results are lacking precise anatomical data to which detected activation patterns are assigned. Therefore, fNIRS always requires spatial registration techniques. Because it is not always feasible to acquire subject-specific head anatomy (for example by using individual MRI scans), current fNIRS studies mostly use MRI-free approaches, whereby the cortical activation patterns obtained via fNIRS measurements over a participant's head surface become assigned to a selected brain atlas (see Figure 2 for an exemplary procedure). Despite this important disadvantage as compared to fMRI assessments, fNIRS is predicted to play a crucial role in future neuro-psychiatric research (Ehlis et al., 2014; Ernst, Schneider, Ehlis & Fallgatter, 2012): In contrast to fMRI, fNIRS allows for brain activity assessments in real-life contexts, and is favourable for large-scale investigations due to its uncomplicated set up and cost-efficiency. Such large-scale studies play a key role in longitudinal studies and imaging genetics which are critical methods to elucidate predictors and etiological factors of mental disorders.

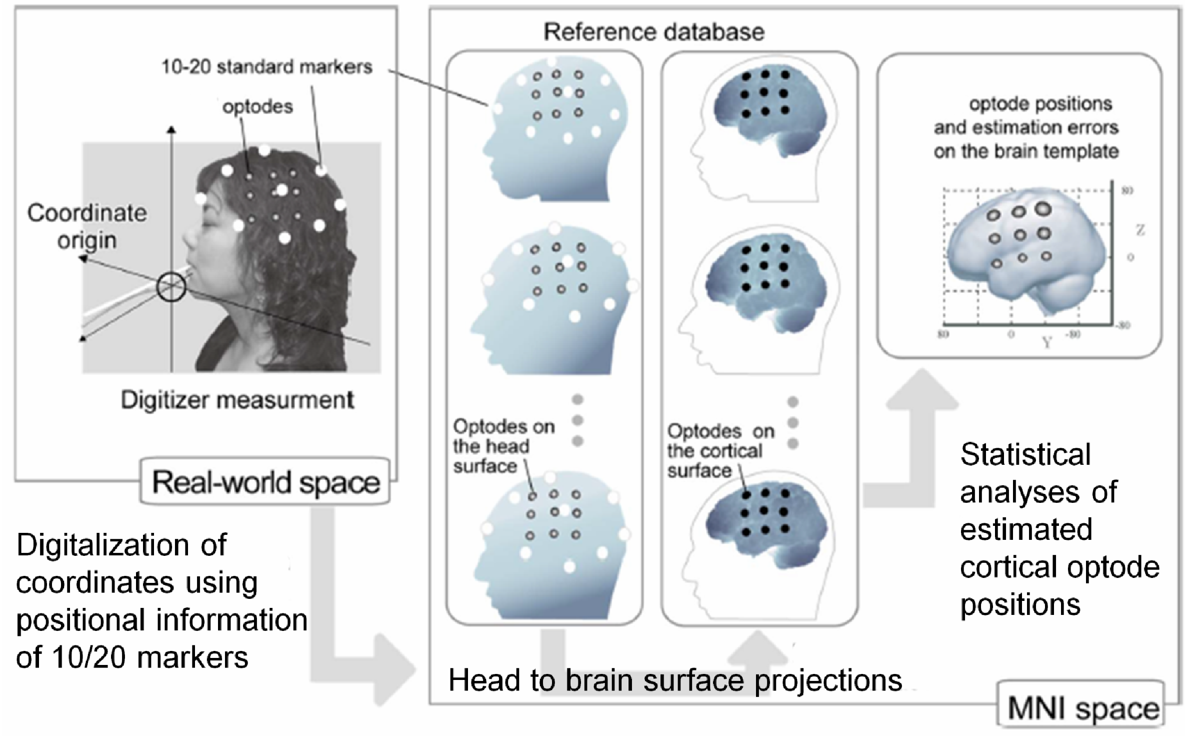

Figure 2. Procedure of virtual spatial registration of NIRS data to normalised brain coordinates. Figure modified from Tsuzuki, Jurcak, Singh, Okamoto, Watanabe and Dan (2007), provided by the Functional Brain Science Lab (Lichi University Tochigi, Japan: http://www.jichi.ac.jp/brainlab/).

While in-advance considerations on measurement applicability, ecological validity, and temporal vs. spatial resolution help choosing a suitable imaging method to investigate neuro-psychiatric issues, interindividual differences and symptom characteristics potentially influence behavioural and functional outcomes independently of the technique applied – and they may not be underrated. This can also be seen as a crucial aspect when interpreting results from neuroimaging studies on psychiatric patients: While most studies are – for statistical and technical reasons - built upon group comparisons pooling subjects that are often highly heterogeneous according to a number of variables (e.g. demographic factors and, more critically, psychological symptoms and characteristics), we may be tempted to draw conclusions and employ them on individual patients. Against this background, attempts to implement brain imaging techniques that have been proven to produce reliable data at *group* level for individual diagnosis, as it can be observed in some Japanese institutions using fNIRS to aid individual diagnostics of mental disorders (Cyranoski, 2011), need to be regarded critically (but see Farah & Gillihan, 2012 for an optimistic perspective). Both researchers and clinicians should keep in mind that psychological diagnostics and interventions focus on individuals and that findings from group analyses can only reflect an excerpt of the individually expressed clinical phenotype. Therefore, both diagnostic and therapeutic instruments that incorporate findings from brain imaging research generally need to be adjusted to the individual conditions and needs of a single patient.

1.3 Current perspectives on the pathogenesis, psychopathology, and neurobiology of schizophrenia

> „Die *Gruppe der Schizophrenien* ist die faszinierendste und komplexeste psychische Störung des Menschen. Durch sie werden die fundamentalen Konstituenten der Person betroffen, nämlich Denken, Fühlen, Wahrnehmung, Willensbildung und Handeln. Der Schizophrenie – wobei wir von keiner nosologischen Entität ausgehen können – liegt eine Störung des Gehirns zugrunde, unserem komplexesten Organ, dessen Funktionsweise wir erst in Ansätzen beginnen zu verstehen."
>
> Kircher and Gauggel (2008, p. V)

1.3.1 Epidemiology, symptomatology and diagnostic aspects

The largely varying appearances of schizophrenia that are referred to as being both "complex" and "fascinating" in the above quoted statement by Kircher and Gauggel have formed a fluctuating construct of schizophrenia as a non-uniform disease, that is frequently undergoing changes and re-conception. Crow (2011) summarised that "no dividing line can be drawn in symptoms […] and different definitions of psychosis identify different patients" (p. 205, right column). Eugen Bleuler, who introduced the term "schizophrenia", already pointed to the heterogeneity of the disorder by naming it "group of schizophrenias" (Bleuler, 1911). In its broadness, schizophrenia is characterised by fundamental impairments in perceiving, sensing, and thinking, that can even result in severe loss of relation to reality. In more detail, fully developed symptoms affect at least the following six functional areas (see Falkai, 2008): (1) attention and concentration; (2) formal thought; (3) ego functions; (4) perception; (5) motivation/drive; (6) affect and psycho-motor functions. While attention and concentration deficits are classified as cognitive symptoms, the latter symptom facets are divided into positive (1-4) and negative (5 & 6) symptoms, indicating that mental phenomena become added to or are missing from normal sensing and psychological functions. Due to the symptoms' heterogeneity, the diagnostic process is often complex and difficult and it requires detailed assessments. Because psychotic symptoms can also result from neurological syndromes, such as dementia or vascular disorders, an intensive neurological assessment is further necessary to rule out this option. In order to aid and facilitate the diagnostic process, clinical classification systems continuously undergo revisions and developments. Only very recently, the previous system to classify psychological syndromes, the diagnostic and statistical manual of mental disorders in its fourth, text-revised edition (DSM-IV-TR; American Psychiatric Association, 2000), has been relieved by its younger version, the DSM-5. Although the new manual mostly keeps key features that define the psychotic disorder (see table 1, first row, "characteristic symptoms") and it only applies minor changes regarding the six diagnostic criteria (criteria A-F, see table 1), some important changes have been made in order to better conceive the syndrome's versatility and variability (for an overview on changes from DSM-IV to DSM-5, see Paulzen & Schneider, 2014; Tandon et al., 2013).

While in both versions at least two A-criteria are obligatory for the diagnosis, now at least one of these two must be delusions, hallucinations, or disorganised speech. Catatonia is still acknowledged as a defining domain, though now the concept is conceived more widely and it now also appears among other disorders as a state description without known aetiology. However, catatonia has been removed as a defined schizophrenia subtype, together with the disorganised, paranoid, and undifferentiated subtypes, because they have been found to "exhibit poor diagnostic stability over time, do not cluster in families, and have limited prognostic value" (Jablensky, 2006; Peralta & Cuesta, 2007; cited by Tandon et al., 2013; p. 6, right column). Moreover, less than 5% of research articles on schizophrenia compare different subtypes on target variables (Braff, Ryan, Rissling & Carpenter, 2013). Finally, so-called specifiers indicating the course of illness are included in the DSM-5. They allow documenting both the current clinical status and the previous course.

Table 1. Schizophrenia in DSM-IV-TR and DSM-5.

DSM-IV criteria for schizophrenia	**Proposed criteria for schizophrenia in DSM-5**
Criterion A: Characteristic symptoms. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). (1) Delusions (2) Hallucinations (3) Disorganised speech (4) Grossly disorganised or catatonic behaviour (5) Negative symptoms, i.e., affective flattening, alogia, or avolition Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other	**Criterion A: Characteristic symptoms.** *(Minor change)* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these should include 1–3: (1) Delusions (2) Hallucinations (3) Disorganised speech (4) Grossly disorganised or catatonic behaviour (5) Negative symptoms, i.e., affective flattening, alogia, or avolition Note: Deleted
Criterion B: Social/occupational dysfunction. For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning, such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).	**Criterion B: Social/occupational dysfunction.** *(No change)*
Criterion C: Duration. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms.	**Criterion C: Duration.** *(No change)*

During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).	
Criterion D: Schizoaffective and major mood disorder exclusion Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.	**Criterion D: Schizoaffective and major mood disorder exclusion** *(No change)*
Criterion E: Substance/general mood condition exclusion The disturbance is not attributed to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.	**Criterion E: Substance/general mood condition exclusion.** *(No change)*
Criterion F: Relationship to Global Developmental Delay or Autism Spectrum. Disorder: If there is a history of autism spectrum disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).	**Criterion F: Relationship to Global Developmental Delay or Autism Spectrum.** Disorder *(Minor change)*: If there is a history of autism spectrum disorder or other communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 month (or less if successfully treated).

Modified from Tandon et al. (2013).

Although cognitive impairments have been discussed to be added as a characteristic symptom, the diagnostic specificity of cognitive deficits (i.e. for distinguishing schizophrenia from related or similar psychological syndromes), especially at the onset of the disorder, has been questioned (e.g. Reichenberg et al., 2009). Although the fundamental diagnostic approach in DSM-5 is, like in its previous version, mostly categorical (Paulzen & Schneider, 2014), the DSM-5 offers the opportunity to rate 8 psychotic symptoms (cognition, depression, and mania in addition to the 5 characteristic symptoms) on five-point rating scales. This approach tries to integrate dimensional considerations of psychopathological characteristics. In sum, the changes made in DSM-5 intend to more accurately account for the complexity and heterogeneity of the disorder. However, as still very different phenotypes are collapsed in the category of schizophrenia[4], the feasibility and validity of genetic and neuro-functional studies are significantly hampered.

The world health organization (WHO) estimates that 24 million people worldwide are affected by schizophrenia (http://www.who.int/mental_health/management/schizophrenia/en/). With about 15 per 100.000 individuals (i.e. 0.015 percent), incidence (registered cases per year) is relatively low and prevalence rates appear higher due to frequent recurrences and the not seldom chronic courses of the disease. The life time prevalence, i.e. the risk of experiencing a schizophrenic episode at least once in a life time, amounts to 0.7-1.4 % (McGrath, Saha, Chant & Welham, 2008). A German study has found 15 % of individuals reporting on isolated delusion symptoms and 4 % on any kind of hallucinations that would not fully meet the criteria for a schizophrenic disease (Wittchen, Höfler, Liebe, Spauwen & Os, 2004). Both the prevalence rates as well as the severity of the disease together with frequent relapses have a strong impact on our health care system: According to the German Health Interview and Examination Survey (Wittchen & Jacobi, 2001) 68 % of patients with schizophrenia, as compared to 36 % of overall psychiatric disorders, made contact with any kind of treatment institution (e.g. ambulant therapy or psychiatric hospital). However, the majority of patients with schizophrenia are still assumed to be not treated adequately.

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[4] This is also being done by other classification systems, such as the International Classification of Diseases 10 (ICD-10). The classification based on Leonhard (1968) more strongly emphasizes the temporal aspects (disease development and course) of schizophrenia, but this classification system has not prevailed – or did so only to a limited degree – in clinical practice.

While in the past it has been suggested that both sexes are equally affected, more recent studies point to a slight majority of men over women, with a ratio of 1.4 : 1 (McGrath et al., 2008). Moreover, there is some evidence that the prognosis is worse in men (Grossman, Harrow, Rosen, Faull & Strauss, 2008; Usall, Ochoa, Araya & Márquez, 2003), except for late-onset cases (over the age of 45). The mean age of onset differs for male and female patients: While the peak of first manifestations in men occurs between the age of 20 and 25, the disease onset in women peaks in the late twenties, between 25 and 30 (Haefner, Maurer, Loeffler & Riecher-Roessler, 1991). A second, much smaller peak is reached at the age of 45 to 50, with more female than male cases at this stage, which is attributed to a reduction of oestrogen at that age (see section 1.3.2). These late-onset disorders are associated with the overall poorest clinical outcome (Haefner et al., 1991).

While the view that the incidence of schizophrenia varies only little between sites was widely accepted for a long time, a review published by McGrath and colleagues (2008) rather indicates location-dependent incident rates of schizophrenia. Interestingly, although "90% of people with untreated schizophrenia are [living] in developing countries" (WHO, 2014), less severe forms and courses of the disease have been observed in these countries (Tandon, Nasrallah & Keshavan, 2009). However, in light of the fast industrial development of emerging countries, continuous reassessments of these relationships will be of interest.

1.3.2 Etiological models: Links to genetics, neurotransmission, and brain anomalies

In the 20th century, an intensive scientific debate has been held between proponents of somatic (Bogerts, 1985; Huber, 1976; Mayer-Gross, 1932) and – at least in part – psychological (Bleuler, 1951) origins of schizophrenia. Today, still far away from a complete understanding of the causes of the disease, the most consensual etiological model of schizophrenia is a multi-factorial one, termed diathesis-stress model or vulnerability-stress model, respectively (e.g. Nuechterlein & Dawson, 1984; Zubin & Spring, 1977). Although the validity of this model has been questioned (McGuffin, Asherson, Owen & Farmer, 1994), it has provided a thoroughly used basis for evolving theories and testing hypotheses regarding the origins of schizophrenia.

Vulnerability factors comprise structural neuronal alterations and/or neurophysiological as well as chemical anomalies in the brain which may be, but not necessarily are, linked to genetic determinants. They can also appear as a consequence of exogenous (i.e. environmental) factors. Many etiological studies suggest exogenous factors that occur very early during development, such as pregnancy and birth complications or infections in uterus, have been suggested in many etiological studies (see Tandon, Keshavan & Nasrallah, 2008 for an overview). On the other hand, support for a strong impact of such factors on the development of schizophrenia has waned with increasing quality of the evidence (Cannon, Jones & Murray, 2002; Crow, 2011). Nonetheless, neural developmental disturbances have been suggested as crucial etiological factors in some etiological models (e.g. Weinberger, 1987). Besides the prenatal–perinatal period, influencing factors during later brain developmental stages have been suggested, such as childhood psychological or physical trauma[5] (David & Prince, 2005; Morgan & Fisher, 2007) or parental separation or death (Morgan et al., 2007). Regarding adolescence, another possible external contributor that can increase vulnerability for schizophrenia relates to substance (especially cannabis) abuse. However, although a relationship between cannabis consumption and psychotic symptoms cannot be denied – considering the drug's potential to provoke psychosis-like symptoms (e. g. D'Souza et al., 2004; Morrison et al., 2009) –, the causal effect on the onset of schizophrenia is controversial (Barnes, Mutsatsa, Hutton, Watt & Joyce, 2006; Hall & Degenhardt, 2008). According to Hall and Degenhardt (2008), it is most plausible that the use of cannabis precipitates schizophrenia in individuals who are already biologically vulnerable. Bugra, Rapp, Studerus, Aston, Borgwardt, and Riecher-Roessler (2012) summarised, that "[…] although a causal relationship between cannabis use and schizophrenic psychoses cannot be definitely proven, the available evidence strongly supports its plausibility" (p. 635). A final clarification of this question is however challenging, considering complex methodological problems when investigating causal effects of cannabis consumption, such as the comparatively low incidence of the illness among cannabis customers, the frequent problem of multiple substance abuse, and a relationship between substance consumption

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[5] In fact, according to the model, psychological childhood trauma could be classified as both an exogenously provoked vulnerability factor and a stressful life event. The former case would be related to childhood traumas that cause functional anomalies/impairments that increase the risk for developing schizophrenia at an older age, while the latter case would be associated with a more immediate onset of psychotic or related symptoms.

rates and urbanicity. The latter fact may be particularly crucial because studies have suggested some impact of urban living on the risk of developing schizophrenia (Kelly et al., 2010; Lewis, David, Andéasson & Allebeck, 1992). The exact nature of this relationship is yet unclear, and the link between city living and schizophrenia incidence might be at least partly explained by social and cultural factors (Heinz, Deserno & Reininghaus, 2013; Zammit, Lewis, Rasbash, Dalman, Gustafsson & Allebeck, 2010). However, there is relative consensus that urbanicity is likely to interact with genetic vulnerability in the course of schizophrenia.

With respect to other potentially influencing factors that manifest during late childhood and adolescence, such as "poor academic achievement, […], 'minor physical anomalies', […], and poor social adjustment" (Tandon et al., 2008, p. 10, right column), it is, until now, not clear whether they constitute risk factors for schizophrenia or instead represent early manifestations (i.e. a prodromal stadium) of the disease itself.

Although not explaining the full variance, an impressive amount of scientific evidence has pointed to genetic factors in the vulnerability for schizophrenia. In fact, genetic predisposition is regarded as the main risk among all vulnerability factors for the disease (Arolt, Ohrmann & Rothermund, 2006), with some researchers mentioning heritability rates of up to 80 % (Boshes, Manschreck & Konigsberg, 2012). Family, twin and adoption studies (reviewed in Shih, Belmonte & Zandi, 2004) were the first to point towards such an apparent heritability. While genomic linkage studies[6] have revealed different loci for potential predisposition genes on certain chromosomes of the deoxyribonucleic acid (DNA; see Maier et al., 1999; Vieland et al., 2014), recent genome-wide association studies[7] and genomic micro array technology allows for a genome-wide discovery of small

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[6] The term linkage refers to a common inheritance (co-segregation) of a genetic marker with a phenotype (e.g. a disease) within a family. Therefore, linkage studies investigate whether, within a family, the presence of a disease marker allele inherited from an afflicted ancestor significantly predicts presence of disease (Arolt et al., 2006). Compared to association studies (see below), linkage studies reach higher specificity (falls-positive results are less likely), but lower sensitivity.

[7] Genome-wide (or whole genome) association studies examine the frequencies of single nucleotide polymorphisms (SNPs) in most of the genes of different subjects with or without a certain disease in order to see how much the gene polymorphisms vary among the affected as compared to the unaffected individuals (Bergen & Petryshen, 2012). In contrast to genome-wide association studies, candidate gene association studies are limited to the examination of single genes.

chromosomal changes[8], named copy number variants (Hosak, 2013). Based on these genome-wide association studies, "more than 70 genes are suspected to be involved in the genetic background of schizophrenia" (Hosak, 2013, p. 58, left column). Candidate genes that have been particularly frequently reported are, for example, the catechol-O-methyltransferase gene (COMT), the gene for the dopamine D2 receptor (*DRD2)*, the gene for the protein dysbindin (DTNBP1) or the Neuregulin (NRG)1 gene (e.g. Wagner & Maier, 2008). In light of obvious negative effects of the disorder and reduced reproduction rates among schizophrenia patients the question has been raised why prevalence rates are not decreasing over time.

To summarise, there is genetic heterogeneity, with multiple genes (and, moreover, multiple chromosomal regions across the genome), instead of a single one or a limited set, associated with the risk of developing schizophrenia. As mentioned in the previous section, current diagnostic conventions may hamper a more convincing identification of distinct (clusters of) genes associated with schizophrenia.

The fact that the above mentioned candidate genes for schizophrenia are linked to the functioning of certain neuro-transmitter systems leads us to the relevance of these systems in the development and course of the disease. Because dopamine agonists can provoke psychotic symptoms, and, conversely, dopamine antagonistic agents ameliorate acute schizophrenia symptoms, dopamine has a prominent role in the pathophysiology of schizophrenia. A contemporary concept suggests an imbalance of mesolimbic-mesocortical dopamine, with a mesolimbic dopamine surplus (hyperdopaminergia) and a dearth of dopamine (hypodopaminergia) in frontal brain areas. The aberrant salience model (Kapur, 2003), that is based on the imbalance hypothesis of dopamine, suggests that chaotic dopamine transmission causes a mal-attribution of significance to events or stimuli normally considered irrelevant. Therefore, the model links the pharmacological factors with cognitive aspects of the disease. According to this model, psychotic symptoms should occur first when the chaotic dopamine transmission induces the attribution bias. This idea was recently confirmed in a study on unmedicated prodromal patients (Roiser, Howes, Chaddock, Joyce & McGuire, 2013). However, recent evidence indicated a relevance of other neurotransmitters such as serotonin, glutamate and adenosine, demanding a broadened view on the neurotransmitter background in schizophrenia (Lau, Wang, Hsu & Liu, 2013; see Figure 3). Firstly, the dopaminergic system is influenced by both the

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[8] Deletions or duplications of a chromosome segment.

glutamate and GABA system: While both adenosine and GABA can inhibit the dopamine system, the glutamate system exhibits an excitatory influence (Falkai, 2008, cf. Fig. 4.1, p. 41). Moreover, the fact that more recently established atypical antipsychotic agents (see also section 1.3.3) exert part of their antipsychotic effect via an antagonistic effect at serotonergic receptors points to additional relevance of other neurotransmitters besides dopamine. Nevertheless, a critical role of dopamine for the schizophrenia phenotype remains in place. Lau et al. (2013) concluded that "dopamine does explain the pathophysiology of schizophrenia, but not necessarily the cause per se" (p. 389, abstract).

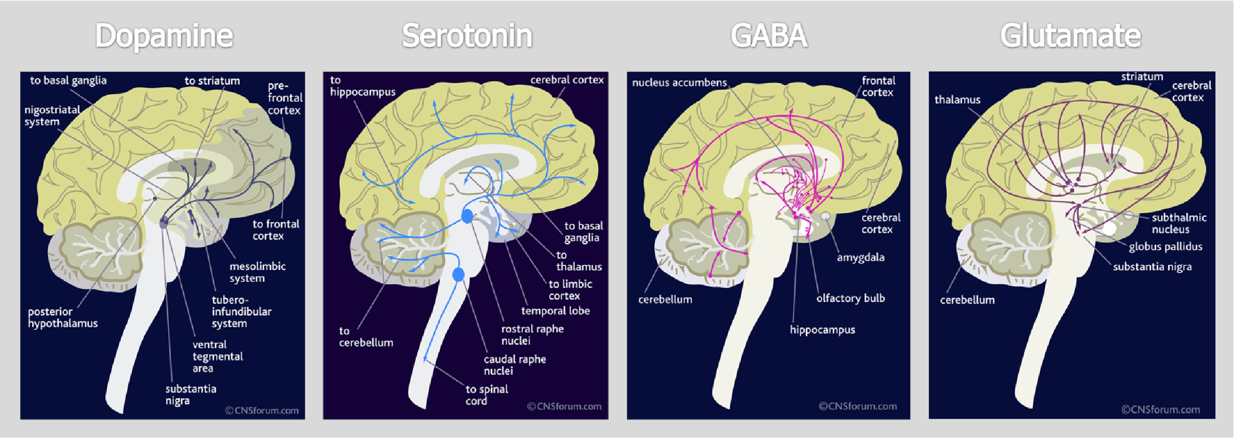

Figure 3. Schematic visualisation of neurotransmitter systems that seem to be involved in the pathophysiology of schizophrenia. Adopted from and modified based on http://www.cnsforum.com/educationalresources/imagebank/normal_brain.

In the past century, research on etiological factors that precede schizophrenia has additionally focused on morphological anomalies of the brain. The earliest and also most replicated findings indicate an enlargement of the inner and outer ventricles (Johnstone, Crow, Frith, Husband & Kreel, 1976; Shenton, Dickey, Frumin & McCarley, 2001). Since the early work published by Johnstone and colleagues, several hundred imaging studies have addressed volumetric changes in schizophrenia. There is some evidence for whole brain volume reductions in patients but, because many studies have also failed to find reduced brain volumes in schizophrenia patients compared to controls (see Shenton et al., 2001), such reductions may be only evident in a subset of patients. An isolated assessment of white matter (WM) and grey matter (GM) volume revealed GM decreases in a large region including subcortical (thalamus and the amygdala/hippocampal complex) as well as mostly fronto-temporal cortical areas, such as the anterior cingulate cortex (ACC), the insula (bilaterally), the medial and inferior frontal gyrus (MFG and IFG), and temporal regions, such as the superior temporal gyrus (STG; Ellison-Wright & Bullmore, 2010; Lawrie & Abukmeil, 1998; Palaniyappan, Balain & Liddle, 2012). Although results regarding WM volume are less consistent, structural WM abnormalities are thought to underlie the structural part of cerebral disconnectivity in schizophrenia (Samartzis, Dima, Fusar-Poli & Kyriakopoulos, 2014), a phenomenon that has received increasing attention. In favour of the network hypothesis, recent anatomical studies have shown increased path lengths and clustering along with a loss of frontal hubs (Griffa, Baumann, Thiran & Hagmann, 2013). Moreover, functional connectivity of resting state networks[9] has been shown to be altered in schizophrenia (Karbasforoushan & Woodward, 2012; Whitfield-Gabrieli & Ford, 2012).

Beyond these rather "static" parameters of abnormal brain structure and function (i.e. unrelated to certain perceptive, cognitive, or motor domains), the last decades yielded a huge amount of evidence on cerebral dysfunctions that are linked to specific psychological functions tested in certain psychological-experimental situations. Some of these are discussed as possible diagnostic markers (i.e., preceding the actual disease onset), while for others there is some evidence that factors related to the course of the disorder, such as social isolation and antipsychotic medication, may cause respective anomalies. A description of all psychophysiological parameters that have been reported to be altered in schizophrenia is beyond the scope of this work. However, an overview over functional brain alterations in the context of both language and emotion perception will be given in the respective sub sections of this dissertation (see sections 2.1 and 2.2).

Besides the various vulnerability factors, psychosocial factors, often also referred to as *stressors*, are critical aspects for the onset, maintenance or relapse of the disorder according to the diathesis-stress model. These stressors encompass both major life events as well as milder daily hassles. A recent prospective study on environmental stressors

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[9] Present research distinguishes between 5 (de Luca, Beckmann, De Stefano, Matthews & Smith, 2006) and 23 (Doucet et al., 2011) resting state networks that can be identified in the human brain. The two most highlighted large-scale networks are the brain default-mode network (DMN; Raichle, MacLeod, Snyder, Powers, Gusnard & Shulman, 2001) and the network routinely activated during goal-directed attention activity (Corbetta & Shulman, 2002). For a sophisticated overview, see Moussa, Steen, Laurienti, and Hayasaka (2012).

showed that children at risk for developing schizophrenia were more frequently exposed to negative life events and/or daily stressors and that these children "reported greater distress resulting from these experiences" (Cullen, Fisher, Roberts, Pariante & Laurens, 2014, p. 358, left column). This finding further emphasises that biological vulnerability and the occurrence of stressful events also interact in the development of schizophrenia. Interestingly, there is some evidence that the relationship between symptoms in the early phases of the disease and stress is mediated by a deregulation of the hypothalamus-pituitary adrenal (HPA) axis (Corcoran et al., 2003; Walker, Brennan, Esterberg, Brasfield, Pearce & Compton, 2010).

In addition to risk or vulnerability factors, the consideration of potential protective factors has opened another perspective on epidemiologic and etiologic research in the field of schizophrenia. The most frequently replicated biological protective factor is the female hormone oestrogen because it modulates impact on the dopaminergic, serotonergic and glutamatergic systems (Haefner et al., 1998; Kulkarni, Hayes & Gavrilidis, 2012). Considering the later disease onset and the mostly milder course of the disease (see section 1.2.1), oestrogen seems to protect against an early onset, while its protective appeal decreases over age together with the hormone's concentration. Because stress is regarded as an important risk factor for schizophrenia, factors related to stress reduction can be seen as protective. Such factors may include internal aspects, such as self efficacy, self esteem, and personal coping abilities, as well as external factors including social recourses and social support (Pruessner, Iyer, Faridi, Joober & Malla, 2011). Emphasising their protective potential, these factors have all been linked to quality of life (QoL)[10] in patients with schizophrenia (Song et al., 2011).

1.3.3 Course of the disease and treatment options

Like the symptom spectrum and the nature of the disease itself, courses of schizophrenia vary largely. The fluctuating and changing symptoms over time that accompany (but also may precede) the disorder are considered in three main phases: the prodromal phase, the acute phase, and the residual phase.

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[10] The term quality of life can be best described as a "multidimensional construct encompassing not only the subjective domain of life-satisfaction, but also the objective domains of functional capacity, psychological status, and social interactions." (Song et al., 2011, p. 201, left column)

In the majority of cases, fully developed schizophrenia symptoms are preceded by an initial prodromal stage which is often characterised by rather unspecific symptoms, including attenuated psychotic symptoms (e.g. transient formal thought disorders, bizarre beliefs, or light negative symptoms), cognitive and social dysfunctions, and a noticeable reduction of general functioning (Chuma & Mahadun, 2011; Haefner, Maurer, Loeffler, der Heiden, Hambrecht & Schultze-Lutter, 2003). During the acute phase, transient and non-specific anomalies become replaced by characteristic psychotic symptoms (e.g. delusions, hallucinations, and disorganisation) which cumulate quickly and reach their climax within varying time spans (usually weeks to months). The residual stage is characterised by remittent psychotic symptoms, whereby some residual, sub-acute symptoms remain. Different approaches have tried to classify symptom courses into reasonable and research-conform clusters. A simple trichotomy differentiates single episodes, several episodes, and chronic courses (Mass, 2010). More sophisticated approaches distinguish more complex course types, which for example consider subtypes with versus without residual symptoms of variable versus fixed intensity between different psychotic episodes (e.g. Ciompi, 1980). The proportion of cases exhibiting only a single schizophrenic episode is around one fifth, while the majority of cases show episodic courses without or with increasing residual symptomatology between subsequent symptom bursts (Bottlender & Moeller, 2006; Watt, Katz & Shepherd, 1983).

Although several findings have previously pointed to a negative impact of long duration of illness (DUI) on clinical outcome and treatment efficacy (Bottlender, Strauss & Moeller, 2000; Norman & Malla, 2001), this concept has recently been questioned (Arolt et al., 2006; Craig, Bromet, Fenning, Tanenberg-Karant, Lavelle & Galambos, 2000).

Given the well-established hypotheses and research findings on pharmacological and cognitive alterations underlying schizophrenia, state-of-the-art treatment of both first-episode schizophrenia and reoccurring psychotic episodes involves antipsychotic medication and psychological intervention (family intervention and individual Cognitive Behavioural Therapy [CBT]), as recommended by the National Institute for Clinical Excellence (NICE) clinical guideline 178: "Psychosis and schizophrenia in adults: treatment and management" (http://guidance.nice.org.uk/CG178). Regarding antipsychotic medication, a large body of clinical trials has so far tried to assess the effects of pharmacological agents on the various symptoms in schizophrenia. Hereby, a frequent target comprises the comparison between of first- and second-generation antipsychotic agents (FGAs versus SGAs) which are assumed to rely on different neurobiological mechanisms of action. Although the exact cellular basis of their therapeutic action is, up till now, not fully understood, previous research suggests that "FGAs primarily block subcortical dopamine (D2) receptors, whereas a common characteristic of SGAs is reflected in their prominent serotonin receptor blocking effect together with D2-receptor antagonism" (Schneider et al., 2013, p. 1912, right column). Superior effects of atypical over typical agents regarding their clinical potency, though frequently reported, are controversially discussed. Researches argued that, up to now, there is no unequivocal evidence for a general superiority of SGAs over FGAs regarding short- and long-term clinical outcome, because methodologically good meta-analyses are rare and results highly depend on the respectively compared agents, dosages, or the occurrence of side-effects (Davis, Chen & Glick, 2003; Hasan et al., 2013; Leucht, Corves, Arbter, Engel, Li & Davis, 2009). While several studies confirmed positive effects of SGAs on the frontal brain and neurocognitive function (e.g. Ehlis, Zielasek, Herrmann, Ringel, Jacob & Fallgatter, 2005; Meltzer & McGurk, 1999; Woodward, Purdon, Meltzer & Zald, 2005) – probably achieved by an enhancement of dopamine, serotonin and acetylcholine levels in prefrontal regions – recent meta-analyses indicated that cognitive advantages of SGAs versus FGAs only reach low effect sizes (Goldberg et al., 2007; Hill, Bishop, Palumbo & Sweeney, 2009; Thornton, Van Snellenberg, Sepehry & Honer, 2006). Regarding social cognition deficits, antipsychotic drugs of either class have been, so far, shown to produce only small positive effects (Kucharska-Pietura & Mortimer, 2013).

Although NICE and other guidelines explicitly recommend psychological interventions in the treatment of schizophrenia, the implementation of CBT and particularly family interventions is still poor (Haddock, Eisner, Boone, Davies, Coogan & Barrowclough, in press). CBT has been proven to be beneficial to increase pharmacological treatment compliance and to ameliorate schizophrenia in patients not responding on medical and other interventions (Kemp, Hayward, Applewhaite, Everitt & David, 1996; Sensky, Turkington, Kingdon & et al., 2000; Tarrier, Beckett, Harwood, Baker, Yusupoff & Uqarteburu, 1993). Previous studies have further reported on positive effects of CBT on different schizophrenia symptoms, including cognitive deficits, mood, negative symptoms and psycho-social outcome (reviews are provided by Chien, Leung, Yeung & Wong, 2013; Jauhar, McKenna, Radua, Fung, Salvador & Laws, 2014). Even for positive symptoms, psychotherapy (without additional pharmacological treatment) was shown to be beneficial in some studies (reviewed in Wiedemann & Klingberg, 2003). Several research groups reported on reduced duration of hospitalisation as well as reduced re-hospitalisation rates (see NICE, 2009). However, a recent meta-analytic review critically discussed the potential of CBT for treating psychotic syndromes (Jauhar et al., 2014). The authors conclude that CBT achieves only small effects on overall symptomatology. Moreover, they argue that different aspects, such as study quality, the use of control interventions, or publication bias, need to be taken into account when interpreting reviews on CBT efficacy for schizophrenia. Furthermore, potentially adverse effects of CBT have recently begun to be examined. Klingberg and colleagues showed that adverse CBT effects are generally low and do not differ from a control treatment, but they identified a small subgroup of patients who exhibited substantial symptom increases.[11] These patients probably require more intensive care beyond treatment as usual and CBT.

Besides the immediate goals to reduce negative and positive psychotic symptoms, a major aim of therapeutic interventions in schizophrenia is to regain live quality. Particularly social and neurocognitive functions are associated with QoL and negative symptoms have been found to be more important with respect to QoL than positive symptoms (Mohamed, Rosenheck, Swartz, Stroup, Lieberman & Keefe, 2008; Song et al., 2011). Therefore, interventions especially targeting QoL enhancement should focus on these symptom classes. Specialised remediation for emotional and cognitive functions become increasingly applied in clinical practice, trying to support individualised treatment strategies. Both types were suggested to be selectively effective. For example, facial emotion recognition trainings can significantly improve patients' ability to correctly identify emotions from social cues (Statucka & Walder, 2013). However, the potential generalisability of remediation effects to broader psychological functions and, in the long run, quality of life, has been poorly investigated so far.

1.4 Social communication in schizophrenia - a neuro-cognitive perspective

Impairments in social communicative representations and systems are crucial factors underlying negative symptoms and social cognitive impairments in schizophrenia. They may further be associated with other psychotic symptoms such as delusions or some types of hallucinations (Wible, 2012). Social communication can be broadly described as the state of "communicating with others […] and functioning in the community" (Couture, Penn & Roberts, 2006, p. S44, left column) and it generally comprises three fundamental modules: social perception, social cognition, and the expression of feelings, thoughts, and

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[11] These result should, however, be cautiously interpreted, because an untreated control group has been lacking in that study.

intentions within social contexts. The former domain, social perception, is defined as an initial state of "evaluating the social communicative intentions of others by and analysis of eye-gaze direction, facial expressions, body movements, and other types of biological motion" (Wible, 2012, p. 1, left column). Social cognition can be understood as "the mental operations underlying social interactions, which include the human ability to perceive the intentions and dispositions of others" (Brothers, 1990; p. 28). Hereby, the ability to communicate with others involves an intact perception and comprehension of both verbal (i.e. language, but also language-related aspects, such as prosody) and nonverbal (e.g. facial expressions and gestures) information and, on the other hand, an adequate expression of these two. While deficits in social functions are observed in many disorders, they are regarded as a defining feature almost exclusively for schizophrenia (Bellack, Morrison, Wixted & Mueser, 1990). Therefore, social communication has been intensively investigated in schizophrenia, whereby the hallmark of impairments is far from being clearly defined. Two US-American initiatives[12] that are concerned with the study of cognitive deficits in schizophrenia have suggested frameworks for conceptualizing schizophrenic impairments in social processing. However, these frameworks give more weight to nonverbal social skills such as emotional processing or attribution styles. Studies investigating these nonverbal social skills consistently found that patients suffering from schizophrenia show impaired attention to and recognition of social stimuli with large effect sizes (see, for example, Savla, Vella, Armstrong, Penn & Twamley, 2013; Wible, 2012), whereby the majority of studies were designated to the perception of emotional facial expressions. Regarding verbal social (i.e. language) comprehension, schizophrenia patients were reported to show impaired pragmatic or context-dependent language understanding (Bazin, Perruchet, Hardy-Bayle & Feline, 2000; Kuperberg, 2010b; Linscott, 2005). Pragmatic language comprehension could be defined as "ability to communicate and comprehend intention in a rule-governed fashion" (Linscott, 2005, p. 225, right column). These deficits could be explained by semantic memory impairments and/or an abnormal use of language context (Kuperberg, 2010b), whereby both mechanisms also interact, particularly as both are linked to working memory. Besides the comprehension of semantics, structural language processing deficits, such as an impaired syntactic processing, were observed in some samples of schizophrenia patients (Kuperberg, Sitnikova, Goff & Holcomb, 2006; Morice & McNiocol, 1985). In case of spoken language,

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[12] (1): Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), and (2): Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia (CNTRICS).

verbal communication conveys social information not only by content but also the shape of speech. Modulations of language rhythm, stress, and intonation are (prosody) were also shown to be dysfunctional in schizophrenia (Edwards, Jackson & Pattison, 2002; Wible, 2012). Another prominent social-cognitive deficit observed in schizophrenia patients involves theory of mind (ToM; see Biedermann, Frajo-Apor & Hofer, 2012; Bora, Yucel & Pantelis, 2009), described as "the ability to perceive other people's opinions, beliefs, and intents, and to establish a connection between these mental states and a person's behaviour" (Biedermann et al., 2012, p. 71, left column). ToM was proposed to resemble a trait marker of the disease. On the expressive domain, studies reported decreased facial and gesture expressiveness (Bruene, Sonntag, Abdel-Hamid, Lehmkaemper, Juckel & Troisi, 2008; Kupper, Ramseyer, Hoffmann, Kalbermatten & Tschacher, 2010; Mandal, Pandey & Prasad, 1998; Sestito et al., 2013), which might be more strongly pronounced for positive emotions (Lotzin, Haack-Dees, Resch, Romer & Ramsauer, 2013), as well as decreased vocal inflection (Alpert, Shaw, Pouget & Lim, 2002; Levin, Hall, Knight & Alpert, 1985; Murphy & Cutting, 1990), the prominent symptom of disorganised speech and also reduced language fluency and complexity (see DeLisi, 2001).

Section 1.2 illustrated that knowledge of brain systems and processes underlying certain psychological functions helps to understand the phenomenology, development, and course of mental disorders. Considering the range of socially relevant functions and skills that have been shown to be reduced in patients with schizophrenia, it is not surprising that a variety of brain anomalies were linked to schizophrenic social communication impairments. Perceptual deficits of nonverbal social signals such as facial expressions and further emotional cues are predominantly linked to aberrant functioning of subcortical (amygdala, basalganglia, hippocampus) structures and a network of temporo-occipito-parietal and frontal cortical areas, including the lateral occipital cortex (LOC), the region around the superior temporal sulcus (STS) extending to the intra-parietal lobule (IPL) and the inferior frontal lobe (IFL; see Li, Chan, McAlonan & Gong, 2010; Marwick & Hall, 2008; Wible, 2012). Brain-morphological changes such as amygda/hippocampal complex, insula, and fusiform volume reductions may also be involved (e.g. Lawrie, Whalley, Job & Johnstone, 2003; Marwick & Hall, 2008). On the other hand, verbal language comprehension deficits and other impairments in cognitive (versus affective) processing of social cues, such as cognitive empathy and ToM, were most strongly associated with prefrontal dysfunctions. In a recent meta-analysis, ToM impairments were particularly linked to activation decreases in the medial prefrontal cortex (MPFC), STS, and the thalamus along with potentially compensatory activation increases in parietal somatosensory areas and the posterior cingulate (Sugranyes, Kyriakopoulos, Corrigall, Taylor & Frangou, 2011). Semantic processing deficits in schizophrenia patients relate most prominently to abnormal functioning of particularly left lateral prefrontal and medial temporal cortical areas. Hereby, disturbances within the language network, in terms of impaired functional connections between network structures, and aberrant hemispheric lateralisation were also suggested (Kircher & Gauggel, 2008). Using electroencephalography, numerous studies confirmed altered neural markers of cerebral language processing, in terms of event-related potentials (ERPs). They can be observed from early to later processing stages, depending on task demands and linguistic stimuli (for example reviewed in Kuperberg, Kreher & Ditman, 2010).

1.5 Specification of the current research topic

The previous section delineated how both verbal and nonverbal communication deficits contribute to impaired social cognition in schizophrenia. Although there are obvious reasons to assume that both domains are strongly intertwined, they are usually regarded separately. Therefore, the present work tested both communication modules using (1) a verbal and (2) a nonverbal perceptual task measuring social-cognitive functions. Experimentally, social information processing – verbal as non verbal – can be approached from a more cognitive or a more affective perspective. In a recent recommendable review, Anticevic and Corlett (2011) argued that to adequately capture the nature of psycho-social symptoms in schizophrenia, both intertwined cognitive and affective subprocesses need to be commonly addressed. Hence, in order to tap both aspects of social perception, two different types of paradigms are established for the current work. The verbal perception paradigm aims at socio-cognitive functions and processes, whereas the nonverbal perception task targets socio-affective functions. Another task requirement is related to task novelty and innovation as well as practical relevance of the assessed function in daily social interactions: Hereby, the current work focuses on particular social-cognitive domains that have so far only very rarely been investigated. Detailed descriptions of these domains will follow (see sections 2.1 and 2.2, respectively).

2. Functional brain imaging of verbal and nonverbal information processing in healthy subjects and patients with schizophrenia: Background and rational for the present projects

2.1 The neural perception and comprehension of verbal signals in schizophrenia

> "Von allem, was die Menschen erfunden und ausgedacht, bei sich gehegt und einander
> überliefert, was sie im Verein mit der in sie gelegten und geschaffenen Natur
> hervorgebracht haben, scheint die Sprache das größte,
> edelste und unentbehrlichste Besitztum."
> Jacob Grimm

Deficits in verbal communication represent one of several diagnostic features of schizophrenia and it has been widely agreed that they contribute significantly to social dysfunctions (Bowie & Harvey, 2008). In clinical contexts, language functions are assessed primarily through examining patients' language output without any theoretical assumptions about underlying causes. On the other hand, problems with the comprehension of language in schizophrenia patients are more subtle than those of language production, and these impairments have been less well documented (Kuperberg, 2010a). To this end, one part of this dissertation is dedicated to the investigation of pragmatic language comprehension in schizophrenia and the present chapter attempts to provide an elaborate overview over the processing and comprehension of language in health and disease, also addressing theoretical concepts and neurobiological bases of this important communicative function.

2.1.1 Comprehending language comprehension: concepts of semantic processing and related brain activity

The investigation of language acquisition, perception, and comprehension has a long tradition within different fields of psychology, such as general psychology, developmental psychology, and cognitive neuroscience. The assessment of the neurobiological background of human language functions and skills has produced a whole stream of research, named neurolinguistics, that is, concerned with the question how our brain manages daily life challenges in a multilingual world. Examples include foreign language acquisition or the comprehension of complex language forms that require cognitive resources and background information, such as metaphor, irony, and other types of non-literal language. In daily life situations, language is organised by means of sentences which are – no matter if spoken or written language is regarded – composed according to defined rules. Analogously, sentence processing – the way in which the words of an utterance are combined to yield an interpretation – relies on certain architectures, mechanisms, and representations. Hereby, human sentence processing is astonishingly fast and efficient, and a number of theories have tried to explain its underlying mechanisms.

2.1.1.1 Linguistic models of sentence processing

There are two basic principles of sentence processing which have been suggested for several decades (Marslen-Wilson, 1973): *Incrementality*, the first principle, refers to the decomposition of a sentence into its elements (e.g. word groups and single words) whereby sentence processing is thought to occur based on these elements. Hence, the recipient parses written sequences of words in a left-to-right order while developing a representation of the sentence meaning. The second principle, *immediacy* of word interpretation, describes the preference of a direct – in terms of an as-fast-as-possible – meaning interpretation of sentence elements. These two principles provide a general framework for most linguistic theories on sentence processing which offer different approaches to the interpretation of a sentence’s meaning. According to Rickheit, Herrmann and Deutsch (2003) these theories can be divided in autonomous and interactive models, whereby the former ones propose an independence of syntactic (i.e. referring to sentence structure) from semantic (i.e. referring to sentence meaning) processing. Interactive sentence processing approaches, in contrast, suggest that syntactic information processing can be influenced by semantic representations.[13] Apart

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[13] The assumption that syntax affects the processing and interpretation of sentence meaning (semantics) is shared by both approaches.

from the autonomous-interactive distinction, linguistic models on sentence processing differ regarding the temporal sequence in which syntactic and semantic information are processed (Hopf, Bader, Meng & Bayer, 2003; Rickheit et al., 2003; cf. Figure 4). Serial models, which represent the classic stream of linguistic positions, assume that syntactic information is prioritised and processed before the semantic content of language. The most popular of these theories is the *garden path model* (Frazier, 1978; Frazier & Fodor, 1978). According to this model, the initial evaluation of a sentence is always syntactical (e.g. identifying verbs, nouns etc. within the phrase), whereas the semantic meaning of the resulting syntax structure will be interpreted at a second step. When faced with ambiguous[14] sentence material, the processor chooses one interpretation option instead of pursuing multiple syntactic analyses. If this initially preferred analysis strategy turns out to be insufficient, the recipient is "led down the 'garden path' and reanalyzes the sentence" (Papadopoulou, 2006, p. 11), meaning that at least parts of the sentence need to be reanalysed to derive the appropriate reading. On the other hand, parallel models (e.g. Gibson, 1991) assume that all possible syntactic analyses are computed at once, i.e. in a parallel manner, whereby alternatives are ranked into more or less preferred syntactic analyses. In general, the analysis strategy that requires least working memory resources would be preferred. However, if syntactic ambiguities arise, incorrect or incompatible syntax analysis strategies "will simply be discarded from working memory while the correct analysis remains" (Hopf et al., 2003).

Empirical evidence from (neuro)-linguistic experiments suggests that the above described sentence processing theories are not mutually exclusive. Both, garden path effects and parallel reading strategies have been experimentally confirmed (Hopf et al., 2003; Rickheit et al., 2003).

With respect to pragmatic language comprehension, however, the fundamentally differing assumptions of the two models should be kept in mind: While serial processing theories suggest that re-analyses of sentences or sentence parts are crucial for solving semantic

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[14] Ambiguity within a sentence occurs whenever such a linear sequence of sentence parts (e.g. single words) leads to different possible interpretations. For example, the sentence *"The police caught a criminal with a shotgun."* can be interpreted in two ways (The police used a shotgun to catch the criminal or the criminal was the one with the shotgun). Serial and parallel models of sentence processing differentially explain how it is possible for a recipient to infer meaning from consecutively incoming words and, thereby, how local syntactic ambiguities are processed.

ambiguities, parallel models give more weight to working memory functions and capacity. Thus, problems in correctly analysing and comprehending ambiguous expressions which may be apparent in people with schizophrenia (see section 2.1.3) can be assigned to different underlying mechanisms, with either re-analysis processes or working memory functions being impaired.

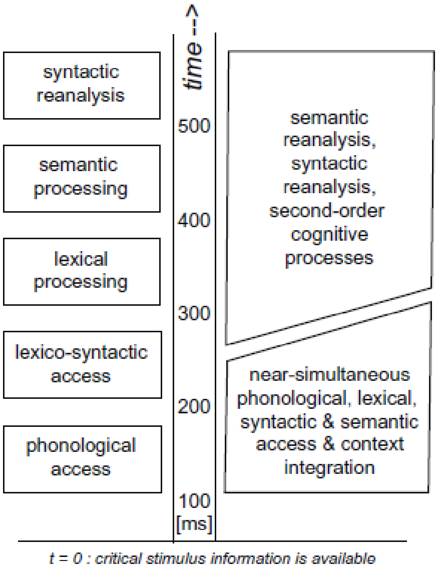

Figure 4. Modular seriality versus interactive parallelism of sentence processing. Adopted from Pulvermueller, Shtyrov and Hauk (2009).

2.1.1.2 *Psychological models of sentence processing*

During the last decades, an intensive and constructive exchange between linguistic and psychological perspectives has led to an establishment of a number of empirically verifiable models on language processing (Rickheit et al., 2003). While some of these models, a selection of which has been described above, focus on linguistic details of word and sentence processing, psychological language processing theories try to embed language processing into broader psychological functions, such as verbal memory, working memory, or other kinds of operations of the human cognitive system.

A comprehensive model of language perception on the basis of words has been introduced by Ellis and Young (1988). This framework accounts for the modularity of language processing, meaning that language can be perceived via different channels, i.e. in a spoken or written manner. On a pre-linguistic level, language cues are perceptually analysed, whereby – depending on the respective communication module – auditory or visual perceptual systems are engaged. Language stimuli perception is thereby based on the segmentation of sentences into words and syllables. This processing step is assumed to occur independently of the semantic lexicons, in which all known word forms are stored. These lexicons become involved during a next step, when the visually or auditory perceived language segments are transferred into mental representations (stage of "lexical access"). Hereby, four types of lexicons (two input and two output lexicons) have been proposed for each semantic processing route which surround the central semantic system. Therefore, the model assumes a separation between the lexical access for spoken and written language processing, but a single semantic system that is accessed from both modalities. Once the information arrives at the semantic system, which identifies the representation and meaning of a word (e.g. cat), modality independent lexical selection takes place, referring to the choice of a correct representation whenever more than one representation is activated (for example the English word "post" may acquire different meanings and would therefore initially activate different mental representations). Access to the semantic system simultaneously activates the phonological output lexicons (comprising information on speech output and graphemic output, respectively) in order to retrieve the word (together with the single letters and phonemes that word is composed of) from the respective representatives. Finally, the selected mental representation becomes integrated into a more global representation (i.e. a processed word meaning gets integrated in the meaning of an entire phrase). An inherent strength in this model is its applicability to analyse language deficits – both on the receptive and expressive side – in monolinguals (Ellis & Young, 1988). An extension of the original model has been proposed, for example, by Martin (2003) who added the processing of picture meanings for which he suggested analogous mechanisms to the processing of written and spoken words.

A central significance is assigned to the semantic system which represents, however, a rather unspecified construct. The semantic system, on which the mental lexicons draw on, can be regarded as mental storage in which information about semantics (i.e. word meanings), syntactics (i.e. how a certain words can be combined with others and imbedded in larger contexts, such as sentences), and word forms (how a word is spoken, written, and pronounced; Straube, Green & Kircher, 2008) are stored. Since a fundamental role in language perception is attributed to this mental storage, the semantic system has been repeatedly subjected to psycho-linguistic investigations, trying to determine its organisational structure and functional principle. There is a wide consensus that semantic systems are organised in terms of network structures. Such a network is thought to exist of associatively linked concepts representing semantic meanings. In other words, semantic networks are conceived as a representational format permitting the meanings of words to be stored, so that humanlike use of these meanings is possible (Quillian, 1968). Thus, deficits in language processing and comprehension, if not occurring on early perceptual processing stages, could be related to an impaired access to and/or retrieval from semantic networks or insufficient associations between network elements. The organisational structures of semantic networks, the temporal access to their elements and respective neurobiological substrates have been targeted in numerous neurolinguistic studies applying different neuroimaging techniques (EEG and fMRI). Based on these studies, different neurobiological models on language processing have been established which now provide frameworks for investigating functional impairments in language comprehension in both neurological and psychiatric patients.

2.1.1.3 Neurobiological models

According to the traditional view of language and the brain, instantiated in the Wernicke-Lichtheim-Geschwind (WLG) model (Geschwind, 1965; Lichtenheim, 1885; Wernicke, 1874), word representations are localised in a posterior section of the superior temporal cortex, known as Wernicke's area, and motor-word representations are localised in a frontal brain region, termed Broca's area after its explorer, the surgeon Paul Broca (Broca, 1861). Specifically, according to the model, Wernicke's area is involved in receptive language processing and is connected through the arcuate fasciculus to Broca's area, which is associated with expressive language processing. This view has largely been substantiated by observations from neurologically damaged patients: "Damage to the motor word representations in Broca's area would result in a disruption of language production with a sparing of comprehension. Damage to sensory word images in

Wernicke's area would impair comprehension but would not produce the mirror image syndrome to Broca's aphasia, as production would also be affected." (Martin, 2003, p. 56). Regarding the distinct processes observed to be impaired in Broca's and Wernicke's aphasia, the traditional view was that a syntactic deficit was underlying the former disorder, whereas the latter one was ascribed to impaired controlled lexical-semantic processes. Modern lesion analysis methods indicate that patients with Wernicke's aphasia may also show problems in comprehending syntactically complex sentences when their lesions extend to anterior parts of the STG (Dronkers, Wilkins, Van Valin Jr, Redfern & Jaeger, 2004). The authors of that work further suggest that the middle temporal gyrus may be most crucial for comprehension at the word level, while other regions, such as the superior temporal lobe, the STS, the angular gyrus, and the mid-frontal cortex may be more important at sentence level. While the descriptions offered by the WLG theory of the neurobiological basis of language have been judged to be oversimplified (Caplan, 2003; Weems & Reggia, 2006), the model is of great historical importance and it continues to exert substantial influence on most contemporary theories of language and its terminology is still in practical use.

The majority of present neurobiological models on language comprehension focus on auditory processing of spoken words and sentences and therefore involve temporal auditory brain regions as cortical starting point of language processing (Friederici, 2002; Friederici & Alter, 2004; Hickok & Poeppel, 2000, 2004, 2007). For example, the dual stream framework proposed by Hickok and Poeppel posits that early cortical speech perception bilaterally involves auditory fields in the superior temporal gyrus, whereby "the left and right hemispheres are differentially sensitive to aspects of speech signals" (Hickok & Poeppel, 2004, p. 81). Analogously to the cortical organisation of visual information (Milner & Goodale, 1995; Ungerleider & Mishkin, 1982) Hickok and Poeppel (2000; 2004) suggest dorsal–ventral partitioning within the auditory system. They assume that the dorsal stream, projecting to parietal (posterior end) and frontal (anterior end) cortices, is critical for auditory–motor integration, a process that would serve both linguistic and non-linguistic perception. In a more recent paper, Hickok and Poeppel suggested the dorsal stream to be strongly left-hemisphere dominant (Hickok & Poeppel, 2007). The ventral stream is proposed to include portions of the middle and inferior temporal gyri. This pathway is assumed to be involved in auditory "what processing", providing the interface of acoustic–phonetic with lexical representations (Hickok & Poeppel, 2004). Regarding language processing at the sentence level, the model ascribes a critical role to the anterior temporal cortex which is thought to be involved in grammatical representations.

Therefore, the framework may offer testable hypotheses for sentence processing, although it was originally formulated based on word processing studies.

A widely known theory, the dynamic dual pathway model introduced by Angela Friederici, proposes an integrative model on neural syntactic, semantic and prosodic processing. According to this model, "syntactic processes are supported by a left lateralised temporo-frontal network including the anterior portion of the superior temporal gyrus and the pars opercularis (Brodmann Areas [BAs] 44 and 46) in the IFG whereas semantic processes are subserved primarily by a left lateralised temporo-frontal network consisting of the posterior portion of the superior and middle temporal gyrus and BA 45/47 in the inferior frontal gyrus" (Friederici & Alter, 2004, p. 274, left column). Regarding prosodic processes at the level of sentences a stronger involvement of right hemispheric structures is suggested, whereby "the more linguistic the nature of either the stimulus or the task the larger the involvement of the left hemisphere" (Friederici & Alter, 2004, p. 274, left column). The interaction of both hemispheres, predominantly supported by the corpus callosum, ensures a dynamic interplay of lexico-semantic and prosodic information processing during language comprehension.

Another theory dedicated to left- and right-hemispheric distinctions in language processing is the fine-coarse semantic coding model (Beeman, 1998; Beeman, Friedman, Grafman, Perez, Diamond & Lindsay, 1994; Jung-Beeman, 2005). The central hypothesis of this framework is that during language comprehension the right hemisphere provides a rather inexact, or coarse, interpretation of linguistic material, whereas fine-semantic coding in order to quickly select a single relevant meaning is predominantly achieved within left-hemisphere regions. Thus, incoming words activate large semantic fields within the right hemisphere, potentially overlapping with semantic fields activated by other words with similar semantic features. Such an overlap has been proposed to be important for "noting distant semantic relations necessary to draw inferences, maintain coherence and integrate complex discourse" (Beeman, 1998, p. 256, last paragraph). A rapid selection and classification of linguistic input that is critical for further meaning processing (i.e. excluding alternative interpretations in order to select the correct meaning of a certain expression) would be instead performed by left-hemispheric activity. This idea of left-right hemispheric distinctions has been supported by neurological and neurophysiological studies. For example, right hemisphere lesions have been reported to produce more diffuse semantic deficits as well as more diffuse language-related ERPs (see Beeman, 1998).

The keen scientific interest in the neurobiology of language processing has recently been emphasised by a review of over one hundred fMRI studies published in 2009 (Price, 2010). According to this review, pre-lexical auditory language signals (and also pseudo-words) mainly recruit areas in the superior temporal gyrus, whereas semantic word processing involves more broadly distributed regions in inferior frontal, middle and inferior temporal as well as parietal cortex areas. At sentence level, the anterior-posterior line in the middle temporal gyrus, extending to the inferior parietal lobe, has been highlighted (see Figure 5). Interestingly, this pattern suggests a more focal system for the comprehension of sentences as compared to words. Binder, Desai, Graves and Conant (2009) added some other regions that they found to correlate with semantic processing, such as the ventral temporal cortex (mid-fusiform and parahippocampal gyrus), dorsomedial and ventromedial PFC and the posterior cingulate gyrus. Notably, the areas reviewed by Cathy Price have been linked to auditory speech comprehension and may thus not be as informative for visual sentence processing. Moreover, as the author herself has acknowledged, "it has not drawn any conclusions about how the different regions are functionally connected or how the systems vary across individuals" (Price, 2010, p. 84, left column).

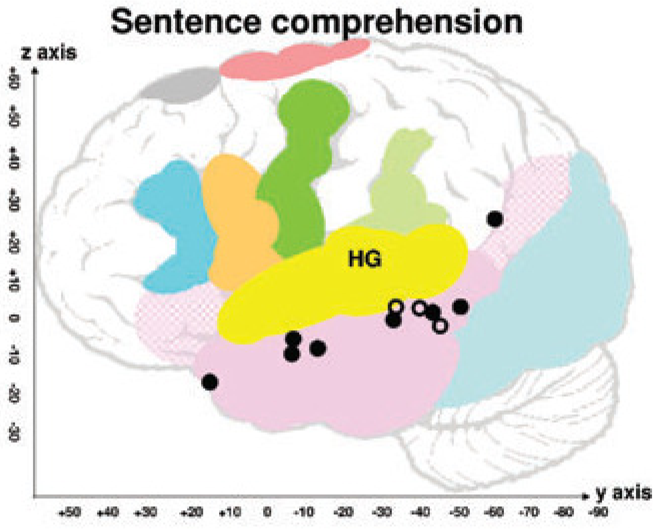

Figure 5. Overview over areas associated with auditory sentence processing. Black circles: comprehension versus incomprehensible sentences; open circles: sentences with versus without visual gestures. Modified from Price (2010).

Using dynamic causal modelling (DCM)[15], Makuuchi and Friederici (2013) addressed both issues. The results of their analyses indicated that sentence reading was associated with brain activation in core language processing regions including the posterior portion of the IFG (pars opercularis) and middle temporal gyrus, a visual word form area within the fusiform gyrus as well as regions related to working memory processes (inferior frontal sulcus and intraparietal sulcus). Moreover, the processing hierarchy seemed to proceed from the visual system over working memory systems to core language systems and an increase of connectivity between regions associated with working memory and lexical language processing was observed with increasing processing load for syntactically complex sentences. At a more fundamental level of visual sentence processing, many researchers have addressed the question on how linearly presented words (the way they appear during sentence reading) are combined in just the right way to correctly comprehend sentence meaning (see, for example, Devauchelle, Oppenheim, Rizzi, Dehaene & Pallier, 2008; Osterhout, Kim & Kuperberg, 2006). According to Osterhout and colleagues (2006) different sets of processes combine words syntactically and semantically, whereby the two neural processing streams involved are thought to operate in parallel most of the time. In simplified terms, these two streams can be separated into an anterior stream which processes syntactical sequence patterns that occur over time. The posterior stream, in contrast, is assumed to be crucial for combining words at a conceptual, and therefore semantic, stage. Electrophysiological evidence for distinguishable syntactic and semantic language processing at sentence level comes from ERP neurolinguistic studies: While morphosyntactic violations are well-known to elicit changes in two distinct ERPs, the early lateralised anterior negativity (ELAN) and the P600 potential, semantic violations have been linked to increases in the N400 component (reviewed in Kutas, Van Petten & Kluender, 2006; Schacht, Martín-Loeches, Casado, Abdel Rahman, Sel & Sommer, 2010). In more detail, ELAN effects have been suggested to reflect the rapid, reflexive syntactic processing that precedes semantic analysis reflected in the N400 potential. The P600 effect is thought to reflect a reanalysis of

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[15] DCM represents a generic approach for inferring hidden neuronal states from measured brain activity (Friston, Harrison & Penny, 2003; Stephan & Friston, 2010). Although DCM was originally introduced for fMR data, DCM techniques have been implied for a range of brain imaging methods, such as also EEG, or MEG. The causal aspect refers to the way in which DC models describe how dynamics in one neuronal population cause dynamics in another and how these interactions are modulated by experimental manipulations or endogenous brain activity (Stephan, Penny, Moran, den Ouden, Daunizeau & Friston, 2010).

syntax, which may become necessary for example when the comprehender is confronted with syntactic ambiguity. However, more recent studies have indicated that this simple correspondence is probably unsustainable (see Kuperberg, 2007). For example, the P600 has been more recently suggested to "reflect the activity of a combinatorial system that integrates both semantic and syntactic information" (Schacht et al., 2010, p. 2 e9742).

2.1.2 Pragmatic language comprehension in healthy subjects

The neurobiological indices of word and sentence processing introduced in the previous section have further been used – besides the establishment and testing of neurobiological models on sentence comprehension – to investigate neurobiological activity associated with pragmatic language functions. The term pragmatic refers to the appropriate use of language according to the respective communicative situations and contexts (Straube et al., 2008) and pragmatic language abilities are classified as higher-order linguistic functions. A traditional theory of pragmatic language comprehension has suggested two main processes: context and utterance analysis (Van Dijk, 1977). During utterance analysis the recipient analyses semantic, syntactic, phonological-prosodic, and paralinguistic (e.g., gesticulation, facial expressions) information to interpret the meaning of an utterance. Context analysis, on the other hand, is associated with analysing the meaning of an utterance based on the context in which it occurred, whereby the comprehender has to draw on background knowledge (e.g. on the speaker or the type of conversation going on), knowledge of social rules, and past experiences.

In the past years, neuroimaging studies have sought to elucidate the neural underpinnings of pragmatic language comprehension in healthy participants. This research revealed that during language comprehension our brain is able to integrate different sources of incoming information immediately and in parallel to interpret the ongoing sentence and discourse (Hagoort & van Berkum, 2007). The left IFG has been shown to play a key role in such integration processes (Ferstl, Neumann, Bogler & von Cramon, 2008; Hagoort, Hald, Bastiaansen & Petersson, 2004; Willems, Ozyurek & Hagoort, 2007). Despite the common agreement that the left hemisphere is dominant for language processing, different neuroimaging studies have reported on additional activation in right hemispheric brain regions during language comprehension, especially when task demands are increased and higher-level language processing is needed, for example in the comprehension of semantically ambiguous sentences or discourse (Lindell, 2006; Marini, Carlomagno, Caltagirone & Nocentini, 2005).

2.1.2.1 Metaphoric Language

The question of whether metaphors[16] are more difficult to understand than literal language reflects an enduring discussion in psycholinguistics. According to the standard pragmatic view, literal language processing is considered to occur automatically, whereas metaphoric language processing is presumably triggered by the failure of a literal interpretation to make sense (Glucksberg, 2003). On the other hand, it has been recognised early on that for some idiomatic expressions the metaphorical meanings are processed as quickly and as automatically as we apprehend literal meanings (e.g. Gibbs, 1989). Moreover, it has been shown that people are barely able to ignore metaphoric interpretations in stroop-like tasks (Glucksberg, 2003; Glucksberg, Gildea & Bookin, 1982; Wolff & Gentner, 2000).

Theories on metaphor comprehension can be divided in models advocating the supremacy of context effects and such emphasising the priority of lexical effects. While all of these accounts acknowledge the effects of context metaphor processing, they make different assumptions concerning context effect size or the time course of metaphoric meaning processing. The *standard pragmatic view* (Grice, 1975; Searle, 1979) postulates that at a first conceptual stage literal meanings of both words and sentences are accessed initially – regardless of contextual information –, while at a second stage, which applies only for metaphors, literal meanings of metaphors need to be suppressed. This particular assumption is incompatible with models favouring the direct access view which suggests

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[16] Different types of figurative expressions can be distinguished when looking at metaphors (for detailed descriptions, see Evans & Green, 2006). The majority of findings cited here have been based on resemblance metaphors, also called image metaphors, which are based on comparisons using imagery (e.g., "Achilles is a lion."). Another type are conceptual metaphors, the meaning of which is interpreted by a conventional association of different conceptual domains. These metaphors are often less stylised and overtly poetic and they are more frequently linked to ordinary ways of everyday talking (e.g. "Look how far we have come."). A typical feature of resemblance metaphors is their mostly nominal structur (An A is a B.), which facilitates the experimental controllability of linguistic material. This might account for the piled use of resemblance metaphors in studies on figurative language processing.

that "contextual information interacts with lexical processes very early on, and when context is sufficiently rich and supportive, it allows [metaphor] comprehension to proceed smoothly and seamlessly, selectively accessing appropriate meanings while blocking incompatible albeit salient ones" (Giora, 2008, p. 147).[17]

A large number of psycholinguistic experiments have shown that listeners and readers can often understand figurative meanings of metaphors, idioms, and proverbs without necessarily having to first analyse and reject their literal meanings, at least when provided in appropriate contexts (Gibbs, 2001). This kind of empirical evidence is not in accordance with the standard pragmatic view, wherefore in present psycholinguistic research the direct access frameworks are most frequently considered.

A model that intends to fill in the theoretical gap between the direct access and the modular (standard pragmatic) view which has received much attention in the psycholinguistic literature is termed the *graded salience hypothesis* (Giora, 1997; Giora & Fein, 1999). According to this account, highly salient meanings of phrases (or words) are automatically processed during the initial stages of figurative language comprehension. Hereby, two distinct mechanisms are proposed which are assumed to run in parallel: A bottom-up, stimulus driven process that is sensitive only to linguistic stimuli, and a top-down process, being predictive of and sensitive to both linguistic and extra-linguistic knowledge. The bottom-up mechanism is the one suggested to be sensitive to salience, i.e. the way in which meanings are coded in the mental lexicon due to conventionality, frequency, familiarity, or prototypically, etc. Thus, this model predicts processing costs for metaphoric as compared to literal expressions only in case of non-salient metaphors, while commonly known figurative expressions would be comprehended as fast as their literal counterparts. The graded salience approach may have great potential as a general framework, not only for metaphor but also for irony and other non-literal figures of language, as both reading-time and word-fragment completion studies have provided evidence for that model. However, the theory mainly accounts for the initial processing stage while the later stage of meaning integration is rather neglected.

Important assumptions on how metaphoric expressions are mentally processed are made by the *contemporary theory of metaphor* (Lakoff, 1993; Lakoff & Johnson, 1980a). In contrast to all other theories mentioned before, Lakoff claims that all our existence is

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[17] For recent specifications of the direct acces view, see, for example the *constraint-based satisfaction model* (Katz & Ferretti, 2001, 2003) or the *underspecification model* (Frisson & Pickering, 2001).

purely metaphorical and that we fill our language with metaphors without any purpose; therefore our conceptual semantic system is built up in a metaphorical way (i.e. in order to understand abstract meanings). According to his idea, metaphor comprehension results from a complicated processing path at the end of which mapping across conceptual domains takes place, whereby a source and a target domain are specified (as for the previous example: "Achilles [target] is a lion [source]."). The mapping account has been proven to be useful to interpret electrophysiological data in figurative language experiments (see below). The underlying mechanism for Lakoff's theory has been adopted by the *structure mapping theory* (SMT; Wolff & Gentner, 2011). Comprehending figurative comparisons (e.g. "Achilles is a lion.") entails structural alignment between the two representations, followed by the directional projection of inferences from the base (lion) to the target (Achilles). According to SMT, novel metaphors are understood as comparisons. As metaphors become more and more conventionalised, a processing shift from comparison to categorization takes place. Based on this model, novel metaphors should be more difficult to process than conventional metaphors as they require comparing concepts and generating mappings on-line.

Particularly within the past decade, great effort has been made to elucidate the neurophysiological substrates of metaphoric meaning processing. The most valuable findings supporting either of the above quoted models arise from electrophysiological studies that offer high resolution of temporal processes. One of the most established language-related ERP components is the N400, a negative wave appearing between 200 and 500 ms after a critical linguistic stimulus, such as a word pair or sentence ending. While the potential was first observed in semantically incongruent sentences (from hereon referred to as semantic violations), meanwhile it has been linked to any kind of semantic stimuli, including words, music, and pictures (Lai, Curran & Menn, 2009). The modulation/amplitude size of the N400 is thought to reflect the ease of mapping incoming word meanings onto semantic memory structure (see de Grauwe, Swain, Holcomb, Ditman & Kuperberg, 2010; Kutas & Federmeier, 2011). Based on this interpretation of the N400, the majority of ERP studies investigating metaphor processing at the sentence level indicate processing costs in terms of enhanced conceptual mapping efforts for metaphoric stimuli, especially if the expressions are unfamiliar (novel) and therefore non-salient (Arzouan, Goldstein & Faust, 2007; Coulson & Van Petten, 2002; de Grauwe et al., 2010; Lai et al., 2009; Pynte, Besson, Robichon & Poli, 1996; see Figure 6). N400 results for metaphoric meanings are therefore consistent with mapping theories of metaphor comprehension, such as the SMT. Moreover, some of these studies have provided results that are in favour of the graded salience hypothesis, with less salient metaphors eliciting higher N400 amplitudes (Arzouan et al., 2007; Pulvermueller et al., 2009; cf. Figure 6). Besides this ERP evidence, fMRI findings from studies comparing BOLD responses to salient versus nonsalient metaphors have also been consistent with Giora's graded salience hypothesis (i.e. higher Bold responses to novel versus salient metaphoric expressions; a review of these studies can be found in Faust, 2012b, p. 413).

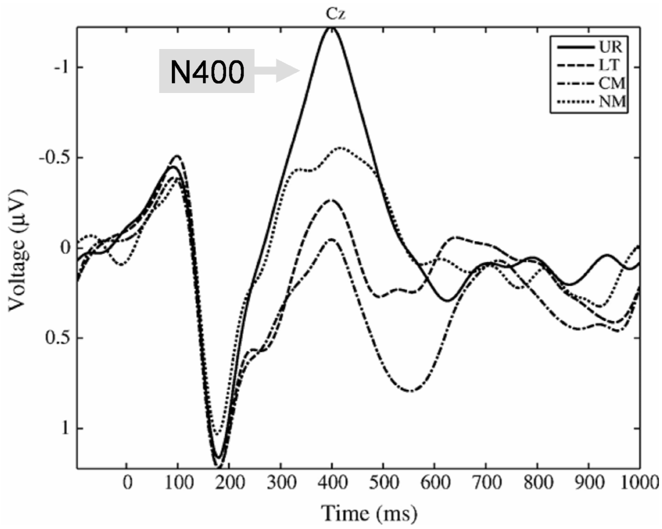

Figure 6. Typical Grand average ERP waveforms in response to semantically different target words of a lexical expression (here: word pairs; Figure modified from Arzouan et al, 2007). UR = unrelated word pairs; LT = literal word pairs; CM = conventional metaphors; NM = novel metaphors.

Psychophysiological investigation and functional imaging studies have further been implemented to assess the hemispheric lateralisation pattern underlying metaphor processing. According to the coarse semantic coding approach introduced in section 2.1.1.3, the ability to adequately interpret and comprehend metaphoric expressions heavily relies on the right brain hemisphere as the model assumes that the right hemisphere sustains multiple interpretations of ambiguous words (Beeman, 1998). A behavioural method for testing the roles of each hemisphere in semantic processing constitutes the split visual field (VF) paradigm. Thereby, priming words are presented centrally to both hemispheres for a very short time and a target stimulus is subsequently presented to either the left VF or the right VF, providing a relative advantage in processing the prime-target expression to the hemisphere opposite to the VF to which the target word was presented. Previous studies implementing linguistic split VF paradigms indicated a possible special role of the right hemisphere for metaphoric expressions, at least if these expressions were unfamiliar (Faust & Mashal, 2007). Combining split VF presentation of metaphoric sentences with ERP analyses (N400) Coulson and Van Petten (2007), however, found that both hemispheres are similarly sensitive to the processing difficulty engendered by metaphoric endings contrary to the predictions of the right hemisphere theory. As revealed by two recent meta-analyses, the majority of functional imaging studies also argue against a privileged role for the right hemisphere in metaphor comprehension (Bohrn, Altmann & Jacobs, 2012; Rapp, Mutschler & Erb, 2012). In fact, critical regions that have most strongly and most frequently been associated with metaphor processing comprise the IFG bilaterally; medial frontal areas, the left middle and superior temporal gyrus, parahippocampal, and inferior parietal regions (see Figure 7). However, recent studies have indicated a possibly special role of the right hemisphere for the integration of novel, complex, non-salient figurative meanings (Mashal, Faust, Hendler & Jung-Beeman, 2007; Pobric, Mashal, Faust & Lavidor, 2007).

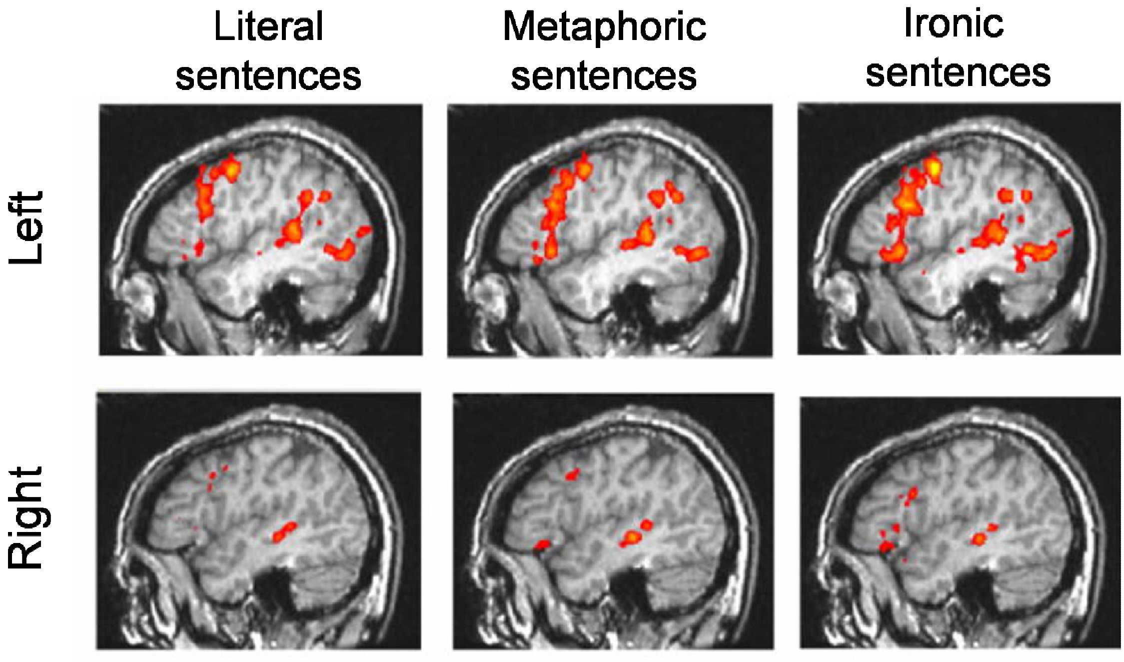

Figure 7. Cortical response patterns during the processing of literal and non-literal (metaphoric and ironic) sentences (figure modified from Eviatar & Just, 2006).

Only very few studies have so far directly compared brain activation patterns for metaphor comprehension as compared to other types of non-literal language in healthy volunteers. These studies suggest processing differences, for instance, between metaphor and irony (Eviatar & Just, 2006), and between metaphor and sarcasm (Uchiyama et al., 2012), indicating that different sub-processes of non-literal language processing could indeed be more relevant for certain types of figurative language (Bohrn et al., 2012).

2.1.3 Pragmatic language comprehension in patients with schizophrenia

Since pragmatic language comprehension is – among other aspects – also built upon the correct analysis of an utterance, including its semantic, syntactic, and phonological features, problems in processing these basic linguistic characteristics may be, at least in part, underlying pragmatic deficits in patients with schizophrenia. Therefore, it is reasonable to consider rather pure linguistic processing alterations in schizophrenia patients, such as syntax processing or semantic processing at word and sentence level, before viewing pragmatic language comprehension impairments as a whole.

The most prominent semantic processing anomaly at word level is increased semantic priming, also termed semantic hyperpriming, which has been found in patients with schizophrenia (Pomarol-Clotet, Oh, Laws & McKenna, 2008). The original idea hypothesising such anomalies goes back to Maher (1983). He suggested that the associative intrusions that are frequent characteristics of schizophrenic speech might be due to an overactive semantic priming effect. While a large number of priming experiments found evidence supporting such an overactive semantic priming mechanism in patients, findings conflicting with Maher’s original hypothesis also exist. Differences regarding the duration of illness, medication effects, methodological issues (especially the length of stimulus onset asynchrony [SOA] used in priming tasks), and differing levels of thought disorder have been suggested as possible explanations for contradictory results (Han & Wible, 2010; Pomarol-Clotet et al., 2008). A meta-analysis on a range of semantic priming studies in patients with schizophrenia found that increased priming has been only consistently reported in patients with thought disorder (Pomarol-Clotet et al., 2008). Moreover, the effect seems to be largest for short SOAs, indicating that the early, automatic spread of activation in semantic networks is altered in these patients. Although changes from hyperpriming to hypopriming with increasing duration of illness have been postulated in the past (Maher, Manschreck, Redmond & Beaudette, 1996), the meta-analysis could not find support for such a relationship.

Notably, although word-based investigations are useful to assess basal linguistic impairments underlying language perception deficits in schizophrenia, the stimuli used in such studies are typically more artificial and farther away from daily language demands, where we are usually confronted with whole sentences and discourse. Therefore, investigations on sentence or discourse processing may provide more valid results for an appraisal of the functionality of social communication in schizophrenia patients.

At sentence level, building up meaning from verbal information appears to be most problematic in schizophrenia. Although syntactical processing deficits have also been reported for schizophrenia patients, these impairments might be at least partly explained by cognitive sequence processing deficits that are not limited to linguistic stimuli and paradigms (Lelekov, Franck, Dominey & Georgieff, 2000). According to Kuperberg, semantic-syntactic integration – in terms of an imbalance between semantic memory-based and syntactically-driven combinatorial processing – is disrupted in schizophrenia (Kuperberg, 2007, 2008, 2010b). This idea is supported by studies showing lacking N400 modulations to semantically incongruent versus congruent sentence contexts in patients with schizophrenia (e.g. Adams et al., 1993; Sitnikova, Salisbury, Kuperberg & Holcomb, 2002). Regarding regional brain activation disturbances, a recently published meta-analysis by Rapp and Steinhäuser (2013) indicates functionally altered language pathways during sentence and text comprehension. Hereby, aberrant activity in fronto-temporal regions has been detected, corresponding to the structures that have been associated with pragmatic language comprehension in healthy subjects (see section 2.1.2.1). Notably, results on regional brain activation anomalies in schizophrenia patients should always be interpreted cautiously, considering generally decreased language lateralisation that has been consistently observed in schizophrenia (Sommer, Ramsey & Kahn, 2001; Spironelli, Angrilli & Stegagno, 2008; van Veelen, Vink, Ramsey, Sommer et al., 2011).

2.1.3.1 Metaphoric Language

Non-literal language comprehension is reported to be impaired in a wide range of developmental disorders, language-based learning disabilities, and patients following a traumatic brain injury (for an overview over studies, see Godbee & Porter, 2013). Among psychiatric illnesses, schizophrenia seems to be the disorder most strongly linked to respective impairments. To this end, comprehension of non-literal utterances in schizophrenia has recently been addressed in a series of studies.

The idea that patients with schizophrenia show impairments in metaphor and proverb comprehension[18] is not new (e.g. Bleuler, 1911; Chapman, 1960; Vigotsky & Kasanin, 1934). Some clinicians and scientists even asserted that impaired proverb understanding might be pathognomonic for schizophrenia (Gorham, 1956). However, after the use of proverbs as a diagnostic tool was criticised due to its poor reliability (particularly inter-rater reliability), this concept was widely abandoned later on (Andreasen, 1977). However, the cognitive deficit underlying an impaired ability to accurately interpret metaphoric meanings seen in schizophrenia patients is still of great interest in clinical and especially neuropsychological research.

Hereby, the main deficit consistently revealed by most studies marks a lacking ability to go beyond the literal meaning of a phrase – which would be necessary in order to retrieve the correct interpretation of a metaphor –, called schizophrenic concretism (de Bonis, Epelbaum, Deffez & Feline, 1997; Kuperberg, 2010a; Strobl & Resch, 1988). Besides the recognition and comprehension of proverbs and metaphors (Bruene & Bodenstein, 2005; de Bonis et al., 1997; Mashal, Vishne, Laor & Titone, 2013; Mo, Su, Chan & Liu, 2008), patients with schizophrenia or schizophrenia-spectrum disorders have been shown to have some problems with paraphrasing of conventional and generating novel metaphoric expressions (Mossaheb et al., 2014). However, in some studies respective deficits depended on psychopathology. For instance, studies using highly familiar language material failed to find comprehension impairments in schizophrenia patients (Elvevag, Helsen, De Hert, Sweers & Storms, 2011; Iakimova, Passerieux, Laurent & Hardy-Bayle, 2005; Titone, Holzman & Levy, 2002). Similar findings have been demonstrated for remitted schizophrenia patients (Herold, Tenvi, Lenard & Trixler, 2002). De Bonis and colleagues (1997) found that paranoid patients were not impaired in detecting metaphoric interpretations. Notably, task difficulty was kept relatively low in this study, possibly contributing to this finding. Nevertheless, the fact that not all schizophrenia patients show

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[18] Notably, metaphors and proverbs do not comprise equal concepts: Unlike metaphors, proverbs can be seen as fixed expressions that are non-creative and need to be learned as a whole. Although they can contain metaphoric meanings, this is not necessarily the case.

impaired metaphor comprehension has also been acknowledged by other researchers (Kuperberg, 2010a; Rapp, 2009).

Neurobiological substrates of metaphoric sentence processing in schizophrenia have been investigated in only a handful of studies. Using a behavioural split VF task, Zeev-Wolf, Goldstein, Levkovitz, and Faust (2014) found that schizophrenia patients display a reversed pattern of hemispheric lateralisation during novel metaphor processing. In an fMRI experiment conducted by Kircher and colleagues, participants read novel nominal metaphors as well as literal and meaningless sentences and judged them with respect to their meaningfulness. Compared to healthy participants, patients demonstrated decreased signal changes for novel metaphors in the right superior/middle temporal gyrus. Within the inferior frontal gyrus, a core region for processing non-literal meanings, different areas were activated between patients and controls. This result was ascribed to "altered lateral frontal lobe structure and function in schizophrenia" (Kircher, Leube, Erb, Grodd & Rapp, 2007, p. 287, left column). In a recent study, Mashal et al. (2013) reported on an overactivation of left brain areas in patients with schizophrenia during novel metaphor processing, including the left middle and inferior frontal gyrus and left precuneus. The hyperactive involvement of these regions was interpreted in terms of a compensatory recruitment.

To assess whether semantic-conceptual mapping deficits underlie the potential metaphor comprehension impairments in patients with schizophrenia, electrophysiological studies are necessary. However, so far only two studies have been published that distinctly addressing this issue. The earlier of these works assessed ERPs while healthy subjects and schizophrenia patients judged the meaningfulness of metaphoric, literal, and incongruous word pairs (Strandburg et al., 1997). In a more recent study, ERPs were measured while participants (again with and without schizophrenia) read common sentences that were, again, either literal, metaphoric, or meaningless (Iakimova et al., 2005). Hereby, Strandburg et al. demonstrated a lacking N400 difference (i.e. N400 effects) of meaningless versus literal or metaphoric versus literal meanings in schizophrenic patients, which was, in contrast, apparent in the healthy subjects group. In contrast, Iakimova and colleagues showed a preserved N400 effect for meaningless as compared to meaningful (both literal and metaphoric) sentence endings in schizophrenic patients, whereby N400 values were overall more negative in patients.[19] The methodological differences between these two studies have been discussed as explanations for the contradictory ERP results. Further research, however, could certainly support clarification.

2.1.3.2 Other types of non-literal language

Besides metaphoric speech, the use of ironic and sarcastic utterances is highly common in everyday social conversations. Irony represents a type of non-literal language whereby language is used in a way to express something different than – or even the opposite of – the literal meaning. The definition of sarcasm is highly similar, whereby sarcasm is further classified as "a form of verbal irony used in a hurtful or critical way" (McDonald & Pearce, 1996, p. 82). The ability to understand ironic expressions emerges at the age of about 7 or 8 years (Ackerman, 1981; Hancock, Dunham & Purdy, 2000), whereby some studies have pointed towards an earlier beginning (Rattray & Tolmie, 2008). Both irony and sarcasm comprehension involve rather complex mental representations, such as the ability to reflect on the speakers' evaluation about the attributed thought, adding to utterance intention. In other words, the listener needs to infer that the speaker does not mean a certain utterance literally and, moreover, that the speaker does not expect to be taken literally. Like metaphoric expressions, irony and sarcasm are used commonly and understood effortlessly in everyday conversations. Beyond a pure enrichment of everyday human conversations, irony and sarcasm serve distinct social functions. For example, it has been suggested that speakers choose irony over literal language "in order to be funny, to soften the edge of an insult, to show themselves to be in control of their emotions, and to avoid damaging their relationship with the addressee" (Dews, Kaplan & Winner, 1995, p. 347).

As for metaphors, two basic approaches that try to model the processing of ironic and sarcastic language can be distinguished: Serial access models, proposing a delayed processing of ironic/sarcastic meanings after an automatic access to literal meaning, and direct access models, which suggest that, if context supports an ironic interpretation of a

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[19] Generally enhanced N400 amplitudes have been repeadedly observed in schizophrenia patients using other language paradigms (Mohammad & DeLisi, 2013) and are generally seen as a result of lacking contextual priming.

statement, this interpretation can be directly accessed without the need to access the literal interpretation first. Linguistic studies have produced support for both accounts, partly depending on context predictiveness (Dews & Winner, 1999; Filik, Leuthold, Wallington & Page, 2014; Gibbs, 1986; Schwoebel, Dews, Winner & Srinivas, 2000; Spotorno, Koun, Prado, Van Der Henst & Noveck, 2012). At a neurobiological level, anterior rostral brain regions (ACC and medial frontal cortex), the right superior frontal gyrus, the right anterior STG, and the right precentral gyrus have been found to be involved in the processing of irony/sarcasm (Bohrn et al., 2012).

The most obvious behavioural measurements of potential irony processing deficits in schizophrenia patients have been obtained in studies where the interpretation of an ironic expression is explicitly enquired. Such studies have yielded mainly consistent results indicating decreased performances in schizophrenia patients when compared to healthy subjects (Kosmidis, Aretouli, Bozikas, Giannakou & Ioannidis, 2008; Langdon, Coltheart, Ward & Catts, 2002; Mo et al., 2008). Langdon and Coltheart (2004) further demonstrated that healthy adults with high-schizotypal personality traits had some difficulties to understand literally contradictory utterances as ironical, even though these subjects were better at recalling story details on a logical memories test. This finding might be revealing as schizotypal personality traits are thought to represent a risk factor for schizophrenia (e.g. Ettinger, Meyhoefer, Steffens, Wagner & Koutsouleris, 2014; Nelson, Seal, Pantelis & Phillips, 2013). Empirical data on the neurobiological background of these irony comprehension impairments is, however, remarkably scarce. In a recent study, schizotypal personality traits have been found to be correlated with activation related to irony processing in the middle temporal gyrus bilaterally (Rapp et al., 2010). Assessing schizophrenia patients, Rapp and colleagues found brain activation decreases for the contrast literal versus irony comprehension in the right middle temporal gyrus and the postcentral gyrus (Rapp, Langohr, Mutschler, Klingberg, Wild & Erb, 2013). In that same study the irony versus baseline contrast revealed enhanced blood oxygen level dependent (BOLD) responses in patients as compared to controls in different brain regions, including the left parahippocampal gyrus. It was concluded that left and right temporal parts of the frontotemporal language system may be crucial in the pathophysiology of difficulties experienced by patients with schizophrenia in interpreting ironic remarks. However, the authors did not observe performance differences regarding irony comprehension between the patient and the control group during their measurements.

One hypothesis on the basis of pragmatic deficits in schizophrenia suggests that impaired perception of prosody and vocal modulation, together with underlying deficits in associated brain regions such as the right superior temporal cortex, are critical for sarcasm and irony detection deficits in schizophrenia (Leitman et al., 2011; Leitman, Ziwich, Pasternak & Javitt, 2006). However, as prosody represents only one among a number of markers for ironic meanings (Attardo, Eisterhold & Poggi, 2003), this might only be a part of the picture. Other possibly contributing factors are discussed within the following section.

2.1.3.3 The role of semantic memory, mentalising abilities, and general cognitive decline

The question whether metaphor interpretation impairments in schizophrenia stand alone or depend on deficits in other cognitive functions remains the subject of an ongoing discussion. Several research groups have argued – and provided respective empirical evidence – that the comprehension of metaphoric language or figurative language in general, is linked with ToM abilities, cognitive and working memory capacities, and/or thought disorder in schizophrenia.

More precisely, at least three different approaches to explain language dysfunction in schizophrenia could be distinguished. The first ascribes language comprehension impairments to structure and function of semantic memory (Spitzer, 1993). According to the second, schizophrenic language dysfunction arises from degraded abilities to construct and maintain internal representations of context (Cohen, Barch, Carter & Servan-Schreiber, 1999; Cohen & Servan-Schreiber, 1992), whereby these abnormalities are usually attributed to poor working memory or general executive function deficits. Another perspective relates pragmatic language comprehension in particular with impaired abilities to mentalise the speaker's intentions (Bruene & Bodenstein, 2005; Langdon, Coltheart et al., 2002).

Using different experimental setups, empirical evidence has been found for each of these approaches. For instance, the semantic network account (approach 1) received support from priming studies which have reported that, under automatic conditions, direct and indirect priming are often increased in schizophrenia patients (see also section 2.1.3). However, semantic priming anomalies may be limited to patients who actually exhibit formal thought disorders (Kuperberg, 2010a) and therefore cannot be a universal explanation.

Many studies have further linked language processing impairments to deficits in working memory, as suggested by the context account (approach 2). For example, Bazin and colleagues (2000) found that patients failed to use priming context sentences in a task in which patients were asked to complete given incomplete sentences which contained an ambiguous word. In line with the assumption that such deficits in building up and using contexts are related to working memory, language comprehension and working memory task performance in schizophrenia patients were strongly correlated in different studies (Bagner, Melinder & Barch, 2003; Condray, Steinhauer, van Kammen & Kasparek, 1996). Regarding a possible link between language comprehension impairment and executive functions, research findings have been somewhat less clear. In Cohen et al. (1999), the degree of reduced context use during a lexical disambiguation task in schizophrenia patients was correlated with task performance in both a Stroop Test and a Continuous Performance Test. More convincing findings were provided by Champange-Lavau and Stip (2010), who found that deficient understanding of non-literal language in schizophrenia patients co-occurred with a lack of flexibility as an example of executive functions. Although Thoma et al. (2009) also claimed such a link, in their study proverb comprehension disabilities in schizophrenia patients were only significantly correlated with divided attention; however attention functions are usually not subordinated to executive cognitive functions (Karnath & Thier, 2006). In addition, it is doubted whether pragmatic language comprehension impairments can be explained by general deficits in working memory and/or executive functioning. Recent research was able to define distinct components of working memory (Barch & Smith, 2008) and executive function (Kerns, Nuechterlein, Braver & Barch, 2008) that may be spared or impaired in schizophrenia, including the ability to hold information online over time, to manipulate information online and perform a given task, to override a prepotent response, to select amongst competing alternatives, and to monitor one’s own responses (Kuperberg, 2010a).

Finally, the mentalising account (approach 3), has gained evidence from studies combining ToM tasks and pragmatic language paradigms in patients with schizophrenia. The results of this research consistently showed that patients’ ToM and semantic-pragmatic functions were both selectively impaired and also associated with each other in patients suffering from schizophrenia (Bruene & Bodenstein2005; Champagne-Lavau & Stip, 2010; Langdon, Coltheart et al., 2002; Langdon, Davies & Coltheart, 2002). Besides metaphor recognition, irony and sarcasm comprehension have been linked to ToM abilities

(Mo et al., 2008; Rattray & Tolmie, 2008; Sullivan, Winner & Hopfield, 1995). Based on that evidence, some researchers have argued that "any observed linguistic anomalies [in schizophrenia] must be located not in patients' *linguistic competence* but in their *communicative competence*" (Gavilan Ibanez & Garcia-Albea Ristol, 2013, p. 443, left coloumn).

To sum up, language processing and comprehension dysfunctions represent a critical feature of schizophrenia which may often be underrated because they appear more subtle as compared to, for example, the more remarkable positive symptoms. Nevertheless, the great impact of verbal communication disabilities on general social functioning underpins the importance of adequately investigating the nature, origin, and variability of respective impairments. Moreover, the way in which this deficit seems to be strongly intertwined with other cognitive functions, such as working memory, executive functions, and mentalising abilities has brought a new perspective to the study of the cognitive functioning in schizophrenia patients in general.

2.2 The neural perception and comprehension of nonverbal signals in schizophrenia

Anomalies in the detection, recognition, and response to nonverbal social signals in patients with schizophrenia have lengthily concerned clinical (neuro)-scientists. The by far largest majority of studies assessing social perception in schizophrenia have used neutral and emotional facial expressions, and a number of interpretations and new hypotheses have been developed based on these studies. Therefore, although in recent years other paradigms have also been implemented with increasing frequency – e.g. paradigms assessing the auditory/audiovisual perception of social stimuli or social perception from human bodies –, understanding the neurobiology of nonverbal language processing in schizophrenia requires a fundamental reflection of findings on neurophysiological face processing.

2.2.1 Processing facial expressions - from theoretical frameworks to empirical findings

2.2.1.1 Face and facial expression perception in healthy subjects

The first neurobiological model of face perception has been introduced by Haxby and colleagues (Haxby, Hoffman & Gobbini, 2000; Haxby, Hoffman & Gobbini, 2002). This model is based on a vast number of functional imaging investigations (e.g. Hoffman & Haxby, 2000; Kanwisher, McDermott & Chun, 1997; Sergent, Ohta & MacDonald, 1992), single cell recordings in humans (e.g. Allison, Puce, Spencer & McCarthy, 1999; McCarthy, Puce, Belger & Allison, 1999) and nonhuman primates (e.g. Hasselmo, Rolls & Baylis, 1989; Perrett, Hietanen, Oram, Benson & Rolls, 1992; Perrett et al., 1984) as well as lesion studies (Hecaen & Angelergues, 1962; McNeil & Warrington, 1993) Generally speaking, face perception requires the coordinated participation of multiple brain regions which can be broadly specified into "core" and "extended" systems (see Figure 8), two systems that are supposed to be hierarchically organised. Hereby, the core system is involved in the visual analysis of faces, bilaterally comprising the inferior occipital gyrus (IOG), the lateral fusiform gyrus (FFG), and the posterior superior temporal sulcus. The extended system processes the meaning of information obtained from these faces, including the intraparietal sulcus (IPS; responsive to shifts in eye gaze direction), the STG (activated during lip reading), anterior middle temporal gyrus (MTG; recognition of familiar faces and name retrieval) as well as areas associated with emotion perception such as the amygdala, the insula, and the orbitofrontal cortex. This model makes analogous postulations to the model proposed by Bruce and Young (1986), which also suggests a cognitive independence of the perception of variant and invariant facial features, but without explicitly formulating assumptions on underlying neural systems. After an initial perception of basic facial features within the IOG, facial identity processing is associated with activation increases in the lateral FFG while emotion processing is rather linked to activation increases within the STS. With respect to emotion recognition, Haxby and colleagues further noted that for different facial affects different parts of the extended system may be jointly activated with the STS. For example, disgusted face perception simultaneously evokes responses in the posterior STS and insula while fearful faces are most strongly linked with a combined activation of the posterior STS and the amygdala (Morris et al., 1996; Phillips et al., 1998; Phillips et al., 1997; Streit et al., 1999).

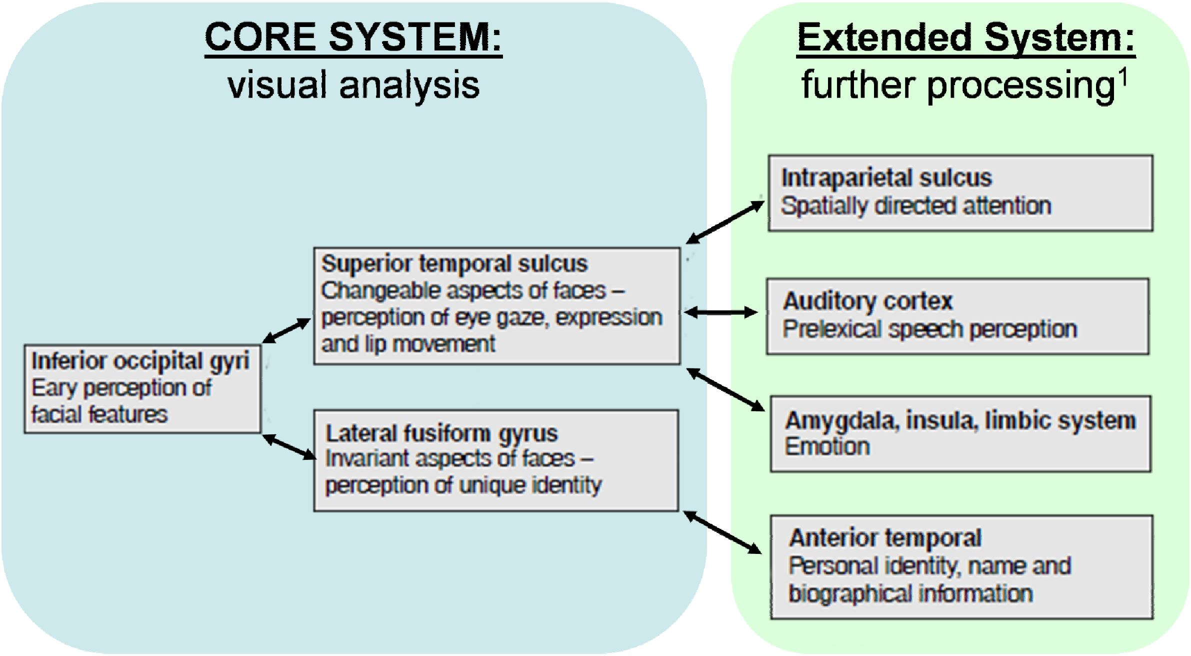

Figure 8. Graphical illustration of the neuronal model of face processing (modified from Haxby et al., 2000). [1] further processing within the extended system occurs in concert with other neural systems.

Against this background, the region around the posterior STS appears to be the probably most interesting cortical area for the processing of socially relevant stimuli (Lahnakoski et al., 2012). Besides the above described role of the STS in facial emotion perception, activity of this region has been further associated with still body pictures (Van den Stock et al., 2014) and biological movements, including movements of the mouth, eyes, complete face, the head or even the whole body (Bonda, Petrides, Ostry & Evans, 1996; Carlin, Rowe, Kriegeskorte, Thompson & Calder, 2012; Grosbras, Beaton & Eickhoff, 2012; Puce, Allison, Bentin, Gore & McCarthy, 1998). The special role of the STS and its interplay with other occipito-temporo-parietal structures during the perception of static and dynamic human bodies will be discussed in the following sections.

In recent years, the separation between identity and emotion decoding brain regions (lateral FFG versus STS) has been challenged by imaging studies showing that FFG activity may be modulated by emotional facial expressions (Engell & Haxby, 2007; Monroe et al., 2013; Trautmann-Lengsfeld, Domínguez-Borràs, Escera, Herrmann & Fehr, 2013; van de Riet, Grèzes & De Gelder, 2009), at least when attention is actually directed towards the emotion (Monroe et al., 2013). Moreover, Atkinson and Adolphs (2011) criticised the proposed strict hierarchical composition of the core systems with basal decoding of facial features in the IOG (often also termed occipital face area [OFA]) which subsequently forwards information to the lateral FFG and STS for decoding identity and expression (along with other variant features), respectively. Based on anatomical lesion studies (Rossion, 2008; Rossion, Caldara, Seghier, Schuller, Lazeyras & Mayer, 2003), the authors state that direct functional connections from other extrastriate areas can activate the fusiform area without ipsilateral OFA inputs. Furthermore, virtual lesion experiments using TMS in healthy participants revealed that the IOG is also involved in higher order face processing (e.g. Dzhelyova, Ellison & Atkinson, 2011; Kadosh, Walsh & Kadosh, 2011; Pitcher, Garrido, Walsh & Duchaine, 2008) that may take place at temporally later stages of face perception and may therefore not be limited to an initial low-level face categorization (e.g. discriminating faces from objects). However, some studies using EEG appear to be in line with the dual routes models for facial identity and emotion processing. For example, several studies have shown that the N170 component of the ERP, an early, negative-going potential strongly related to face-specific processes (cf. Figure 9), is not or only very slightly modulated by emotional significance in facial expressions (Eimer & Holmes, 2002, 2007; Stekelenburg & Gelder, 2004). Because the N170 is most likely generated at the conjunction of the posterior FFG and the lateral OFA (see Eimer, 2011; p. 332), these findings are in accordance with an emotion-independent face processing within these areas.[20]

In sum, recent research findings suggest that slight modifications of the present neurobiological model of facial (emotion) processing could be beneficial, for example considering possible expression-identity interactions or an integration of direct lateral FFG connections with extrastriate cortical areas other than the IOG. Nonetheless, Haxby's et al.'s neurobiological model provides a clear idea of the brain regions critically involved in the processing of human faces and facial emotions, the relevance of which is – up till now – undisputed.

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[20] On the other hand, some studies showing N170 modulations by emotional expressions also exist (Batty & Taylor, 2003; Hendriks, van Boxtel & Vingerhoets, 2007).

2.2.1.2 Face and facial expression perception in patients with schizophrenia

The basic recognition of faces or distinct facial features (other than emotional expression) in patients with schizophrenia has been investigated in numerous experimental studies using a wide range of facial stimuli and tasks. Previous findings indicate that patients with schizophrenia show a preserved ability to discriminate a person's sex from original as well as computationally morphed faces (Bediou et al., 2007; Bediou et al., 2005), while age classifications were impaired in some studies, especially when fine-tuned judgements rather than rough estimations (e.g. judging whether a presented face is younger or older than thirty) were demanded (Kohler, Bilker, Hagendoorn, Gur & Gur, 2000; Schneider, Gur, Gur & Shtasel, 1995). If the recognition of the entire facial identity instead of single facial features is regarded, there is a great heterogeneity across studies. While most studies that used the Benton Test of Facial Recognition (Benton, 1983) reported impaired identity recognition performances in schizophrenia patients (e.g. Addington & Addington, 1998; Kucharska-Pietura, David, Masiak & Phillips, 2005; Soria Bauser, Thoma, Aizenberg, Bruene, Juckel & Daum, 2012), some did not (Hall et al., 2004; Scholten, Aleman, Montagne & Kahn, 2005). Mixed results have also been provided by studies using serial matching-to-sample tasks in which two serially presented faces have to be judged as being identical or different, with several (e.g. Butler et al., 2008; Martin, Baudouin, Tiberghien & Franck, 2005) but not all studies (e.g. Edwards, Pattison, Jackson & Wales, 2001) pointing to respective impairments in patients. The most probable, yet little satisfying, explanations for these inconsistent findings comprise essential differences in (1) factors concerning study samples, such as patient's age, duration of illness, gender, or their comparability to control subjects, and (2) factors relating to the task or stimulus types chosen in these studies. An elaborate meta-analysis including all studies that have so far assessed facial identity recognition in schizophrenia patients could possibly help to disentangle how these factors potentially contribute to sometimes conflicting results. Moreover, studies investigating self- versus other-face recognition tasks may further contribute to the identity recognition debate in schizophrenia, whereby one such study found a specific self-face processing deficit in patients with schizophrenia that was related to symptom severity (Kircher, Seiferth, Plewnia, Baar & Schwabe, 2007). Importantly, facial identity recognition impairments become more obvious in studies using more complex task designs, e.g. tasks that involve memory for facial identities (Calkins, Gur, Ragland & Gur, 2005; Sachs, Steger-Wuchse, Kryspin-Exner, Gur & Katschnig, 2004).

However, in these studies facial recognition deficits and potential mnestic impairments are likely overlapping and cannot clearly be separated.

The origin of face recognition deficits outside the context of emotional processing in schizophrenia is still a matter of debate. A fundamental deficit in configural processing of facial stimuli has been proposed and partly shown, in terms of a reduced inversion effect for patients with schizophrenia (Kim et al., 2010; Shin, Kang, Choi, Kim & Kwon, 2008; Soria Bauser & Suchan, 2013). In line with these findings, schizophrenia patients have further been reported to show abnormal visual scanning of faces (Beedie, Benson & St. Clair, 2011; Loughland, Williams & Gordon, 2002; Obayashi, Matsushima, Ando, Ando & Kojima, 2003). In addition to possible configural face processing deficits, a generalised impairment of processing complex visual stimuli that is not restricted to faces (Butler et al., 2008), as well as global deficits in visuo-spatial attention (Baudouin, Martin, Tiberghien, Verlut & Franck, 2002) or in processing socially relevant stimuli (Kim et al., 2010) are discussed. Of course, these different approaches are not necessarily mutually exclusive. Difficulties in processing socially relevant targets, can therefore be superimposed on deficits concerning more basal bottom-up (perceptual) and top-down (e.g. attention-related) processes. On the neurobiological level, disease related impairments in face perception/recognition have been associated with N170 reductions (Ibánez et al., 2012) as well as bilateral grey matter reductions of the fusiform gyrus (Onitsuka et al., 2006) and reversed asymmetry of fusiform grey matter (McDonald et al., 2000), whereby electrophysiological and neuroanatomical anomalies were further found to be correlated (Onitsuka et al., 2006).

During the last decades, a wealth of research has tried to illuminate the different facets of facial emotion recognition in schizophrenia. Although the exact relationship to cognitive impairments, basal visual and general face perception deficits (see Darke, Peterman, Park, Sundram & Carter, 2013) is still under debate (cf. Kohler, Turner, Gur & Gur, 2004; Marwick & Hall, 2008), there is some evidence, driven by recent meta-analyses, that facial emotion recognition impairments in schizophrenia are severe (Chan, Li, Cheung & Gong, 2010; Kohler, Walker, Martin, Healey & Moberg, 2010), and may be more strongly pronounced compared to deficits in facial perception (e.g. as measured in age or gender discrimination tasks; see also below) per se (Chan et al., 2010). The fact that only astonishingly few studies failed to find facial emotion recognition deficits in schizophrenia and that large effect sizes have been ascertained for both facial affect labelling and discrimination tasks (Kohler et al., 2010), further supports the consensual view that affect perception from faces is seriously impaired in patients with schizophrenia. Contextual information may, under certain circumstances, enhance the ability of facial emotion processing in patients (Chung & Barch, 2011; Chung, Mathews & Barch, 2011). Hereby, studies using complex and/or interactional contexts rather suggested that also emotional context perception is deficient in schizophrenia (Baez et al., 2013; Green, Waldron, Simpson & Coltheart, 2008; Monkul, Green, Barrett, Robinson, Velligan & Glahn, 2007). Regarding the nature of abnormal facial emotion processing, some studies report on selective deficits for certain emotions or valences, respectively (Edwards et al., 2001; Hall et al., 2008; Kohler et al., 2003), whereas others indicate a rather broad impairment to recognise any kind of emotional faces (e.g. Kucharska-Pietura et al., 2005; Turetsky, Kohler, Indersmitten, Bhati, Charbonnier & Gur, 2007). Considering recent reviews and meta-analyses, one core deficit in emotional face processing in schizophrenia patients refers to an aberrant attribution of emotional meaning to neutral faces (Habel et al., 2010; Kohler et al., 2003; Kohler et al., 2004). Such negative attribution biases are thought to be critically involved in the development and stabilization of paranoia and delusions of reference (Habel et al., 2010; Kapur, 2003). Although antipsychotic medication may contribute to some aspects of impaired facial emotion recognition (Lawrence, Calder, McGowan & Grasby, 2002), the full range of deficits observed in schizophrenia patients cannot be explained by medication effects alone, as respective impairments have also been reported for cases of untreated first-episode schizophrenia (Addington, Saeedi & Addington, 2006; Edwards et al., 2001).

The investigation of the neurobiological background of facial emotion recognition impairments in schizophrenia patients has produced a variety of mixed results during the last decade. While structural abnormalities, pointing to volume reductions in (among other regions) the insula, basal ganglia, and the medial temporal lobe including amygdala and hippocampus (Glenthoj et al., 2007; Honea, Crow, Passingham & Mackay, 2005; Wright, Rabe-Hesketh, Woodruff, David, Murray & Bullmore, 2000) have been suggested to be linked to emotion processing deficits in patients (Marwick & Hall, 2008), functional imaging studies using tasks including facial emotion identification or discrimination can more directly assess the relationship of these brain regions with the observed behavioural deficits. Regarding medial temporal activity in particular, many different studies have reported reduced activation within the amygdala/parahippocampal region during the perception of affective versus neutral faces (see Delvecchio, Sugranyes & Frangou, 2013; Li et al., 2010). In recent years, these findings have been more or less mutually attributed to elevated responses of these cerebral structures to neutral faces in schizophrenia patients (Anticevic, Van Snellenberg, Cohen, Repovs, Dowd & Barch, 2012; Delvecchio et al., 2013; Hall et al., 2008; Holt et al., 2006; Surguladze et al., 2006), resulting in decreased activity when the contrast emotional – neutral is regarded. This view is in accordance with the reported tendency of schizophrenia patients to attribute negative valence to actually neutral faces. In line with these findings, Habel and colleagues (2010) reported elevated brain responses to neutral faces in a number of regions, such as the PFC, orbitofrontal cortex (OFC), subgenual ACC, putamen, and parietal cortex. On the behavioural level, patients were only impaired in rejecting non-target emotional faces, due to a tendency to assign negative emotions to neutral faces, while the detection of target faces was intact. During the processing of emotional facial expressions, attenuated activation has been observed within prefrontal areas (dorsal ACC, ventro-lateral and medial PFC), the thalamus, the hippocampus as well as temporal regions, crucially including the face-responsive area within the fusiform cortex. Hereby, the latter hypoactivation may also be, at least in part, associated with more general facial perception deficits in schizophrenia (see above). A general hyperactivation that has been observed across emotion categories in the inferior frontal cortex in patients was interpreted as compensatory processes induced to counterbalance deficient face and facial emotion processing (Habel et al., 2010).

There is no conclusive evidence whether facial emotion recognition deficits constitute a state (Pinkham, Penn, Perkins, Graham & Siegel, 2007) or trait (Bediou et al., 2007; Edwards et al., 2001; Kucharska-Pietura et al., 2005) marker of the disease (Marwick & Hall, 2008). The majority of studies point towards a trait-like deficit which, however, may vary across disease duration and symptom intensity (Gessler, Cutting, Frith & Weinman, 1989; Kucharska-Pietura et al., 2005) and may respond to certain kinds of treatment, whereby specific emotional remediation approaches have been shown to be efficient (Combs, Adams, Penn, Roberts, Tiegreen & Stem, 2007; Kurtz & Richardson, 2012). In one study, long-time CBT without emotion-specific intervention over a period of more than six months has induced clinical improvement, but was not associated with an enhancement of facial emotion recognition abilities (Kumari et al., 2011). However, this result could have been due to ceiling effects of performance. Interestingly, attenuation of cerebral responses to fearful and angry expressions in the IFG, anterior insula, putamen, thalamus, and visual cortical regions during facial emotion perception has been observed (Kumari et al., 2011) after CBT treatment. This finding is particularly interesting regarding the IFG responses, as the IFG has been shown to be hyperactive in schizophrenia as a potentially compensatory mechanism during the recognition of facial expressions (Habel et al., 2010; see above). Besides its relevance concerning therapeutic questions, facial emotion perception in particular may also be of diagnostic significance, as it seems to be more strongly impaired in schizophrenia than in other clinical groups, e.g. affective disorders (Addington & Addington, 1998; Feinberg, Rifkin, Schaffer & Walker, 1986; Gaebel & Woelwer, 1992).

2.2.2 The processing of static and dynamic human bodies and their expressions

> "We respond to gestures with an extreme alertness and,
> one might almost say, in accordance with an elaborate and secret code
> that is written nowhere, known by none, and understood by all"
>
> Edward Sapir.

2.2.2.1 Body posture perception in healthy subjects

Human faces and bodies, often (but not always) co-occurring in our daily life, share a number of features that uniquely distinguish them from other visual stimuli, such as objects. Both stimulus types consist of a defined set of parts (eyes, nose, mouth, etc., and torso, arms, legs, etc.), the spatial relationships of which are fairly fixed. Viewed from the front, both are symmetrical along the vertical axis and both faces and bodies saliently provide information about identity-related attributes (e.g. age, gender, attractiveness) and convey social information about others' emotions and intentions. Therefore, one may easily assume that faces and bodies are processed along a similar perceptual-cognitive route. However, some profound differences suggest that the processing pathway for human bodies may also be somewhat deviating from that for faces. More precisely, the perceptual informative content of faces suffers comparably little when a face is presented motionless, whereby a great deal of the information conveyed by bodies is present during dynamic movements. For example, inferring a person's emotional state or direction of attention is easiest when the body is in motion.

Unlike for faces and facial expression, no elaborate theoretical model on (at least static) human body perception and recognition has been composed so far. Therefore, our knowledge of how and where the brain processes visual representations of human bodies is mostly driven from functional neuroimaging studies. Electrophysiological studies revealed that, similar to faces, bodies provoke prolonged latencies of the N100 component, which is then peaking at around 170 ms post stimulus, pointing towards similar neural mechanisms during face and body perception. One study, however, suggested that this ERP might yet be distinguishable for faces and bodies, with a somewhat later peak (around 190 ms) when viewing bodies as well as a different surface topography and neural source (Thierry, Pegna, Dodds, Roberts, Basan & Downing, 2006). Analogously to facial stimuli, the N170 (or N190, respectively) is delayed and enhanced by image inversion (Minnebusch, Keune, Suchan & Daum, 2010; Minnebusch, Suchan & Daum, 2008; Soria Bauser & Suchan, 2013; Stekelenburg & Gelder, 2004; see Figure 9) and reduced by distortion (Gliga & Dehaene-Lambertz, 2005; Soria Bauser & Suchan, 2013). Hereby, the inversion effect for bodies has also been observed on the behavioural level (i.e. impaired recognition of inverted bodies; e.g. Minnebusch et al., 2008; 2010; Reed, Stone, Bozova & Tanaka, 2003) suggesting configural processing of human body images. Moreover, a study using an inattentional blindness paradigm could show that bodies, like faces, may be prioritised for attentional selection (Downing, Bray, Rogers & Childs, 2004).

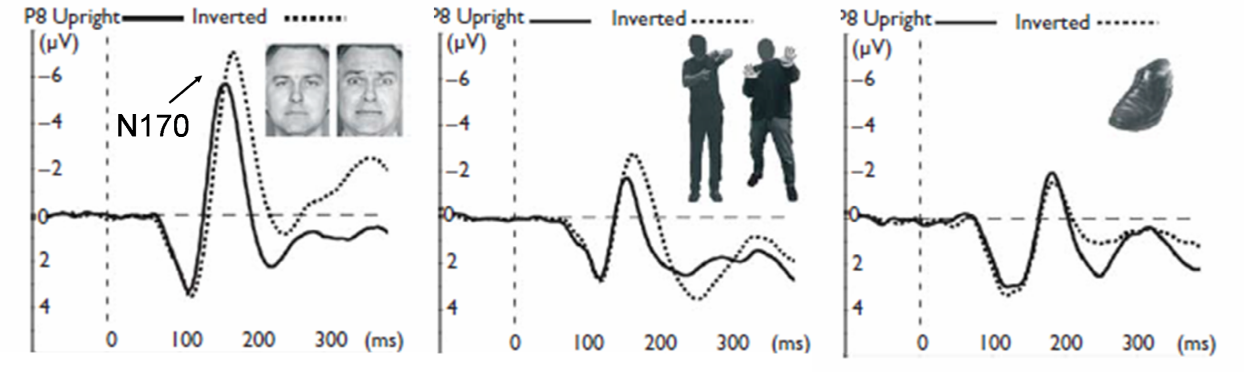

Figure 9. N170 amplitude effects of body inversion (middle panel), face inversion (left panel), and object inversion (right panel). Object inversion does not evoke N170 modulations (figure modified from Stekelenburg & Gelder, 2004).

Developmental studies investigating the perception of face and body pictures in young infants so far delivered mixed results and therefore cannot satisfyingly answer if human bodies and faces are processed equivalently or differently in the developing brain. Slaughter, Heron and Sim (2002) found that infants of 12 months of age preferably looked at intact versus scrambled facial stimuli, whereas no such attentional preference was observed when intact versus scrambled bodies were presented. In contrast, Gliga & Dehaene-Lambertz reported on similar N100 amplitudes for static faces and bodies (intact versus distorted) in three months old babies, indicating a sensitivity to configuration, in both faces and bodies, in these very young infants (Gliga & Dehaene-Lambertz, 2005).

Despite the similarities between face and body perception revealed by electrophysiological findings, fMRI studies provide rather clear evidence of apparently body-selective brain regions in the human brain. The first region that has been reported to show selective activity for body images has been found in the lateral occipitotemporal cortex (at the junction between occipital cortex and middle and/or inferior temporal gyrus), adjacent to the OFA but not overlapping with it (Berlucchi & Aglioti, 2010; Peelen & Downing, 2005b). Some studies report a partial overlap of body-selective voxels with the dorsally located human motion-selective area (hMT; van de Riet, 2009; but see Downing, Jiang, Shuman & Kanwisher, 2001). This region has been named extra-striate body area (EBA; Downing et al., 2001) and it responds distinctly to images of human body parts or entire bodies, even if these are displayed in a "non-biological" fashion (e.g. as stick figures, line drawings or silhouettes), suggesting that it codes a rather abstract representation of specific visual body features (see Berlucchi & Aglioti, 2010; Peelen & Downing, 2007, for an overview). Evidence from fMRI investigations (reviewed, for example, in Peelen & Downing, 2007), intracranial recordings (Pourtois, Peelen, Spinelli, Seeck & Vuilleumier, 2007), and virtual lesion studies using TMS (Pitcher, Charles, Devlin, Walsh & Duchaine, 2009; Urgesi, Berlucchi & Aglioti, 2004; Urgesi, Candidi, Ionta & Aglioti, 2007) emphasise that the EBA responds selectively to bodies and body parts as contrasted not only to objects but also to human faces and animal bodies, whereby animal bodies (especially mammals) evoke higher EBA activation than objects (Downing, Chan, Peelen, Dodds & Kanwisher, 2006). Beyond the perception of other person's bodies or body parts, the EBA (among other regions especially located in the parietal and frontal cortices) seems to be further associated with a mental representation of our own body, also known as "body schema" (Astafiev, Stanley, Shulman & Corbetta, 2004; Peelen & Downing, 2005a). Therefore, the EBA may be crucial in bridging perceptual self-other distinctions.

A second region associated with higher BOLD responses to human bodies versus both faces and objects was found in the fusiform cortex, therefore labelled fusiform body area (FBA; Peelen & Downing, 2005b). While some fMRI studies in humans have indicated that this particular region may overlap with the previously described fusiform face area (see Schwarzlose, Baker & Kanwisher, 2005), high resolution fMRI studies and recent applications of multivariate analysis strategies for fMRI data (so-called Multi-Voxel Pattern Analyses [MVPA; Norman et al., 2006]) rather suggest dense clusters of neurons that respond selectively to faces *or* bodies (Peelen, Wiggett & Downing, 2006; Schwarzlose et al., 2005). Such a double dissociation pattern is further supported by evidence from single cell recordings in monkeys (Desimone, Albright, Gross & Bruce, 1984; Kiani, Esteky, Mirpour & Tanaka, 2007).

Similar to the proposed division of the face recognition network into regions associated with invariant (identity) and variant features (see section 2.2.1.1), there recently have been attempts to assign the EBA and FBA, respectively, to such differential contributions. For example, Taylor and Wiggett and Downing (2007) found that the EBA but not the FBA was selective for even small body parts (e.g. fingers or hands), whereas the FBA showed by far the highest activation after whole bodies have been presented. The authors concluded that the EBA may decode human bodies at the level of parts, while the FBA is rather involved in configural body processing which is also the basis for the recognition of invariant aspects such as identity. Hodzic, Kaas, Muckli, Stirn and Singer (2009) further showed that EBA activity was related to body detection but did not differ when familiar versus unknown versus own body images were presented, while, in contrast, this was true for the FBA, indicating its involvement in body recognition. However, empirical evidence is currently too sparse to allow for conclusive interpretations.

In recent years, emotional modulation of body-selective brain activity has been reported for both areas, the EBA and the FBA (see de Gelder, Van den Stock, Meeren, Sinke, Kret & Tamietto, 2010, for a detailled overview). Interestingly, in several studies, emotion triggered activation increases in body-selective cortical areas were not only accompanied by but also correlated with congruent amygdala activation (Hadjikhani & de Gelder, 2003; Peelen, Atkinson, Andersson & Vuilleumier, 2007). This same relationship has been previously reported for viewing facial expressions (Rotshtein, Malach, Hadar, Graif & Hendler, 2001) and is interpreted in terms of a feed forward relationship with the amygdala being a possible source of the activity modulation within extrastriate body-selective cortical areas. Studies on patients with destruction of the primary visual cortex indeed point towards direct connections between subcortical limbic structures (e.g. the amygdala) and the EBA (Van den Stock et al., 2014). Notably, when reviewing literature on body-based emotion perception within the EBA and the FBA, evidence for activation increases within the EBA is most convincing when dynamic bodies (i.e. emotional body movements) are presented, whereas most studies using static body pictures consistently report increased FBA responses (Berlucchi & Aglioti, 2010; de Gelder et al., 2010). In fact, evidence for elevated EBA responses to static emotional body cues is often lacking (Lamm & Decety, 2008; van de Riet et al., 2009). Figure 10 provides an overview over brain regions that have most strongly been linked to the processing of emotional body movements.

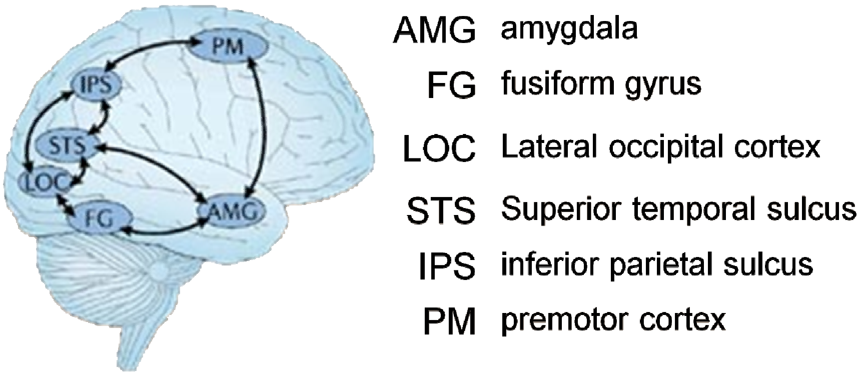

Figure 10. Schematic illustration of (sub)cortical areas associated with the visoumotor processing of emotional body language (modified from de Gelder, 2006).

Taken together, findings from behavioural, developmental, and electrophysiological studies clearly demonstrated that – like faces – human bodies constitute a special visual category that is processed along distinct perceptual routes. These neural pathways, however, seem to be distinguishable from those for facial stimuli. Emotional body expressions as conveyers of social information trigger activation increases in the Amygdala and the cortical core units for body perception, the FBA and, at least when dynamic body movements are viewed, the EBA. The emotional modulation of these body-selective cortical areas is thought to increase speed and accuracy of the detection and recognition of emotionally salient – and therefore socially relevant –body actions.

2.2.2.2 Body movement perception in healthy subjects

The detection and perception of social communication signals is inextricably linked with the visual recognition of biological motion which describes the "visual perception of a biological entity engaged in a recognizable activity" (Pelphrey & Morris, 2006). In fact, the term biological motion encompasses dynamic sequences of facial expressions, gestures, locomotion, and motor actions of body parts or whole bodies, and is therefore not restricted to body movements. However, as noted in the beginning of section 2.2.2.1, a critical feature of human *body* appearances is their intense relationship with motion. Therefore, dynamic movements of body cues shall be focused here.

The first and still one of the most elegant methodological approaches to investigate the perception and recognition of biological kinematics is the use of animated point-light displays (PL displays or PLDs), firstly introduced by Johansson (1973). Such animations can convey simple to complex human actions by means of markers (dots) that are positioned on the joints and head of the human body (see Figure 11A). They constitute the most frequently used class of stimuli in biological motion research, because the information transferred by PLDs is almost entirely limited to the biological motion they consist of (see also below). For these special visual stimuli, it has been shown early on that observers are able to – though not perfectly – recognise a PL walker's identity, sex, or the type of activity the PLD is executing, such as dancing or walking (see Giese & Poggio, 2003). Even more interestingly, these animations, while carrying a minimum of visual cues, further reveal socially relevant information about the walker, such as emotional state, sexual orientation, social dominance, or vulnerability to attacks. For animated PLDs, the perception of biological motion is remarkably robust even under highly ambiguous or impoverished conditions, i.e. when the dots are blurred or embedded in an arrangement of dynamic noise (i.e. randomly placed) dots (Ahlström, Blake & Ahlström, 1997; Ikeda, Blake & Watanabe, 2005), as illustrated in Figure 11C. Like for faces and static body images, an inversion effect has been reported for PLDs, indicating that human movements are also processed configurally (Pavlova & Sokolov, 2000; Sumi, 1984). However, the inversion effect for biological motion stimuli may also be explained differently: Because inverted displays of human movements on hands (which, perceptually, more or less corresponds to an upright-moving individual) impairs movement recognition (Shipley, 2003), the orientation of gravity rather than form seems to be crucial for recognition of human motion.

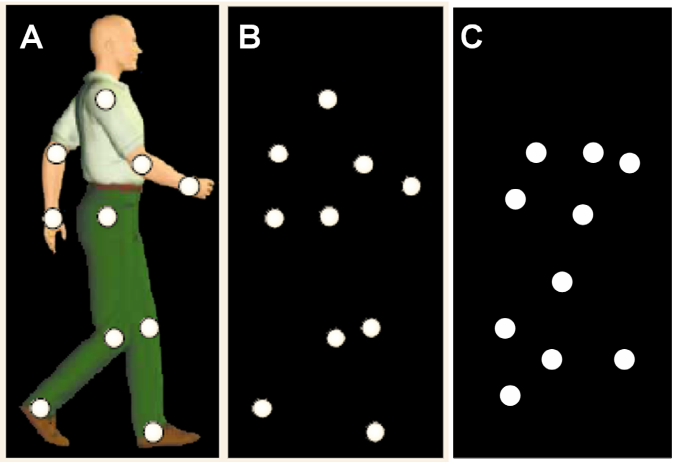

Figure 11. Creation and final physiognomy of point-light displays depicting a human walk. A. Light bulbs are attached to the actor's joints and he is video taped while walking. B. The final PLD videos only show the moving light dots against black background. C. Example for PLD noise (the same number of light dots as in B gets randomly placed). Figure modified from Giese and Poggio (2003).

Developmental studies provide evidence that the ability to perceive human motion evolves very early in life. Infants as young as 4-6 months of age prefer to look at intact as compared to scrambled PLDs whereby this looking preference is restricted to upright presentations (Bertenthal, Proffitt & Kramer, 1987; Fox & McDaniel, 1982). Electrophysiological findings confirmed this pattern for eight-months-old babies (Hirai & Hiraki, 2005; Reid, Hoehl & Striano, 2006). While more recent work indicated that even 2-day-old newborns prefer biological motion over control PLDs (Bardi, Regolin & Simion, 2010; Simion, Regolin & Bulf, 2008), children may not yet be completely adult-like in their sensitivity to human motion at this young age (Pinto, 2006). Pavlova et al. (2001) suggested that 5-year-olds already exhibit the level of adult recognition performance. The here-mentioned findings, however, may be limited to the perception of human body *motion,* as developmental studies using *static* body images so far had shown less consistent results: While Slaughter and Heron (2004) reported that infants do not discriminate scrambled from intact human body pictures before the age of 15-18 months, an electrophysiological study revealed distinct ERPs to intact versus distorted static body images in infants of just three months of age. Although certainly of interest, unfortunately nothing is known about the developmental course of emotion recognition abilities from human movements because thus far, no studies have investigated at what age individuals begin to selectively process emotional versus neutral biological motion.

Notably, single static frames of the dots shown in a PLD only resemble a meaningless arrangement of dots while the aforementioned recognitions can only be performed when PLDs are shown in rapid succession (Johansson, 1973), suggesting that the appearance of biological motion is crucial for detecting (social) features from PLDs (which is not imperative for full light body displays; see section 2.2.2.1). Conversely, there is also evidence that the perception of body forms contributes significantly to the perception of human motion (Beintema & Lappe, 2002; Hiris et al., 2005; Wittinghofer et al., 2012), especially the fact that even a single image of a body in action (e.g. a photograph of a soccer player kicking the ball) can reveal information about the suggested motion (also referred to as "implied motion"; Kourtzi & Kanwisher, 2000). To account for both findings and integrate them into a common psychophysical framework, Giese and Poggio (2003) developed a quantitative model on biological motion processing which is based on a rich body of psychophysical, neurophysiological and functional imaging studies and tested by means of computer simulations. The model generally proposes the existence of two processing streams working in parallel, one analysing the body form and the other analysing optic flow information (i.e. the movement itself). These two theoretical streams are thought to be analogous to the dorsal (optic flow) and ventral (body form) perceptual pathways, respectively, and they both comprise hierarchically organised feature detecting neurons (extracting either form or optic flow features), with increasing complexity along the hierarchy (Giese & Poggio, 2003). As a central assumption of the model, motion patterns are encoded as a) snapshots of body shapes by neurons in the form pathway and b) sequences of optic flow patterns by neurons belonging to the motion stream. In short, this computational model suggests that biological motion is perceived and recognised as a result of form and movement (optic flow) decoding along the ventral and dorsal pathways. However, the model (as the authors themselves acknowledge) cannot explain how the information from the two pathways is combined, nor can it clarify how top-down processes, such as attention, may influence the recognition process. In a recent review, Thompson and Parasuraman (2012) have emphasised the role that attention may play for biological motion processing depending on task type and the dynamic stimuli used.

In accordance with the model proposed by Giese and Poggio, a number of fMRI studies in humans (including both healthy and neurological patients) have shown that the posterior STS, which represents some point of convergence between the dorsal and ventral visual streams (Blake & Shiffrar, 2007; Felleman & Van Essen, 1991), is most exclusively activated when dynamic PLDs are presented (see Blake & Shiffrar, 2007 for an excellent overview; Bonda et al., 1996; Grossman et al., 2000; Grossman & Blake, 2002; Saygin, 2007), with some evidence suggesting a bias towards the right hemisphere (Grossman et al., 2000; Pelphrey, Mitchell, McKeown, Goldstein, Allison & McCarthy, 2003; Peuskens, Vanrie, Verfaillie & Orban, 2005). Earlier single-cell recordings from the macaque brain are highly consistent with these results (Perrett et al., 1985). Studies using dynamic stick figures or full-light displays (FLDs) of moving bodies could further demonstrate that the pSTS is also robustly activated by human motions other than PLD sequences(Grèzes, Pichon & de Gelder, 2007; Pelphrey et al., 2003; Pichon, De Gelder & Grèzes, 2008). Beyond the posterior STS, the roles of general motion processing areas have also been discussed to be involved in biological movement perception, such as the kinetic occipital region (KOR) and the hMT (e.g. Peuskens et al., 2005; Vaina et al., 2001). However, Grossman, Battelli and Pascual-Leone (2005) showed that TMS over the STS but not over the hMT affected biological motion perception from PLDs.

In line with Giese's and Poggio's idea of the ventral pathway analysing body form contributions to biological movements, Downing and Peelen (2011) argued that the majority of empirical evidence indicates that neurons in the EBA and FBA encode fine details of the shape and posture of the bodies appearing in the visual scene. Accordingly, an elegant recent fMRI study using MVPA and TMS approaches confirmed dissociable functions of the EBA and the pSTS, with the EBA decoding invariant information about the body form of an acting human and the pSTS carrying kinematical information about that moving body (Vangeneugden, Peelen, Tadin & Battelli, 2014). Pointing to body form preferences of the FBA, Beauchamp, Lee, Haxby and Martin (2003) found that ventral temporal cortex activation was stronger for full-light body displays than for PLDs. After the model established by Giese and Poggio, so-called template-matching models have been introduced that are, generally speaking, based on similar assumptions but with a stronger emphasis on the contributions of global body forms to biological motion perception (Lange & Lappe, 2006; Lee & Wong, 2004) therefore giving more weight to neural activity related to form perception from biological motion in the EBA and FBA.

Additional areas that have shown activations during biological motion processing are located within the premotor (Grèzes et al., 2007) and parietal cortex. Both regions comprise putative mirror neurons (Rizzolatti & Craighero, 2004; Rizzolatti, Fogassi & Gallese, 2001), a class of cells responding when a certain motor activity is executed and, importantly, when one observes this same activity being executed by another individual. Against this background, various neuropsychological studies have underpinned that the visual perception of motor behaviour is influenced by motor learning. For example, subjects can improve their visual recognition performance for novel and rather unusual actions when they were trained to execute these actions themselves (Casile & Giese, 2006). In another study, a person born without hands that had never perceived phantom sensations showed impairments in recognising upper limb movements compared to normally limbed-observers (Funk, Shiffrar & Brugger, 2005).

The theoretical models and empirical findings discussed so far do not provide implications for neural processes underlying the recognition of *emotional* biological motion. Indeed, several studies using both, PLDs and full-light body movements have addressed this special kind of human motion perception. In one of the earliest studies addressing this question, Pollick, Paterson, Bruderlin and Sanford (2001) showed that observers can readily detect affect from PLDs of simple arm movements (here: door knocking). Presenting whole body PLDs and FLDs, Atkinson, Dittrich, Gemmel and Young (2004) further demonstrated subjects' ability to identify emotions from biological motion, whereby movement exaggeration facilitated affect recognition for all emotions except sadness. This ability has been subsequently reported for very basal human movements (gait; Chouchourelou, Matsuka & Harber, 2006) and more complex social scenes depicted by dancing (Dittrich, Troscianko, Lea & Morgan, 1996) or two interacting PLDs (Clarke, Bradshaw, Field, Hampson & Rose, 2005). Notably, the ability to recognise emotion from biological movement is disrupted when the stimulus is inverted (Dittrich et al., 1996). Heberlein, Adolphs, Tranel and Damasio (2004) used dynamic point-light stimuli that were based on walking actors expressing four different emotions (happiness, anger, fear, and sadness) to determine cortical regions that are involved in emotion recognition in healthy subjects and patients with brain damage. Their findings suggest a crucial role of the right parietal cortex in emotion recognition from point-light walkers. Using similar stimulus material, Atkinson et al. (2007) reported a case in which a patient showed normal emotion discrimination during the spot-light walkers' paradigm despite complete bilateral amygdala lesion. In contrast, the patient was heavily impaired in recognising emotions from facial expressions, indicating that cortical structures may be crucially involved in emotion perception from point-light walkers. Such areas have been later identified as comprising the EBA and right FBA (Atkinson, Vuong & Smithson, 2012; Kret, Pichon, Grèzes & de Gelder, 2011; Sinke, Sorger, Goebel & De Gelder, 2010). Emotional modulations caused by affective biological motion stimuli have been also reported for subcortical structures such as the amygdala and hypothalamus (Grèzes et al., 2007; Sinke et al., 2010), the STS region (Atkinson et al., 2012; Grèzes & Decety, 2001; Sinke et al., 2010; van de Riet et al., 2009), the temporo-parietal junction (TPJ; Kret et al., 2011; Sinke et al., 2010) as well as motor areas (Grèzes & Decety, 2001; Grèzes et al., 2007; Sinke et al., 2010). In most of these studies, not only point-light animations but also full-light body movements and even videos depicting interactive scenes (Sinke et al., 2010) have been used, pointing to the recruitment of an increasing number of brain regions when more natural/realistic stimuli showing human movements are used.

2.2.2.3 The perception and recognition of (emotional) body postures and movements in patients with schizophrenia

Only very recently, the processing of (emotional) body cues has been started to be investigated among clinical samples, i.e. people suffering from psychological or psychiatric illness (Peterman, Christensen, Giese & Park, 2014; Van den Stock, de Jong, Hodiamont & de Gelder, 2011) and there is a dearth of functional imaging studies addressing respective neurobiological substrates.

In section 2.2.1.2, it has been noted that patients with schizophrenia show a reduced inversion effect (i.e. prolonged reaction times for inverted versus upright stimuli) for faces. Soria Bauser and colleagues (2012) replicated the same finding for static body images, suggesting that configural processing deficits reported for schizophrenia are not restricted to facial stimuli. In an ERP study, the same research group found a diminished emotional modulation of two event-related potentials, namely the P100 and the N170: While healthy participants showed enhanced amplitudes for changes in emotional valence (compared to same emotions) in a serial sample-matching task, in which emotion (same versus different) and identity (same versus different) judgements were demanded for two subsequently presented body images, this pattern was not found in patients with schizophrenia. Although these results point towards aberrant processing of changing body stimulus conditions, they do not provide clear evidence for deficient processing of emotional as compared to neutral body cues, as such comparisons were not regarded in this study.

Targeting sensitivity to contextual social cues rather than emotional body perception itself, Monkul et al. (2007) investigated the impact of contextual information on the perception of emotional intensity in scenes depicting human bodies (including faces). They found that intensity judgements of schizophrenic patients were less influenced by social context information than in healthy controls. In Bigelow et al. (2006) healthy subjects and patients with schizophrenia performed an emotion labelling task using dynamic PLDs (adopted from Heberlein et al., 2004) together with other tasks in which still body postures depicting emotional versus neutral content were presented. While task performance decreases observed in the schizophrenia sample scarcely failed to reach statistical significance for the point-light movies task, task performance deficits in patients were found when the emotional content of still body postures had to be judged. However, valence or emotion specificity of these deficits have not been analysed in this work. Couture et al. (2010) used the same point-light displays test among other tasks testing social-cognitive skills in persons with schizophrenia and autism. Both patient groups performed more poorly in the point-light emotion recognition test than control subjects, independent of emotional valence. The first fMRI study using PLDs in a sample of healthy subjects and participants with schizophrenia was provided by Kim, Park and Blake (2011). The authors presented dynamically moving PLDs consisting of 12 light dots that were engaged in different activities (e.g. stairway walking or climbing) that were masked by a field of randomly moving noise dots. Schizophrenia patients were not only impaired in the detection and discrimination of biological motion, the fMRI experiment further revealed that posterior STS activation was not selectively enhanced in response to biological versus scrambled motion in patients, whereas this effect was clearly detected in the healthy control group.

In a recent behavioural study, Van den Stock, de Jong, et al. (2011) presented static pictures of emotional body postures with their faces blurred to healthy subjects and patients with schizophrenia or non-schizophrenic psychosis. Schizophrenia patients were significantly impaired in recognising body expressions, but again, these deficits were not emotion specific. The ability of schizophrenia patients to recognise emotional states from human gait patterns was recently investigated in a study by Peterman et al. (2014). They presented a set of volumetric, faceless avatars expressing either a neutral, happy, or angry state while walking. Discrimination sensitivity was reduced in schizophrenia compared to healthy controls with respect to emotion recognition as well as gender recognition, suggesting that disease related deficits in extracting information from human gait were not limited to emotions. However, patients showed the same response biases like control subjects towards identifying avatar walks more often as happy or male, respectively. The authors concluded that reduced sensitivity to social cues in schizophrenia did not depend on a distorted perception of one particular emotion. However, it is not clear how schizophrenia patients would perform if more than just two emotional (plus neutral) walks were presented. Moreover, because so far no neuroimaging study has been published, nothing is known about functional brain alterations that may underlie the reported (emotion) recognition deficits from human body movements.

2.3 Aims and linkage of the present studies

As previously indicated, the present dissertation is dedicated to the investigation of neurophysiological correlates of verbal and nonverbal perceptual communication abilities that are of high relevance for everyday social functioning in patients with schizophrenia. To similarly address cognitive and affective facets of schizophrenic communication abilities, the verbal (i.e. language) processing paradigm should be designed to predominantly test social-cognitive comprehension, whereas the nonverbal paradigm should assess social-affective processing aspects.[21]

Regarding the investigation of verbal language comprehension, the pragmatic language was chosen because (1) this type of language has been, so far, less frequently assessed by means of neuroimaging methods, and (2) semantic-pragmatic deficits are remarkably manifested in everyday social communication. Hereby, metaphoric expressions are focussed instead of ironic remarks as pragmatic language form for several reasons. First, different elaborate theoretical frameworks exist that can be easily applied to and tested based on the data of both healthy subjects and schizophrenia patients (although, of

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[21] Of course, a complete assessment of cognitive and affective aspects of verbal and nonverbal communication would additionally require reversed considerations, i.e. the use of paradigms assessing cognitive aspects of nonverbal information processing and emotional aspects of verbal language processing, respectively. The current approach was favoured in order to stay within the limits of this dissertation.

course, some of these accounts could be equally considered for ironic expressions). Second, comprehension impairments of schizophrenia patients have been less consistently reported for metaphoric as – for example – compared to ironic expressions, which is why metaphors are an appropriate subject of ongoing research. Third, other than ironical utterances, a metaphor in its most basic form (i.e. nominal metaphors) is simply structured, allowing for a sound experimental controllability of these expressions. Moreover, after a thorough literature review on pragmatic language forms and their embodiment into everyday human conversations, it seems likely that metaphoric language is - in its different forms – used and integrated more frequently and also more naturally into common parlance, an assumption that has been vividly underpinned in Lakoff and Johnson's modern classic "Metaphors we live by" (Lakoff & Johnson, 1980b). Therefore, it might be closer to the social functions of linguistic pragmatics which might be impaired and very relevant in schizophrenia. Another reason for choosing metaphoric meanings is that at the electrophysiological level, up till now only two studies on schizophrenia patients have been conducted, with both revealing rather conflicting results. Hence, the use of metaphoric expressions in a combined EEG/NIRS study simultaneously assessing neural and topographic-haemodynamic cerebral activation patterns would allow us to address several key questions at once:

1. Can simultaneous EEG/NIRS measurements of metaphor processing help to elucidate the linkage of neural and haemodynamic substrates underlying pragmatic language comprehension? – *Basic question;*

2. Are these measurements promising tools to assess potential neurobiological markers (N400 and/or left fronto-temporal activity anomalies) of semantic-pragmatic impairments in patients with schizophrenia? – *General clinical question;*

3. Is metaphor processing in patients with schizophrenia accompanied by altered ERP components and, respectively, malactivation of the left fronto-temporal language network? If so, how do these alterations relate to clinical symptomatology? – *Specific clinical questions.*

With respect to the investigation of nonverbal social information processing, an emotional paradigm was established and tested regarding its potential to systematically assess nonverbal emotion recognition in schizophrenia. Hereby, the ability to recognise emotional states from body movements was addressed for several reasons: First, as demonstrated in section 2.2.1.2, emotion recognition from facial expressions in schizophrenia has been exhaustively investigated in the past decades and it would be questionable whether and how future studies can significantly contribute to the findings gained from present state-of-the-art studies and meta-analyses, which have already properly integrated previous results (see, for example, Habel et al., 2010; Kohler et al., 2010). In contrast, body-based emotion perception and recognition reflects an upcoming research field. The ability to correctly perceive and process emotional cues from body postures and movements will be important for everyday life social situations, especially when facial cues are not available or might be inconclusive, providing another argument for choosing body movements instead of faces as stimuli for the present projects. In particular, *dynamic* body movements conveying information about emotional states of the presenter have been chosen for two reasons: First, this type of body stimuli certainly has higher ecological validity (i.e. they are closer to the appearance of bodies in real-life situations). Second, recent studies have indicated that emotion recognition from static bodies is more difficult than from dynamic body movements and task difficulty should be kept minimal so that potential emotion recognition impairments in schizophrenia patients would not be linked to task difficulty itself. The third reason is of a rather practical nature. The University of Tuebingen Campus together with all its associated research facilities (such as the Max-Planck-Institute for Biological Cybernetics or the Hertie-Institute for Clinical Brain Research, or the Center for Integrative Neuroscience) provides an outstanding expertise in various neuroscientific and clinical research fields which we intended to utilise through fruitful scientific collaborations. Within such a stimulating collaboration, the Section for Computational Sensomotorics at the Centre for Integrative Neuroscience has significantly contributed to the research presented in this dissertation by providing a validated set of biological motion stimuli in terms of video sequences that show moving human bodies, shaped in the form of avatars (see Figure 12). Using these videos in our experiments investigating cortical haemodynamic activity in healthy subjects and patients with schizophrenia by means of fNIRS measurements, the following research questions should be addressed:

1. Can fNIRS measurements detect cortical activation changes that are related to emotion processing from body movements? *– Basic question;*

2. Are patients with schizophrenia impaired in recognising emotional states from dynamic body stimuli? *– General clinical question;*

3. Do patients with schizophrenia show distinct cortical activation patterns during body-based emotion processing that differ from those seen in healthy subjects or other psychiatric groups? If so, how do these alterations relate to clinical symptomatology? *– Specific clinical questions.*

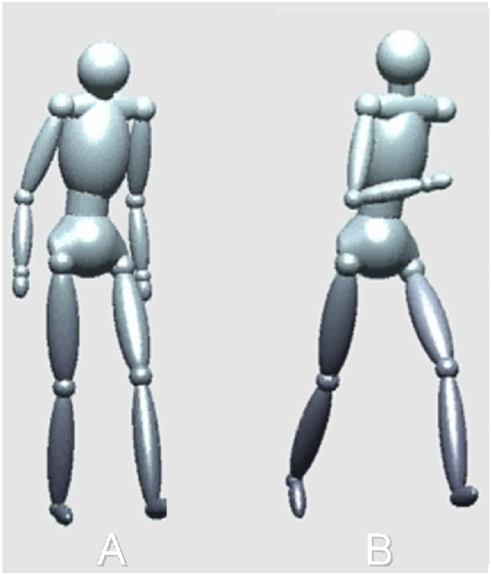

Figure 12. Example still images of the full-light walking displays created by the Section for Computational Sensomotorics (Head: Prof. M. A. Giese). A: sad walk. B: angry walk.

Despite of the high specialization within the two projects separately investigating verbal and nonverbal communication anomalies in schizophrenia patients, the studies are overall linked via a common underlying research aim: The neurophysiological bases of both cognitive and affective aspects of verbal and nonverbal information processing in schizophrenia shall be elucidated to provide a preferably broad and holistic overview over social communication dysfunctions that may be apparent in patients suffering from schizophrenia. Hereby, both projects focus on an innovative implementation of neuroimaging methods that may be particularly promising for future neuropsychiatric research.

2.3.1 Methodological aspects – Choice of brain imaging techniques

An important aim of the present projects focuses on the implementation of functional neuroimaging techniques that show characteristics that are well compatible with the specific demands of neuropsychiatric research. The fact that psychiatric patients, especially when currently hospitalised, are far less stressable is often underrated. Moreover, I am convinced that a valid assessment of any psychological function – but particularly socio-cognitive functions – requires measurement settings and surroundings of high ecological validity which are not intimidating or overexert the patients. Well-established methods that often require complex measurement setups but which are, on the other hand, highly informative, such as fMRI, PET, and MEG, will certainly retain their prominent status and functional imaging research in psychiatry will never work without these techniques. However, depending on the respective research question(s), sample size, and sample characteristics (e.g. patient groups with special needs or features that need to be considered), these techniques may not always be the methods of choice. The following studies (particularly studies 1 & 3) aimed to test the accessibility of critical neurophysiological markers of verbal and nonverbal social information processing during newly established cognitive and affective paradigms by fNIRS measurements, applied either alone or in combination with EEG. Throughout the clinically oriented studies (studies 2 & 4), the implementation of these measurements in studies on schizophrenia patients – in order to assess functional anomalies during the processing of verbal and nonverbal communication signals in this patient group – is investigated.

Hereby, verbal language processing and comprehension will be addressed by means of simultaneous EEG-fNIRS measurements. Because language comprehension has been described as a fast, linear process, the application of a method providing excellent temporal resolution (such as EEG) is highly appropriate. Additional fNIRS measurements can shed light on the cortio-spatial distribution of brain activation without the need for probabilistic source localisation methods for EEG, which are tied to additional requirements (see Belardinelli, Ortiz, Barnes, Noppeney & Preissl, 2012; Grech et al., 2008). Moreover, most socio-cognitive experiments involve the activity of different, partly large areas of the brain and in these cases especially source localisation methods using dipole models are likely to perform poorly, making topographical imaging methods, such as fNIRS, potentially more suitable.

The recognition of nonverbal social information shall be investigated using multi-channel fNIRS measurements. Because most previous fMRI studies on emotion recognition have consistently pointed towards the significance of cortical regions, including the posterior STS and the EBA, the limited depth resolution of fNIRS measurements might be less obstructive. In contrast, the chance of measuring social perception in schizophrenia patients in a more naturalistic social setting (as compared to fMRI or PET measurements) and to compare them to other clinical groups (due to the fast, uncomplicated setup) were indicative for the choice of fNIRS in this context. The latter aspect can be important particularly with respect to the fact that the processing of social signals is often altered in other psychological diagnoses, such as major depression (e.g. Cusi, Nazarov, Holshausen, Macqueen & McKinnon, 2012). Hence, the possibility to assess multiple patients with different diagnoses allows us to investigate which neurophysiological mechanisms may be diagnostic for one specific disorder or shared by different groups of illnesses, respectively.

2.3.2 Overview over the studies

Table 2. Aims and methods of the four studies forming the practical part of the present work.

	Study 1	**Study 2**	**Study 3**	**Study 4**
target / psycho-social domain addressed	verbal communication/ cognitive domain	verbal communication/ cognitive domain	nonverbal communication affective domain	nonverbal communication/ affective domain
study aim	neurophysiological correlates of figurative sentence comprehension in healthy subjects	neurophysiological correlates of figurative sentence comprehension in schizophrenia	haemodynamic correlates of emotion processing from body movements and their accessibility via NIRS	haemodynamic correlates of emotion processing from body movements in schizophrenia patients
Paradigm	Sentence classification paradigm	Sentence classification paradigm	walking avatar videos – Emotion labelling and waking speed judgement tasks	walking avatar videos – Emotion labelling and waking speed judgement tasks
Sample	healthy subjects	healthy subjects schizophrenia patients	healthy subjects	healthy subjects schizophrenia patients depression patients
Sample Size (final data sets)	N = 20	N = 44 (22 per group)	N = 33	N = 60 (20 per group)
Brain imaging method(s)	EEG, fNIRS	EEG, fNIRS	fNIRS	fNIRS
Main dependent variables	Behavioural: Metaphor comprehension (paper-pencil test), sentence meaningfulness judgements in the sentence classification paradigm Neurophysiological ERPs, cortical concentration changes of (de)oxygenated Hb, correlations between ERPs and haemodynamic parameters		Behavioural: Emotion recognition performance Neurophysiological cortical concentration changes of (de)oxygenated Hb	Neuro-physiological cortical concentration changes of (de)oxygenated Hb; functional connectivity of cortical areas

Analyses (behavioural data)	relative frequency of correctly classified sentences; RTs in the sentence classification paradigm; preferred interpretation styles in metaphor comprehension test		relative frequency of correctly recognised emotions; RTs in the emotion labelling paradigm; Subjective arousal and recognisability ratings of the stimuli	
Analyses (brain imaging data)	event-related EEG and NIRS data analyses; peak and average amplitude comparisons (ERPs); peak comparisons (fNIRS)	event-related EEG and NIRS data analyses; peak and average amplitude comparisons (ERPs); peak comparisons (fNIRS)	event-related NIRS data analyses: GLM-based HRF analyses and average amplitude comparisons	event-related NIRS data analyses: average amplitude comparisons functional connectivity analyses: cross-correlations of haemodynamic time-courses between different NIRS ROIs
Analysis programs	IBM-SPSS 19, MATLAB R2009b, Brain Vision Analyzer 2.0, SPM 8	IBM-SPSS 19-21, MATLAB R2009b, Brain Vision Analyzer 2.0, SPM 8	IBM-SPSS 19-21, MATLAB R2009b, SPM 8	IBM-SPSS 21, MATLAB R2009b, MRIcron, SPM 8

GLM: general linear model; Hb: haemoglobin HRF: haemodynamic response function; RTs: reaction times; ROIs: regions of interest.

3. Verbal communication in schizophrenia: deficient non-literal language comprehension

3.1 Study 1:

Beyond the N400: Complementary access to early neural correlates of novel metaphor comprehension using combined electrophysiological and haemodynamic measurements

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3.1.1 Abstract

The simultaneous application of different neuroimaging methods combining high temporal and spatial resolution can uniquely contribute to current issues and open questions in the field of pragmatic language perception. In the present study, comprehension of novel metaphors was investigated using near-infrared spectroscopy (NIRS) combined with the simultaneous acquisition of electroencephalography (EEG)/event-related potentials (ERPs). For the first time, we investigated the effects of figurative language on early electrophysiological markers (P200, N400) and their functional relationship to cortical haemodynamic responses within the language network (Broca's area, Wernicke's area). To this end, 20 healthy subjects judged 120 sentences with respect to their meaningfulness, whereby phrases were either literal, metaphoric, or meaningless. Our results indicated a metaphor specific P200 reduction and a linear increase of N400 amplitudes from literal over metaphoric to meaningless sentences. Moreover, there were metaphor related effects on haemodynamic responses accessed with NIRS, especially within the left lateral frontal cortex (Broca's area). Significant correlations between electrophysiological and haemodynamic responses indicated that P200 reductions during metaphor comprehension were associated with an increased recruitment of neural activity within left Wernicke's area, indicating a link between variations in neural activity and haemodynamic changes within Wernicke's area. This link may reflect processes related to interindividual differences regarding the ability to classify novel metaphors. The present study underlines the usefulness of simultaneous NIRS-EEG measurements in language paradigms – especially for investigating the functional significance of neurophysiological markers that have so far been rarely examined – as these measurements are easily and efficiently realizable and allow for a complementary examination of neural activity and associated metabolic changes in cortical areas.

3.1.2 Introduction

Pragmatic types of language, such as metaphoric speech, are remarkably frequent in everyday language (Lakoff & Johnson, 1980a; Pollio, Barlow, Fine & Polio, 1977). Metaphors integrate semantic entities that are "normally" not related. The literal meaning of metaphors may or may not be plausible, but in either case needs to be suppressed (Giora, 2003; Glucksberg, 2003; Ortony, 1993). Scientific approaches which try to account for the particular cognitive operations underlying metaphor comprehension address the question how the brain distinguishes between metaphoric and literal meanings. Especially earlier research assumed that the literal meaning of metaphors is processed first, then rejected and replaced by the correct metaphoric interpretation (Ortony, 1993). This model would imply that metaphors essentially require additional cognitive processes relative to literal sentences. However, research on the processing speed indicates that, within a conclusive context, metaphoric expressions are processed with equal speed, a finding that is not compatible with the sequential model (see Glucksberg, 2003).

A number of studies addressed difficulties in metaphor comprehension in different clinical populations (Rapp & Wild, 2011; Thoma & Daum, 2006). This anomaly was confirmed in patients with schizophrenia (Kircher, Leube et al., 2007; Mitchell & Crow, 2005; Rapp, 2009; Spitzer, 1997), autism (Giora, Gazal, Goldstein, Fein & Stringaris, 2012; Gold & Faust, 2012), brain lesions (Rapp, 2012; Winner & Gardner, 1977), and recently extended to other neurodevelopmental disorders (e.g., Williams Syndrome, Annaz et al. 2009; Faust, 2012b) and dementias (Rapp & Wild, 2011). Compared with other language functions, metaphor comprehension evolves relatively late during development (Nippold, Hegel, Uhden & Bustamante, 1998; Nippold, Martin & Erskine, 1988) and this process is further delayed in neurodevelopmental disorders (Annaz et al., 2009).

From a neurobiological perspective, an elaborate investigation of the functional and structural bases of pragmatic language comprehension is associated with a number of methodological and technical challenges. Due to its fast temporal processing and its representation and integration among complex, widespread neural networks, the perception of language and its neurobiological correlates should preferably be examined by means of imaging methods that offer both good temporal as well as spatial resolution. Because most non-invasive neuroimaging techniques exhibit either high temporal (e.g. electroencephalography [EEG], magnetoencephalography [MEG]) or spatial resolution (e.g. functional magnet resonance imaging [fMRI], positron emission tomography [PET]), a combination of methods can strongly enhance measurement validity. The simultaneous application of EEG and NIRS (near-infrared spectroscopy) is not only economic and offers very good ecological validity, it is also particularly useful for language studies (Dieler, Tupak & Fallgatter, 2012; Horovitz & Gore, 2004; Wallois, Mahmoudzadeh, Patil & Grebe, 2012), as there is no irritating noise possibly interfering with language perception (as compared to fMRI), there is no need for the injection of radioactive agents (as compared to PET), both techniques exhibit higher temporal resolution compared to fMRI, PET and SPECT, and the absence of side effects makes this specific combination of methods particularly suitable for studies with children (i.e. for language development studies). Moreover, EEG-NIRS combinations are not tainted with technical interferences as both methods rely on different aspects of brain activation: Whereas EEG assesses neural responses directly based on electrical activity, NIRS gathers local haemodynamic responses based on the distinct optical properties of oxygenated and deoxygenated haemoglobin in order to indirectly measure activation changes in the brain. Hence, EEG-NIRS combined measurements allow for a complementary examination of neural as well as haemodynamic aspects of brain activation. We, therefore, applied simultaneous EEG-NIRS measurements to systematically assess both electrophysiological markers (i.e., event-related potentials - ERPs) – focussing also on early processes beyond the classically reported N400 component (see also below) – and haemodynamic correlates of activation within the language perception network, in order to gain new insights into the functional meaning and complex interplay of different aspects of novel metaphor comprehension. Although, up to now, no studies have used NIRS to investigate cortical haemodynamic responses specifically related to metaphoric language, the method has been repeatedly applied in various language perception studies in infants and adults and has been proven to be a useful and reliable tool in determining the neural basis of language comprehension during several task types (see Dieler et al., 2012, for an overview). Distinct frontal, temporal, and temporo-parietal activation patterns could be identified using NIRS in studies during auditory (Homae, Watanabe, Nakano & Taga, 2007; Noguchi, Takeuchi & Sakai, 2002; Saito et al., 2007; Sato, Takeuchi & Sakai, 1999; Sato, Sogabe & Mazuka, 2007), audiovisual (Bortfeld, Wruck & Boas, 2007), and visual (Fallgatter, Mueller & Strik, 1998; Hofmann et al., 2008; Liu, Borrett, Cheng, Gasparro & Kwan, 2008) language presentation.

Examining the functional correlates of non-literal language processing in particular, a wide range of imaging studies has been conducted using fMRI. At least 15 brain lesion studies (Lundgren, Brownell, Cayer-Meade, Milione & Kearns., 2011; see Rapp, 2012) and at least 20 functional magnetic resonance imaging (fMRI) studies (Prat, Mason & Just, 2012; Rapp et al., 2012; Shibata, Toyomura, Motoyama, Itoh, Kawabata & Abe, 2012) addressed the functional division of language associated brain structures and the role of the hemispheres during metaphor comprehension. FMRI based research suggests that left and – to a smaller degree – right inferior frontal and middle temporal brain structures and the parahippocampal gyrus may play a key role for metaphor comprehension. While some studies support the idea that right hemispheric areas are crucial for metaphor comprehension (Anaki, Faust & Kravetz, 1998; Faust, 2012a, 2012b), a recent review and meta-analysis of the fMRI evidence suggests a predominantly left lateralised fronto-temporal network that is crucial for metaphor comprehension (Rapp et al., 2012). The left anterior inferior frontal gyrus is part of this network and could possibly be a functional correlate of the process of mapping semantic domains of the "source" and "target" during metaphor comprehension (Rapp, Leube, Erb, Grodd & Kircher, 2004; Rapp et al., 2012). Further, this brain region is involved in selecting between alternative meanings (Rapp et al., 2012) and integrating words with lower cloze probability into a sentence context (Baumgaertner, Weiller & Buechel, 2002).

The majority of studies using event-related potentials (ERPs) to register neural responses to external language presentation are concerned with the N400, a negative-going centro-parietal component of the ERP starting at ~200 ms and peaking at ~400 ms after stimulus onset, that is sensitive to – among various other types of incoherence (e.g. phonological, categorical, associative) – violations or anomalies regarding semantic relatedness (Kutas & Hillyard, 1980, 1983). Linguistically, larger N400 peak values have been reported for words that are unpredictable or incongruous (Kutas & Hillyard, 1980), respectively, regarding the preceding context, i.e., the beginning of a word group, sentence (Kutas & Hillyard, 1980, 1983, 1984) or discourse (Salmon & Pratt, 2002; Van Berkum, Hagoort & Brown, 1999), as well as taxonomic affiliation between word groups or sentences (Federmeier & Kutas, 1999a, 1999b). However, it has also been demonstrated that meaningful, expected, and semantically related phrase endings often elicit an N400 component which is characterised by a smaller amplitude compared to unpredictable, unrelated endings, whereby the magnitude of negativity depends on the word's expectancy, also called cloze probability (DeLong, Urbach & Kutas, 2005; Kutas & Federmeier, 2000; Van Berkum, Brown, Zwitserlood, Kooijman & Hagoort, 2005). Generally speaking, the N400 has been suggested to reflect the ease or, on the other side, the difficulty of mapping between forthcoming word meanings and conceptual domains (Coulson & Van Petten, 2002; Davenport & Coulson, 2011; Federmeier & Kutas, 1999b; Holt, Lynn & Kuperberg, 2009; Kutas & Federmeier, 2011; Van Berkum, Sauerland & Yatsushiro, 2009; Van Berkum et al., 1999). Studies addressing the electrophysiological response to figurative language, such as metaphors, predominantly suggest higher (more negative) N400 amplitudes to metaphoric compared to literal meanings (Coulson & Van Petten, 2002; 2007; de Grauwe et al., 2010; Lai et al., 2009; Pynte et al., 1996). This effect may be interpreted in terms of increased mapping difficulties for metaphoric compared to literal meanings, whereby the underlying language processing mechanisms are assumed to be the same (Coulson & Van Petten, 2002; Kutas & Federmeier, 2011;

Kutas et al., 2006). This explanation could also account for findings that suggested similar N400 amplitudes for literal meanings and conventional metaphors (Arzouan et al., 2007; Iakimova et al., 2005) which do not tax conceptual mapping because of their high salience and familiarity (Giora, 1997; Giora, 2003).

In contrast to the N400, the P200, a positive-going potential reflecting early, probably bottom-up related processes during lexical perception, has been focussed far less often in pragmatic language studies. Up till now, the P200 has been mainly investigated in studies addressing the first two levels of language processing, namely lexical access and lexical selection at the word level, respectively (e.g., Dambacher, Kliegl, Hofmann & Jacobs 2006; Federmeier, Segal, Lombrozo & Kutas, 2000). However, recent findings suggest that the P200 may also represent early processes of higher order language comprehension, such as irony (Regel, Coulson & Gunter, 2010; Regel, Gunter & Friederici, 2011), emotional salience detection in spoken language (Paulmann, Ott & Kotz, 2011), and comprehension of semantic relatedness in skilled and less-skilled comprehenders (Landi & Perfetti, 2007). Findings from fundamental linguistic experiments using full sentences already pointed to changes in P200 amplitude that may be linked to the predictability of a sentence ending (Federmeier, Mai & Kutas, 2005; Lee, Liu & Tsai, 2012) – with less predictable endings eliciting reduced P200 peaks – or sentential constraint (Wlotko & Federmeier, 2007) – with weakly constrained sentences completions provoking reduced P200 peaks. In the context of pragmatic language types, enhanced P200 amplitudes were reported for ironic versus non-ironic expressions, especially if study participants had to perform an irony comprehension task (Regel et al., 2011). Moreover, findings reported by Landi and Perfetti (2007) suggest attenuated P200 peaks for unrelated versus related word pairs as well as for categorically versus associatively related word pairs in skilled readers, whereby in unskilled readers only a slight P200 reduction was observed between semantically and categorically related pairs. While these studies suggest that the lexical P200 may not only represent purely perceptual features but may also reflect an extended early semantic analysis of sentence endings, the specific significance of the P200 during figurative language processing has so far been poorly examined. Although some studies on metaphor comprehension report N400 effects related to figurative language that sometimes start quite early (<300 ms; e.g. Iakimova et al., 2005; see also Fig. 4 in Coulson & Van Petten, 2002), a possible affection of components preceding the N400 has not yet been regarded. Therefore, it is still unclear to what extent non-literal expressions may be represented in early electrophysiological parameters beyond the N400, and, if such early effects are detectable, what their functional interpretation would be in relation to both the N400 and specific elements of the language perception network. We suggest that a combined assessment of electroencephalographic and haemodynamic responses to literal vs. non-literal sentences can uniquely help to investigate these new issues: Attending different time windows within the ERP we can focus on (possibly) differential language effects on distinct EEG components (i.e., P200, N400). The additional use of a topographic method (i.e., NIRS) measuring cortical haemodynamic responses to language stimuli allows us to (1) investigate regional cortical activation changes that are related to semantic manipulations in general and (2) link certain ERP effects to these regional haemodynamic changes. The latter strategy enables us to investigate whether and how specific metaphor related ERP effects are associated with distinct cortical activation patterns within the language perception network.

In order to systematically address these research questions the present study aims at a complementary investigation of haemodynamic as well as electrophysiological (i.e., neural) responses to different kinds of language, namely meaningful and literal, meaningful and metaphoric as well as meaningless sentence types, using combined NIRS-EEG measurements. We hypothesise condition-related ERP amplitude differences: With respect to the P200 component, we expected reduced amplitudes for metaphoric and meaningless sentence endings, based on studies that indicate a P200 decrease for sentence endings that are rather unexpected (e.g. Federmeier et al., 2005). Concerning the N400, a more negative amplitude for meaningless compared to meaningful and for metaphoric compared to literal phrases (based on, e.g., Coulson & Van Petten, 2002; 2007; Lai et al., 2009) would be expected. Relying on state-of-the-art fMRI literature we further propose a predominant increase in O_2 metabolism in left-anterior cortical areas for both literal and metaphoric compared to meaningless phrases, whereby stronger haemodynamic responses are also expected for metaphors compared to literal meanings. Taken NIRS and ERP data together, we finally expect to find a relationship between oxygenation increases and the two ERP components that are of specific interest in this study, the P200 and the N400. This relationship would reflect a direct connection between neural activation and regional changes in cerebral metabolism and could thus provide new characteristics of the temporal and topographic activation patterns specifically related to different types of language comprehension. It moreover will help to clarify whether P200 and N400 represent functionally related or distinguishable correlates of figurative language recognition.

3.1.3 Materials and Methods

3.1.3.1 Subjects

Twenty-eight (16 males, 12 females) healthy, right handed, native German speakers were enrolled in the study. All subjects were recruited at the Department of Psychology and the University Hospital Tuebingen. Exclusion criteria were sinistrality, past or present psychiatric illness or a current chronic or untreated severe physical illness (e.g. instable hypertonus). Right-handedness was ensured by means of the dinburgh Handedness Inventory (EHI, Oldfield, 1971). Permission for the study was obtained from the local Ethics Committee of the University of Tuebingen; all study procedures were in line with the Declaration of Helsinki in its latest version. After a complete study description, written informed consent was obtained. Data from eight subjects had to be excluded due to equipment problems (n=1), noisy EEG data (n=2), uncorrectable NIRS artefacts (n=1) or an insufficient number of correct trials in one of the three experimental conditions (n=4) throughout the experiment, leading to a final sample size of 20 subjects (10 males, 10 females). The age range was 18-59 years (M=30.1 years).

3.1.3.2 Material

The stimulus set consisted of three sentence categories: (1) literal and meaningful, (2) metaphoric and meaningful, and (3) meaningless, with each sentence type consisting of 60 sentences. Categories were matched for grammar, tense and syntactic structure. Literal, metaphoric and meaningless sentences differed only in their endings, including the last one to three words (critical word(s); CW) of a sentence (e.g., literal category: "Der Hundertjährige ist *ein Greis*." ["The one hundred-year-old man is *a doter*."]; metaphoric category: "Der Hundertjährige ist *eine Eiche*." ["The one hundred-year-old man is *an oak*."]; meaningless category: "Der Hundertjährige ist *eine Ampel*." ["The one hundred-year-old man is *a traffic light*."]). Sentence categories were further matched for tense, with half of the phrases written in present and the other half written in past tense, as well as for number of words, CW length, and CW frequency (each $F(2,78)<1$, n.s.). Literal and metaphoric phrases were mostly taken from a previous study (Rapp et al., 2004) and in part newly created. Meaningless stimuli were entirely created de novo for the present study. Notably, all metaphoric stimuli were non-salient. Novelty of stimuli was confirmed using the German linguistic corpus DEREKO and the web platform **COSMAS II$_{\text{web}}$** corpus.

Most sentences were of the "X is/was Y" format. We chose this simple form of stimuli to exclude possible confounding factors such as sentence length or complex syntactic processing.

Table 3. Overview over sentence ratings and cloze probabilities obtained in pre-tests underlying the development of the study material.

Sentence type	**Meaning-fulness** Mean ± SD	**Imagery**[1] Mean ± SD	**Figurative-ness**[1] Mean ± SD	**Familiarity** Mean ± SD	**Con-notation** Mean ± SD	**Cloze probability** (in %) Mean ± SD
LIT	5.71 ± .23	1.32 ± .27	2.22 ± .58	4.55 ± .57	.20 ± 1.56	2.5 ± 5.98
MET	4.75 ± .54	5.23 ± .43	4.54 ±.56	3.22 ± .76	-.32 ± 1.70	.5 ± 1.98
INC	1.15 ± .23	1.35 ± .19	1.76 ± .33	1.05 ± .07	-.11 ± .15	.00 ± .00

Statistical comparisons	Meaning-fulness *t*(df), *p*-value	Imagery *t*(df), *p*-value	Figurative-ness *t*(df), *p*-value	Familiarity *t*(df), *p*-value	Connotation *t*(df), *p*-value	Cloze probability *χ*(df), *p*-value
LIT vs. MET	*t*(78)=10.3; *p*<.001**	*t*(65)=-48.3; *p*<.001**	*t*(78)=-18.2; *p*<.001**	*t*(73)=8.8; *p*<.001**	*t*(77)=1.41; *p*=.16	*χ* (3)=1.39; *p*=.81
LIT vs. INC	*t*(78)=99.0; *p*<.001**	*t*(70)=.63; *p*=.53	*t*(62)=4.35; *p*<.001**	*t*(40)=38.1; *p*<.001**	*t*(40)=1.25; *p*=.22	*t* (42)=2.74; *p*<.01**,[2]
MET vs. INC	*t*(47)=40.1; *p*<.001**	*t*(54)=51.6; *p*<.001**	*t*(64)=27.0; *p*<.001**	*t*(40)=18.0; *p*<.001**	*t*(40)=0.76; *p*=.45	*t* (42)=1.78; *p*=.08[2]

** significant correlation coefficients; p≤.05).

LIT/MET/INC: literal/metaphoric/incongruent (meaningless) phrases.

[1] Raters received detailed instructions and all rating scales were explained using an example sentence. In addition, a short written clarification of the words "imagery" and "figurativeness" was provided. The explanations were as follows: *figurativeness:* "something is meant in a transferred (metaphorical) sense." *imagery:* "While reading and comprehending an expression, a virtual image may appear in ones mind's eye. That means that the content of a sentence is easy to visualize."

[2] one sample *t*-tests were performed because cloze probability for meaningless sentences was 0.

Prior to the neurophysiological study, a set of 180 German sentences was evaluated in a pilot survey by 20 raters who did not participate in the neuroimaging study. All phrases were rated on a six-point Likert Scale regarding their meaningfulness (1=completely absurd; 6=completely meaningful), imagery (1=completely literal meaning; 6=completely metaphoric meaning), figurativeness (1=not figurative; 6=highly figurative), and familiarity (1=not familiar, 6=highly familiar) and further on a seven-point Likert scale regarding their content (-3=very negative content, 0=neutral content, 3=very positive content). Indices were computed for each item of each category, indicating literality ($I_{literality}=(Mean_{meaningfulness}*(6-Mean_{imagery}))/Max(numerator)*100$) and imagery ($I_{Imagery}=(Mean_{meaningfulness}*Mean_{imagery})/Max(numerator)*100$), respectively. Regarding the literal phrases category, those 20 sentences that scored most poorly on the literality index were removed from the stimulus set, whereas for the metaphoric category, those 20 phrases that scored most poorly on the imagery index were rejected. Concerning the meaningless sentences, those 20 phrases that scored highest on either the literality or the imagery index were excluded from the original pool of sentences, leading to a total set of 120 phrases that were eventually presented in the EEG/NIRS experiment. Table 3 provides a detailed description of the linguistic stimulus material.

3.1.3.3 Experimental Task

Participants were seated comfortably in a sound- and light-attenuated, electrically shielded room approximately 80 cm in front of a computer screen. They were instructed to read all sentences attentively and silently and judge whether a presented phrase made sense or not. Sentences were presented in white colour on a black background (font size: 70pt) word-by-word in randomised order with each word being displayed for 400 ms with an interstimulus interval (ISI) of 500 ms and a jittered interphrase interval of 4000-7000 ms. At the beginning of each trial, a fixation cross was presented in the centre of the screen for 500 ms. The presentation of a sentence was always followed by a blank screen that lasted 750 ms, serving as a gap between CW and reaction in order to prevent contamination of the electrophysiological response by lateralised readiness potentials (LRPs). After this gap, a question mark appeared on the screen centre indicating that subjects had to provide their meaningfulness judgements via button press (meaningfulness judgement task) with the index finger and the middle finger, respectively, of the right hand, whereas key assignment was counterbalanced across participants. Therefore, reaction times (RTs) were quantified as the time lapsing from the appearance of the question mark until the button press was performed (see section 2.8). At the beginning of the session, six sentences (two per category) which were not presented during the main experiment were used as practice trials. The main experiment consisted of 40 trials per sentence category, leading to a number of 120 sentences. Total experiment duration was approximately 25 minutes. To prevent weariness, the experiment was divided into two blocks separated by a short break in the middle of the task, the duration of which could be determined by the participant.

3.1.3.4 Neuropsychological Assessment and Metaphor Comprehension

Prior to the actual experiment, all subjects performed two neuropsychological tests, the "Digit Span" (Wechsler, 1997) and the "MWT-B" ("Mehrfachwahl-Wortschatz-Test", version B; Lehrl, Triebig & Fischer, 1995). The Digit Span is a subscale of the Wechsler Adult Intelligence Scale (WAIS) that was used to measure working memory capacity in the present study, whereby both the forward and the backward version were implemented. In the forward Digit Span test, participants were instructed to repeat a set of increasing lists of numbers in correct order and in the backward version they were instructed to repeat items in reverse order. In both cases, the maximum list of items a subject could repeat correctly was counted. The MWT-B is a short scale consisting of 37 items that is used to assess verbal intelligence. Each item contains one real word (=target word) and four fictively constructed terms, and subjects are instructed to identify the real word per item. Thus, a total score of correctly identified target words can be computed for each subject.

After participants finished the neurophysiologic measurement, they were asked to judge all metaphoric sentences which were presented throughout the experiment according to their meaningfulness (1=completely absurd; 7=completely meaningful) and subjective familiarity (1=not familiar, 7=highly familiar). In order to assure that participants had not read any of the metaphoric expressions used in the EEG/NIRS paradigm before (i.e., to avoid possible repetition effects), metaphor ratings were performed strictly afterwards. These measures (metaphor ratings) were used later on in order to determine the ease of metaphor comprehensibility in the present sample.

3.1.3.5 Electrophysiological Recordings

Measurements took place in a sound-attenuated, electrically shielded room at the University Hospital for Psychiatry and Psychotherapy Tuebingen (Germany). The researcher in charge of the measurement was with the subject throughout the entire session to instruct and monitor performance. The EEG was recorded from 21 scalp electrodes embedded in an elastic cap (Easycap GmbH, Munich, Germany) and placed according to the International 10/20-System (Jasper, 1958). To identify eye movement artefacts in the EEG, electrooculography (EOG) activity was recorded from three additional electrodes, one placed below the right eye, two placed at the lateral canthi of both eyes. The ground electrode was placed on the forehead and FCz was used as recording reference. Two mastoid electrodes were additionally applied for subsequent offline re-referencing. Electrode impedances were kept below 5 kΩ. Data were recorded with a 64-channel DC-amplifier and the software "Vision Recorder" (Brain Products, Munich, Germany). All physiological data were digitalised at a rate of 1000 Hz. EEG and EOG were filtered online at .1-100 Hz.

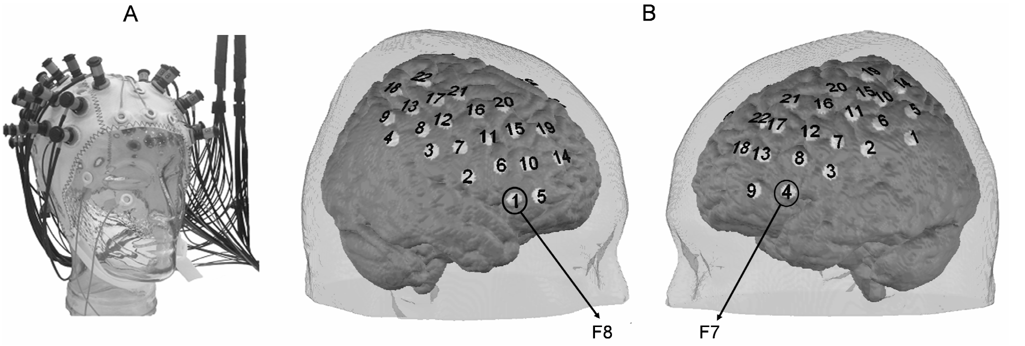

Figure 13. (A) Picture of the combined EEG-NIRS cap used in the present experiment (prototype provided by Hitachi Medical Co., Japan). (B) Illustration of NIRS channel positions on the head according to 10/20 system-based optode arrangement and the neuronavigation-based spatial registration method. Numbers indicate measurement channels. Circle size is associated with the probability of the respective channel-brain structure assignment.

3.1.3.6 Near-Infrared Spectroscopy (NIRS)

NIRS measurements were conducted with the ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) using two separate 22-channel arrays of optodes (8 sources/emitters and 7 detectors on each array) covering fronto-temporo-parietal areas on the left and on the right side of the head, respectively. Emitter-detector distance was 30 mm for contiguous optodes. Sources emitted near-infrared light of two wavelengths (695 and 830 nm, respectively). NIRS optodes were attached to the subject's head by plastic optode holders that were integrated in the elastic EEG cap (see Figure 13A). This procedure guaranteed a stable NIRS channel placement from one recording to the other according to the International 10/20 system on heads with average occipitofrontal head circumferences of 54-58 cm in Caucasians. The first channel of the bottom row which is located in between the first two optodes of that row was located over F7/F8 on the left and right side of the head, respectively (see Figure 13A).

3.1.3.7 Data Analyses

ERP data were analysed using the software "Vision Analyzer" (Brain Products, Munich, Germany). After a visual inspection of the EEG, all data were subsequently filtered using a high pass filter of .1 Hz (24 db/oct) and a 40 Hz low pass (24 db/oct). After that, eye movement artefact correction was performed (Gratton, Coles & Donchin, 1989) and data were re-referenced to linked mastoids. Stimulus-locked epochs beginning 150 ms before and extending 1000 ms beyond the CW of each sentence were then created separately for the three sentence conditions (literal, metaphoric, meaningless). Only trials with correct meaningfulness judgements were analysed with a minimum trial number of 15 per category. Segments containing amplitudes exceeding ± 70 µV or voltage-steps of more than 70 µV per ms as well as epochs with low activity of amplitude changes of less than.1 µV per 100 ms were excluded. After averaging of the stimulus-locked segments per category, baseline correction of the averaged ERP data within 150 ms prior to stimulus onset was performed. Peaks were individually determined in the respective averaged data of the three conditions within a defined time-window for the P200 (200–270 ms) at the following electrode positions: Fz, FCz, and Cz which were chosen in order to meet previous P200 literature and our own results regarding the potential's topographical distribution. These exact P200 peak values were exported for subsequent statistical analyses. To quantify the N400, mean amplitude values within a predefined time window

(300-500 ms, based on the guidelines provided by Duncan et al., 2009) were exported for the electrode positions F3, Fz, F4 (anterior line), C3, Cz, C4 (central line), and P3, Pz, P4 (parietal line) to account for the observation that N400 amplitudes may be largest over central to centro-parietal sites.

With the ETG-4000, changes in the concentration of oxygenated haemoglobin (O_2Hb) and deoxygenated haemoglobin (HHb) were recorded from a 10 s starting baseline continuously throughout the entire language paradigm. Signals were measured with a sampling rate of 10 Hz, and analysed and transformed according to their wavelength and location, resulting in values for the changes in the concentration of O_2Hb and HHb, for each of the 22 NIRS channels per head side. Haemoglobin quantity is scaled in Mm*mm, implying that all concentration changes depend on the path length of the NIR light in the brain.

Following a .008-.25 Hz band pass data filtering, 12 s segments of each of the three conditions were averaged and corrected with respect to a 2 s pre-stimulus baseline using MATLAB (The MathWorks Inc., Natick, USA). Although this time window has a little longer duration than the mean inter-trial-interval (ITI), this temporal overlap of segments can be handled by using enhanced and jittered ITIs in a randomised study design (please see, e.g., Goghari and MacDonald, 2007; Soon et al., 2003 for jittering in haemodynamic measurements).

An automatic peak detection algorithm was used to determine maximum positive (for O_2Hb) and negative (for HHb) peaks, respectively, of the haemodynamic responses (see Figure 14) within 4-10 seconds following the CW. Visual data inspection confirmed the results of this automatic peak detection. Exact peak values were exported in order to perform subsequent statistical analysis. Because only O_2Hb peak values shall be reported here (see below), only maximum positive values of respective concentration values are provided.

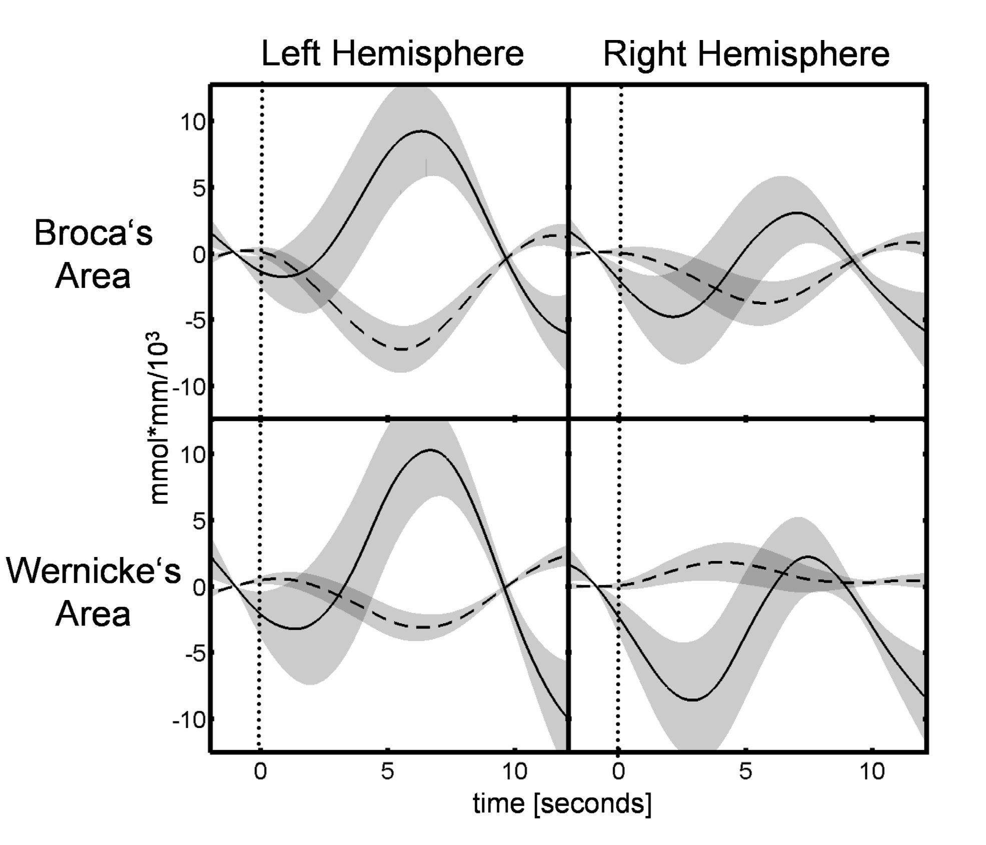

Figure 14. Typical course of the haemodynamic response function (HRF) within the four ROIs averaged over subjects (n=20) exemplarily for the literal sentence type. Dashed vertical lines mark the critical word (CW) onset. Dotted curve: oxygenated haemoglobin, solid curve: deoxygenated haemoglobin. Central thin lines represent mean HRF values; bright thick lines indicate HRF standard deviations.

For hypotheses-driven data analyses, haemodynamic responses within two a priori defined clusters of NIRS channels were analysed, forming one prefrontally located (anterior channels #4, 8, 9, 13 left, channels #1, 5, 6, 10 right) and one more posterior located (channels #1, 5, left, channels #4, 9 right) region of interest (ROI, see Figure 13b). These ROIs were chosen based on the results of a neuronavigation procedure that was performed in order to precisely determine brain-anatomic assignment of NIRS channels. For this procedure, the plastic optode holder arrays were placed on a volunteer's head and respective optode positions were defined using a neuronavigation system [LOCALITE GmbH, St. Augustin, Germany]. Resulting optode coordinates were transferred from the volunteer's native MRI space to the standard Montreal National Institute (MNI) space by applying normalization routines from Statistic Parametric

Mapping (SPM) 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Eventually, these normalised coordinates were projected on a brain template. Figure 13 displays the so-estimated cortical projection points of the NIRS channels. According to this probabilistic channel- anatomy assignment procedure, the selected posterior ROI channels corresponded to the anterior supramarginal gyrus (part of Wernicke's area) and the anterior ROI channels were assigned to the pars triangularis (channels 4, 9, 13 left / channels 1, 5, 10 right) and the pars opercularis (ch. 8 left / ch. 6 right), both part of Broca's area.

3.1.3.8 Statistics

Statistically, analyses of variances (ANOVAs) for repeated measures comprising the within-subject factor sentence type were performed to analyse behavioural data (correctness of the response and quasi reaction times [RTs]). Notably, the quasi RTs are thought to reflect the time that subjects actually needed for performing the semantic judgement across all stimulus categories rather than directly represent the time taken for semantic judgements, because subjects were instructed to wait until the question mark appeared on the screen. In order to analyse ERP components, 3 x 3 ANOVAs for repeated measures were conducted for the P200 peak values and 3 x 3 x 3 ANOVAs for repeated measures for the N400 mean amplitude values. Due to the distinct fronto-central topographical patterns (see also Figure 15), P200 analyses included the within-subject factors sentence type (literal, metaphoric, meaningless) and region (frontal [Fz], frontocentral [FCz], and central [Cz]). With respect to the N400, which revealed a somewhat more complex left-fronto-central topographic distribution, within-subjects factors were sentence type, region (frontal, medial/central, parietal) and hemisphere (left hemisphere, midline, right hemisphere). Accordingly, nine electrode positions were assigned with respect to region (frontal: F3, Fz, F4; medial: C3, Cz, C4; parietal: P3, Pz, P4) and hemisphere (left: F3, C3, P3; midline: Fz, Cz, Pz; right: F4, C4, P4), respectively. In case of significant interaction effects, subsequent ANOVAs were calculated separately for each sentence type, region, or hemisphere. The Huynh-Feldt procedure was used to correct the degrees of freedom whenever Mauchly's test of sphericity revealed significant results ($p<.20$). In case of a significant main effect of sentence type, post-hoc *t*-tests for paired samples were conducted comparing mean ERP values of each of the three sentence categories.

Regarding the statistical analysis of the NIRS data, only O_2Hb peak values, depicting the maximum of O_2Hb concentration increases after a CW, are reported. HHB values were in accordance with the respective O_2Hb data (see Figure 14) but were associated with lower statistical power (i.e., the absolute values of concentration changes in O_2Hb are many times higher than for HHb) and are therefore currently unattended. In a first step, one-sample *t*-tests were used to contrast O_2Hb concentration values within the respective ROIs (left/right Broca and left/right Wernicke area) against zero (alpha levels were corrected using Bonferroni-Holm [BH] correction), in order to test for general activation effects within these predefined cortical areas. Thereafter, univariate ANOVAs for repeated measures were conducted, comprising the factor sentence type, for each ROI and hemisphere. Here, mean O_2Hb peak values averaged over the respective ROI channels were used as dependent variables. If a main effect of sentence type was observed, paired *t*-tests were performed separately to test for statistical differences in O_2Hb peak values between the three sentence conditions. As fNIRS data (i.e., amplitudes of the haemodynamic responses) depend on the path length of NIR light in the brain and since cortical regions differ regarding their relative scalp-to-cortex distance (Okamoto et al., 2004; Haeussinger et al., 2011), a direct comparison of fNIRS data stemming from different cortical areas – i.e. an inclusion of the factor "ROI" in the above-mentioned ANOVA – is not feasible.

Pearson's correlation coefficients were computed, firstly, between meaningfulness judgement performance during the EEG/NIRS experiment (i.e., the number of metaphoric sentences correctly judged as meaningful) and the results of the metaphor ratings (i.e., the average meaningfulness judgements obtained during the rating procedure following the experiment), in order to test whether the sentences were judged consistently by the participants. This analysis showed a positive correlation between these two variables ($r=.66$, $p<.01$). This correlation reveals a strong accordance between the judgement of metaphors throughout the experiment itself and the subsequent metaphor ratings.

In addition, Pearson's correlation coefficients were computed between neurophysiological data (P200 at Fz and Cz, N400 at midline, and O_2Hb peak values of the NIRS ROIs) and (1) behavioural data assessed during the meaningfulness judgement task (task performance = number of correctly categorised sentences, and quasi RTs); (2) the sum scores of the neuropsychological scales (Digit Span forward & backward, MWT-B), and (3) metaphor ratings. Again, two-sided testing procedures were used and Bonferroni-Holm

(BH) correction method was applied in order to adjust the alpha level due to multiple testing of the correlation coefficients.

In order to analyse the relationship between the haemodynamic response indicated by the NIRS data and temporal aspects of language processing indicated by the ERP data, Pearson's correlation coefficients were calculated between the P200/N400 peak values at midline (Fz, FCz & Cz with respect to the P200; Fz, Cz, Pz with respect to the N400) and mean O_2Hb concentration peak values of those ROIs that had previously shown an activity modulation by sentence type. Two-sided testing procedures were used throughout and again, BH-correction method was applied per sentence type in order to adjust the alpha level due to multiple statistical testing.

3.1.4 Results

3.1.4.1 Behavioural Data

Participants responded more correctly to literal [M=38.3, standard deviation(SD)=1.13 out of a total of 40 trials] and to meaningless phrases (M=38.7, SD=1.27) compared to metaphoric sentences (M=29.3, SD=7.21, $5.56<t<5.61$, $p<.001$). Moreover, quasi RTs were significantly slower for metaphoric phrases (M=418.70 ms, SD=69.56 ms), compared to both the literal (M=369.53 ms, SD=48.74 ms, $t(19)=4.14$, $p<.001$) as well as the meaningless sentence condition (M=378.84 ms, SD=59.91 ms, $t(19)=3.55$, $p<.01$).

3.1.4.2 ERP Data

P200. The sentence type x region x hemisphere ANOVA for repeated measures revealed a prominent difference between P200 amplitudes at midline ($F(2,38)=3.80$, $p<.05$, $\eta^2=.17$; cf. Figure 15 and Figure 16) with lower peak values for metaphoric phrases ($M=4.83$ µV, $SD=3.72$ µV) compared to literal ($M=5.88$ µV, $SD=3.68$ µV, $t(19)=2.66$, $p<.05$) and meaningless (M=5.82 µV, SD=4.53 µV, $t(19)=2.69$, $p<.05$) sentences which did, among themselves, not differ significantly ($t(19)=.12$, n.s.). Figure 15 illustrates the topographic pattern of the P200 and Figure 16 depicts the sentence type related peak differences in the P200.

N400. The sentence type x region x hemisphere ANOVA revealed significant main effects of sentence type ($F(2,38)=17.82$, $p<.001$, $\eta^2=.48$) and region ($F(2,38)=4.22$, $p<.05$, $\eta^2=.18$) and an additional significant interaction region x hemisphere ($F(4,76)=3.80$, $p<.01$, $\eta^2=.18$). Post hoc t-tests comparing mean N400 amplitudes for the three sentence categories averaged over electrode positions showed a significant amplitude difference for the literal versus metaphoric condition ($t(19)=5.59$, $p<.001$). Metaphoric sentences were linked to more negative N400 values compared to literal ($t(19)=3.66$, $p<.01$) and more positive N400 amplitudes compared to meaningless phrases, while in the latter case the difference did not meet two-sided 5% alpha level ($t(19)=1.82$, $p=.08$). However, this result pattern pointed towards a linear relationship of the three sentence types. A post-hoc linear trend analysis testing the contrast (literal > metaphoric > meaningless; with > indicating more negative mean amplitude values) confirmed such a linear relationship of the three sentence categories ($F(1,19)=31.25$, $p<.001$, $\eta^2=.62$), whereas a quadratic trend model did not explain a significant amount of variance ($F(1,19)=2.25$, n.s.). In order to unveil the region x hemisphere interaction, further post-hoc ANOVAs with the within-subject factor hemisphere were conducted separately for all three levels of the factor region (frontal, central, parietal). These ANOVAs resulted in a significant effect of hemisphere only for the central row ($F(2,38)=3.84$, $p<.05$, $\eta^2=.17$) Paired t-tests indicated that, within the central row, mean N400 amplitudes were most negative at Cz and C3 as compared to C4 ($t_{C3\text{-}C4}(19)=-2.05$, $p\leq.05$; $t_{Cz\text{-}C4}(19)=-2.37$, $p<.05$). These results can be summarised as a left-central accentuation of the relative N400 peak that is in accordance with topographic patterns of this potential (see Figure 15).

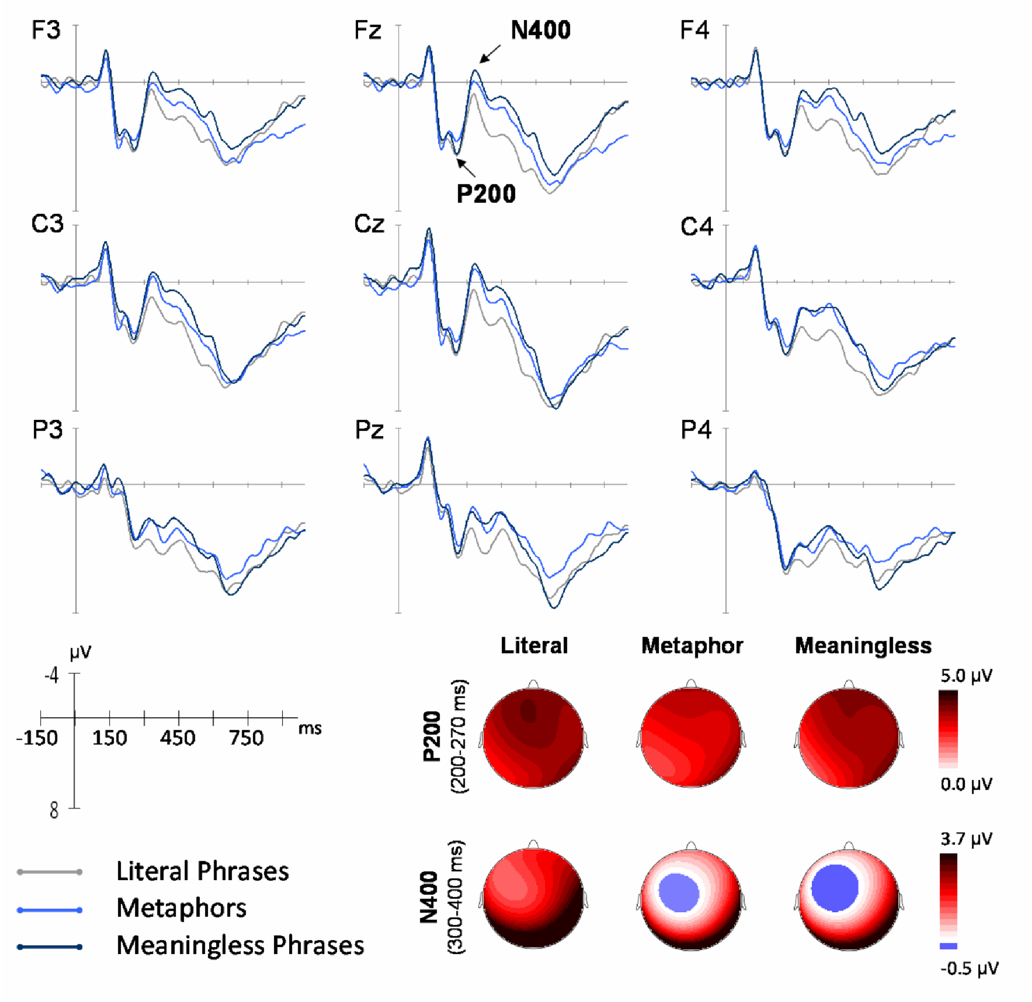

Figure 15. Time-locked ERPs with respect to the CW and baseline corrected regarding 150 ms prior to the CW. Topographic illustrations of the P200 and N400 amplitudes per condition are presented at the bottom.

Correlations. P200 peak values did not correlate with task performance during the meaningfulness judgement paradigm, but they correlated negatively with the quasi RTs regarding literal (r_{Fz}=-.64, r_{Fcz}=-.66, p<.0056; BH-corrected) and meaningless sentences (r_{Fz}=-.69, r_{Fcz}=-.64, r_{Cz}=-.68, p<.0056, BH-corrected). N400 values showed positive correlations with task performance with respect to the metaphoric sentence type (r_{Fz}=.59, p<.0056, BH-corrected, r_{Cz}=.48, p<.05, uncorrected). In addition, there was a marginal positive correlation between metaphor ratings (meaningfulness scale) and the N400 at Cz (r_{Cz}=.50, p<.05, uncorrected). Neither P200 nor relative N400 values correlated significantly with Digit Span performance or the MWT-B score.

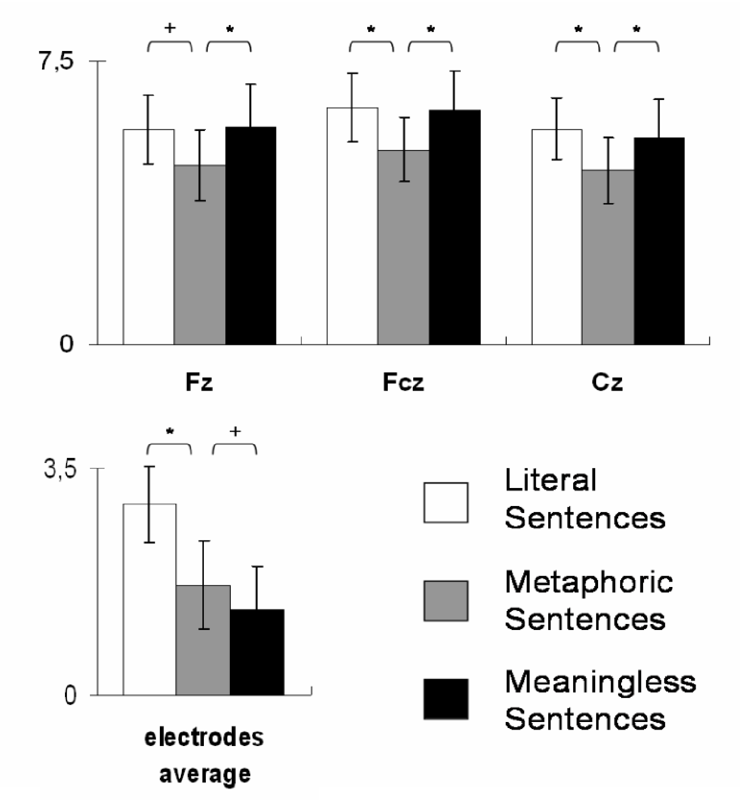

Figure 16. *Upper panel:* Mean values of P200 amplitudes for the three sentence types over the central electrode line (Fz, FCz, Cz). *Lower panel:* Mean values of N400 amplitudes for the three sentence types averaged over the nine electrode positions (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4), reflecting the main effect of sentence type for the mean N400. Error bars represent standard errors (SE). (*) indexes significant differences between mean amplitudes (p<.05), (+) indicates a statistical trend (p<.10).

3.1.4.3 NIRS Data

One-sample t-tests revealed significant O_2Hb concentration increases against baseline for all ROI channels for each sentence type and hemisphere ($2.07<t<3.74$; $.0033<p<.05$, BH-corrected) except for channel 4, right hemisphere for the meaningless stimuli ($t(19)=1.55$, $p=.13$).

Figure 17A shows *t*-maps of the difference in O_2Hb concentration between the peak value and the corresponding pre-stimulus baseline exemplarily for the literal condition. Differential O_2Hb peak values for literal versus meaningless and metaphoric compared to both literal and meaningless phrases are depicted in Figure 17B. In detail, for the left anterior ROI, the univariate AVOVA for repeated measures revealed a significant effect of sentence type ($F(2,38)=6.58$, $p<.01$, $\eta^2=.26$) whereupon post-hoc *t*-tests resulted in significantly higher O_2Hb peak values in the metaphoric compared to the meaningless sentence condition ($t(19)=3.66$, $p<.01$) and also compared to the literal condition ($t(19)=2.36$, $p<.05$). Also regarding the left posterior ROI, the conducted ANOVA showed a significant main effect of sentence type ($F(2,38)=3.11$, $p<.05$, $\eta^2=.14$). This time, O_2Hb peak values were significantly higher for both the literal and the metaphoric compared to the meaningless condition ($t_{literal\text{-}meaningless}(19)=2.26$, $p<.05$; $t_{metaphoric\text{-}meaningless}(19)=2.29$, $p<.05$). With respect to the right hemisphere, univariate ANOVAs did not show main effects of sentence type, neither for the anterior ROI ($F(2,38)<1$; $p=.83$), nor for the posterior ROI ($F(2,38)=1.76$; $p=.19$).

Correlations. Regarding the association of NIRS data and behavioural data, O_2Hb peak values did not correlate significantly with task performance or quasi RTs in any of the ROIs. Correlation analyses conducted in order to assess the relationship between NIRS data and neuropsychological measures as well as the metaphor ratings solely revealed a significant negative correlation between performance in the backward version of the Digit Span and O_2Hb peak values in both the left frontal and the left posterior ROI for metaphoric sentences ($r=-.61$, $p<.01$, BH-corrected. Moreover, backwards Digit Span performance tented to correlate with O_2Hb peak values for the meaningless sentence condition ($r=-.49$, $p<.05$, uncorrected).

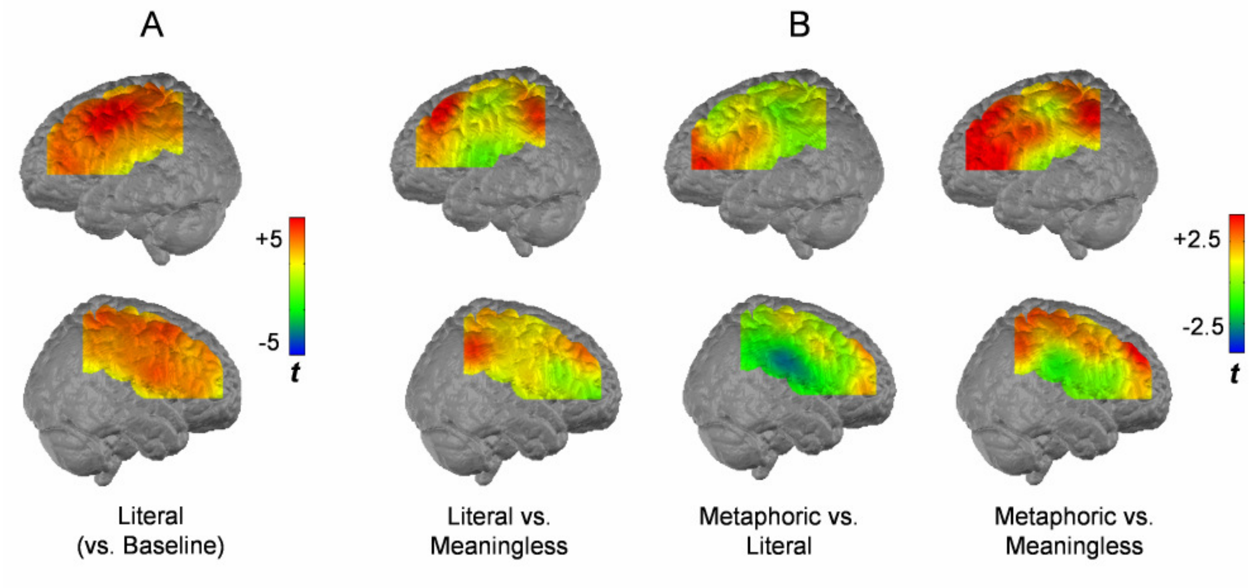

Figure 17. Illustration of O_2HB concentration changes in the literal sentence condition (A), and B: contrast maps indicating relative O_2HB concentration increases for literal compared to meaningless and metaphoric compared to literal as well as to meaningless phrases.

3.1.4.4 Relationship between haemodynamic responses and ERPs

Pearson's correlation coefficients between ERP amplitudes and O_2Hb concentration peak values were calculated only for left-hemispheric ROIs as only they showed significant haemodynamic response modulations by sentence type. There were significant negative correlations between P200 amplitudes at Cz and Fz and O_2Hb peak values in the left posterior ROI ($r_{FZ}=-.53$; $r_{CZ}=-.46$, $p<.05$, BH-corrected) only in the metaphoric sentence condition.

3.1.5 Discussion

3.1.5.1 Behavioural Data

Behavioural data analyses suggest that metaphoric meanings were significantly harder to correctly process compared to both literal and incongruous items which was expressed in longer quasi RTs and reduced accuracy for metaphoric sentences. Enhanced quasi RTs are interpreted in terms of an aggravated decision concerning sentence meaningfulness for the metaphoric compared to the other two sentence conditions, which may be explained by a stronger ambiguity for metaphoric sentences regarding their meaningfulness. Unlike in Iakimova et al. (2005), the present study used newly created metaphoric phrases which could explain the contrary results compared to Iakimova et al. who reported equal RTs between literal phrases and conventional, highly familiar metaphors (see also Desai, Binder, Conant, Mano & Seidenberg, 2011; Giora, 1997). This interpretation is supported by findings reported by Coulson and Van Petten (2007), De Grauwe et al. (2010), and Lai et al. (2009) who also demonstrated longer reaction times and/or reduced accuracy with respect to the meaningfulness judgements for novel metaphors compared to literal sentences.

3.1.5.2 ERP Data

Analyses of the ERP data revealed two major findings. First, ANOVAs yielded a left-frontally pronounced P200 amplitude which was more positive for literal and incongruous (i.e. meaningless) compared to metaphoric sentence endings. Second, mean N400 values differed across sentence conditions, with a linear increase in amplitudes from literal over metaphoric to meaningless phrases.

The former finding suggested a frontal P200 amplitude that was more positive for literal and incongruous compared to metaphoric sentence endings. This finding does not confirm our hypothesised effect (literal>metaphoric/meaningless), rather suggesting a metaphor-specific effect, as expressed by the attenuated P200 peak, occurring at an early stage of sentence processing. Therefore, the P200 effect observed in the present study is not compatible with the assumption that the P200 may reflect the predictability of the sentence endings. Considering the analogue effect of sentence type on the behavioural outcomes (quasi RTs, accuracy), we instead suggest that here the P200 reflects the ease of decision making in the meaningfulness judgement task (cf. Landi & Perfetti, 2007; see also below). As described above, subjects had more difficulties comprehending novel metaphors and thus judging them correctly as 'meaningful' due to their ambiguity, whereas literal as well as incongruous sentences were more likely to be fast and correctly judged as either making sense or not. The attenuated P200 amplitude that was observed for metaphors compared to the, concerning their meaningfulness, easily distinguishable literal and senseless phrases indicates that semantic processing already occurs at an early stage of language processing, manifested prior to the most commonly focused N400. This early step might be related to a broad, undifferentiated sentence comprehension, such as the first impression of whether a read sentence could make sense or not, whereby later components of the ERP (e.g. the N400) would rather reflect a more elaborate processing of semantic content, i.e. later-stage contextual integration (Gunter, Jackson & Mulder, 1995; Holcomb, 1993), which is further suggested to depend on working memory capacity (Gunter et al., 1995). This interpretation is supported by differential relationships of the P200 and the N400 to behavioural task performance: Whereas higher P200 peaks were associated with faster meaningfulness judgements, more negative N400 peaks for metaphoric sentences were associated with decreased metaphor comprehension. The former finding supports the interpretation of the P200 as an early marker for broad sentence classification, because faster classifications were related to enhanced P200 amplitudes. Hence, while increased N400 peaks for metaphoric sentences seem to reflect difficulties in the conceptual mapping process of metaphoric language in order to correctly interpret its meaning (see below), the P200 may represent early language classification processes.

Up till now, comparatively few studies have discussed the specific role of the P200 in semantic processing as this component has been primarily assessed in studies on the first and second level of language processing, i.e. the stage of lexical access and lexical selection at the word level, respectively (e.g., Dambacher et al. 2006; Federmeier et al. 2000). One study that directly focussed on effects of semantic relatedness on the P200 amplitude reported diminished P200 values for word pairs that were semantically unrelated in contrast to related items especially in highly-skilled comprehenders during a semantic decision task (Landi & Perfetti, 2007). These results are in line with the predictability approach, according to which P200 decreases reflect a feature mismatch of predicted and upcoming words. However, the results would also be in accordance with our interpretation of the P200. Whereas, in word pairs, semantically related items (e.g. cat-dog) can be easily judged as related or unrelated, categorically related items (e.g. banana-tomato) are associated with somewhat more uncertainty and unrelated items (e.g. bear-truck) with even more uncertainty concerning this decision due to a lacking context. Our interpretation is also in line with findings reported by Federmeier et al. (2000) who observed left-frontal P200 amplitudes for unambiguous verbs occurring in an appropriate context that were diminished or even suppressed for ambiguous words, indicating that the P200 may reflect lexical ambiguity at word level. At sentence and discourse level, novel metaphors may also cause ambiguity at an early, perceptual categorization process. This early processed ambiguity might then affect the meaningfulness judgement of novel metaphors, as here – unlike in conventional metaphors – the (wrong) literal interpretation needs to be inhibited in favour of the non-literal sentence meaning (Glucksberg, Newsome & Goldvarg, 2001). In contrast, CWs which are clearly unrelated to the preceding sentence context do not leave space for such an ambiguity as reflected by a distinct positivity similar to that observed for literal sentence meanings. In line with this interpretation of the P200, Evans and Federmeier (2007) suggest that the P200 is sensitive to higher order perceptual mapping processes "that occur when a stimulus is being compared with mental representations that were either stored in memory or built from a linguistic context" (Evans & Federmeier, 2007, p. 1781). In line with our interpretation, Wlotko and Federmeier (2007) confirmed that P200 values do probably not index expectancy of the CW, but rather an alignment of context information with upcoming words. In case of novel metaphors, this alignment is apparently associated with ambiguity regarding meaningfulness judgements resulting in an attenuated P200.

ERP analyses further revealed a linear relationship of the three sentence categories with respect to the N400, indicating highest amplitudes for meaningless phrases, followed by metaphors and lowest peak values for literal sentences. Hence, our results replicate previous findings investigating N400 effects caused by unconventional metaphors (Coulson & Van Petten, 2002, 2007; de Grauwe et al., 2010; Lai et al., 2009; Pynte et al., 1996) and therefore emphasise the proposed functional meaning of the N400 as an indicator for the difficulty in conceptual mapping during language perception. This interpretation is also in line with the N400 effect caused by incongruous sentence endings, which by nature evoke a maximum of difficulty in the activation of conceptual knowledge associated with the upcoming word meaning. Additional support for the conceptual model of the N400 is provided by behavioural data, especially metaphor recognition accuracy. Our sample showed marked interindividual differences with respect to metaphor categorization performance, a finding that is consistently reported in the metaphor comprehension literature (Blasko, 1999; Blasko & Kazmerski, 2006; Humphrey, Bryson & Grimshaw, 2010). Interestingly, the N400 did not correlate with verbal IQ (indexed by MWT-B performances) indicating that the N400 effect can be seen as fairly specific and is not strictly linked to verbal intelligence. A marginal positive correlation between the N400 after metaphors and mean metaphor meaningfulness ratings further indicated that subjects with a better understanding of figurative meanings tended to show less negative N400 values. Moreover, the N400 amplitude was correlated with performance in the meaningfulness judgement task particularly for metaphoric sentences. This relationship is further in accordance with the idea that the N400 reflects conceptual mapping: Enhanced N400 amplitudes, representing increasing difficulties regarding this mapping process, were associated with increased erroneous judgements of metaphors as meaningless which can be seen as a behavioural result of these increased difficulties in mapping incoming word meanings and existing conceptual domains.

3.1.5.3 NIRS Data

Analyses of the simultaneously recorded NIRS data assessing regional cortical haemodynamic changes revealed the following major findings: Firstly, sentence processing triggered significant O_2HB concentration increases (as reflected in positive O_2HB concentration peak values) in the predefined cluster of NIRS channels reflecting an anterior-frontal and a more posterior temporal ROI. According to probabilistic spatial registration of our NIRS data, these regions were, at least partly, assigned to Broca's and Wernicke's areas. Second, we observed a distinct activation pattern within these ROIs depending on the sentence type that was presented. Over the left hemisphere, notably higher O_2HB peak values were observed in response to literal compared to unrelated CW, reflecting the process of semantic comprehension of literal, meaningful sentences. Most interestingly, metaphors also elicited significantly higher O_2HB peak values compared to meaningless phrases and, with respect to the left frontal ROI (Broca), compared to literal sentences as well. This result confirms our prediction and indicates a differential activation pattern for metaphors in the left lateral prefrontal cortex (PFC). In more detail, this differential O_2HB increase in both the literal and metaphoric compared to the meaningless sentence condition can be regarded as the neurophysiological correlate of semantic (meaning) processing which does, by nature, not take place for meaningless phrases. This result is in line with findings demonstrated in fMRI studies indicating a key role of the lateral PFC for comprehension of novel metaphoric (Mashal et al., 2007; Rapp et al., 2012; Shibata, Abe, Terao & Miyamoto, 2007) and other non-literal (Rapp et al., 2012; Rapp & Wild, 2011) stimuli in contrast to meaningless sentences. Our results further suggest an additional mechanism reflecting a difference between literal and figurative language perception, both forms of meaningful language. With respect to left Broca's area, metaphors elicited higher O_2HB peak values than literal phrase meanings. In line with fMRI (Rapp et al., 2012) and source localisation research (Arzouan et al., 2007), this finding may indicate a metaphor-specific increase in oxygen requirement in a circumscribed region of PFC that might reflect the recruitment of additional cognitive resources. These additional cognitive resources may be required in order to perform the, in case of metaphoric compared to literal meaning, aggravated conceptual mapping (Coulson & Van Petten, 2002, 2007; Kutas & Federmeier, 2011; Lai et al., 2009; Lakoff, 2008; Lakoff & Johnson, 1980a). This interpretation is further supported by the significant correlation between working memory performance and oxygenation increases within the left Broca area for metaphoric sentences. The positive correlation confirms that the abstraction of figurative meaning requires working memory capacities (Monetta & Pell, 2007; Pierce, MacLaren & Chiappe, 2010b; Prat et al., 2012).

3.1.5.4 Relationship between neural and haemodynamic responses

In order to unravel the relationship of the haemodynamic and the electrophysiological data assessed during language perception, we conducted bivariate correlation analyses between the haemodynamic responses and amplitude values of the examined ERP components (P200, N400). Although Pearson's correlation coefficients indicated a negative relationship between the P200 peaks and mean O_2HB concentration peak values in both the left Broca and the left Wernicke area for metaphoric phrases, only the correlation between the metaphor related P200 and activity in the Wernicke area was actually significant. In other words, attenuated P200 amplitudes were associated with a more pronounced increase in O_2HB peaks during metaphor perception within this brain region, which may reflect enhanced activation in areas relevant for semantic processing in subjects exhibiting deficits in bottom-up related processes during lexical perception of metaphoric phrases. Considering our interpretation of the P200 as an indicator of the ease of decision making in lexical meaningfulness judgements, our findings suggest that difficulties in the initial sentence classification in terms of meaningfulness, which may strongly vary across individuals, require an enhanced recruitment of neurons within Wernicke’s area. Wernicke’s area represents a crucial region for language perception and understanding. Therefore, the detected relationship seems quite reasonable.

As differential activation increases for metaphoric versus literal sentences were observed only in left Broca’s area, we suggest that abstraction of figurative meaning was related to activity of this region. Therefore, one could expect the N400, a potential marker of conceptual mapping, to correlate with Broca activity. However, no significant correlation was observed. We conclude that the abstraction and comprehension of figurative meaning includes several complex processes and can therefore not clearly be assigned to one isolated brain region or ERP. The significant correlation between left-posterior cortical activity and metaphor-specific attenuation of the P200 amplitude may represent a first step in elucidating this complex entity of probably interacting processes.

3.1.6 General conclusions & future perspectives

The present study intended to provide a holistic view of the perception, comprehension, and the neural representation of metaphoric language as a special form of pragmatic language. For the first time, the effects of figurative language perception on early neural markers (N400 and P200) and their possible functional interpretation in this context have been investigated by means of a combined application of EEG and NIRS. Our findings suggest a metaphor-specific neural response that seems to be related to the plausibility judgement of figurative expressions. Whereas the process of conceptual mapping appears to be represented by changes in the fairly well explored N400 amplitude of the ERP, the comprehensibility judgement was depicted in the P200 component that was itself connected to haemodynamic concentration changes within left Wernicke's area. This link between variations in neural activity (P200) and haemodynamic changes within Wernicke's area may reflect processes related to interindividual differences regarding the ability to comprehend novel metaphors. Therefore, combined EEG-NIRS measurements represent an innovative approach to investigate interindividual differences and possible alterations in pragmatic language processing, e.g. in clinical samples, quickly and easily. Hence, this study emphasises the usefulness of simultaneous EEG-NIRS measurements in language paradigms, particularly to investigate the functional significance of neurophysiological markers that have so far rarely been examined, as they allow for a complementary examination of neural activity and associated metabolic changes in cortical areas.

In future studies, the present findings may be, firstly, integrated into state-of-the-art models of semantic knowledge representation, whereby distinct neurophysiological markers of the (meaningfulness) *classification* versus (meaning) *interpretation* of metaphoric language might be better distinguished. It might be of interest, for example, if these two concepts exhibit a different time course during both normal and pathological development (developmental approach) or how they can be utilised for an improvement of natural language production in human-computer-interaction (production approach). Second, the present integrative investigation of neural and haemodynamic correlates of figurative language comprehension may be used to elucidate pathological alterations of brain activity during different stages of pragmatic language processing in clinical samples. Hereby, recent progress in the field of both computational linguistics and neuroimaging methods will surely help to conduct well-controlled and methodologically sophisticated studies.

3.2 Study 2

Neurophysiological markers of deficient pragmatic language comprehension in schizophrenia measured with simultaneous EEG/NIRS

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3.2.1 Abstract

Objectives: The present study aimed at investigating neurophysiological markers of language perception in schizophrenia using simultaneous near-infrared spectroscopy (NIRS) and event-related potentials (ERPs) applications, which have been proven to be useful for studying language processing abilities in psychiatric patients. The study shall clarify heterogeneous findings from previous ERP and fMRI studies on figurative language comprehension in schizophrenia and elucidate how neural and haemodynamic markers of language processing are related.

Methods: 22 healthy subjects and 22 schizophrenia patients judged 120 sentences regarding their meaningfulness. Phrases were literal, metaphoric, or meaningless. EEG/NIRS signals were recorded throughout the entire experiment.

Results: Schizophrenia patients showed deficient and delayed sentence comprehension. Both the early N400 and left-hemispheric activation during language comprehension were altered in patients. Correlation analyses showed that metaphor-related ERPs were strongly linked to haemodynamic cortical activity in healthy subjects, but not in patients.

Conclusion: Our results indicate group differences in cortical neural and haemodynamic activation that represent rather general impairments in the processing of complex language. Simultaneous EEG/NIRS applications are useful to depict these neurophysiological markers and to investigate their relationship. Future studies are needed to clarify the nature of respective anomalies and their potential as putative biomarkers in schizophrenia research.

3.2.2 Introduction

Language perception deficits constitute frequent impairments in schizophrenia and they have been strongly linked to cognitive dysfunctions (e.g. Thoma et al., 2009), social functioning (e.g. Bowie, Gupta & Holshausen, 2011), quality of life (e.g. Ulas, Akdede, Ozbay & Alptekin, 2008) and general functionality (e.g. Wilcox, Winokur & Tsuang, 2012) of patients. One specific type of language comprehension deficit in schizophrenia refers to difficulties in correctly interpreting and understanding non-literal speech, known as schizophrenic concretism (Kircher, Leube et al., 2007; Strobl & Resch, 1988). The concrete (literal) misinterpretation of metaphoric meanings leads to a failure of understanding the intended message, which may cause severe communication problems as metaphoric speech is frequently used in our everyday language (Lakoff & Johnson, 1980a; Pollio et al., 1977).

At the neural level, different neurophysiological correlates have already been identified in healthy as well as clinical populations. On the one hand, event-related potentials (ERPs) represent a commonly used methodological approach to measure time-resolved neuro-functional processes that occur during the perception of speech, such as auditory encoding or reading of syllables, words, phrases or narratives. People with schizophrenia have been lengthly reported to show alterations of the N400 ERP (Kutas & Federmeier, 2011; Kutas & Hillyard, 1980, 1983) during different types of semantic processing (Mohammad & DeLisi, 2013; Wang, Cheung, Gong & Chan, 2011) including figurative language comprehension (Iakimova et al., 2005; Strandburg et al., 1997). Hereby, however, perception deficits for figurative language in schizophrenia are far less understood than the most frequently investigated semantic priming impairments. In a first study addressing metaphoric meaning perception, Strandburg et al. (1997) demonstrated an increased N400 potential to figurative and literal word pairs together with a lacking N400 difference between meaningless and literal or metaphoric and literal meanings (the so-called N400-effect) in schizophrenic patients. In contrast, in a more recent study, Iakimova and colleagues showed a preserved N400 effect for unrelated/meaningless compared to meaningful (both literal and metaphoric) sentence endings in schizophrenic patients, whereby N400 values were overall more negative in patients vs. controls. These two rather conflicting findings, which may be based on different symptom profiles (Kuperberg et al., 2010) or different linguistic materials (Iakimova et al., 2005) used in both studies, emphasise the so far poor evidence on electrophysiological markers of altered figurative language comprehension processes in schizophrenia. Moreover, ERP studies conducted so far neglected early neural parameters (i.e. ERPs occurring prior to the N400) of pragmatic sentence comprehension. In a previous study on healthy participants, our own group identified the P200 as a potential index for ambiguity in sentence processing, with lower P200 peaks for more ambiguous (regarding sentence meaningfulness) novel metaphors as compared to literal sentences and clearly meaningless phrases. It should be clarified whether such early parameters may be altered in schizophrenia and could therefore complement present neuropsychologic research.

Another opportunity to identify cerebral markers of metaphoric content processing in schizophrenia is provided by imaging techniques depicting haemodynamic responses to semantic processing within certain brain regions. So far, different studies using functional magnetic resonance imaging (fMRI) have addressed brain activation patterns related to figurative language perception. Focusing on healthy subjects, a recent meta-analysis indicated that left prefrontal and temporal structures, including the inferior frontal gyrus (IFG)/Broca's area, Wernicke's area, and the parahippocampal gyrus, show strongest activation increases after figurative language perception (Rapp et al., 2012). Addressing the neural basis of schizophrenic impairments in non-literal language comprehension, fMRI studies have so far revealed anomalies regarding hemispheric lateralization of cerebral activation (Kircher et al., 2001; Mitchell & Crow, 2005) as well as lateral prefrontal (left IFG) and temporal (right superior temporal cortex; STG) dysfunctions (Kircher, Leube et al., 2007; Mashal et al., 2013).

Again, however, the findings reported in these studies do not draw a uniform picture. For example, Kircher and colleagues (2007) found decreased signal changes in schizophrenia patients for novel metaphors in the right superior/middle temporal gyrus. Mashal et al. (2013) did not replicate this finding. They even reported MTG activation increases in patients when conventional metaphors were processed. Moreover, the same group reported on hyperactivity of medial frontal areas in patients during novel metaphor processing, whereas Kircher et al. found that different sub-areas of the inferior frontal gyrus were activated between patients and controls.

Importantly, such heterogeneous and partly even contradictory findings hamper the usability of these neural markers of pragmatic language processing as potential biomarkers. While for more basal semantic operations at word level both N400 and Broca activity alterations have been separately proposed as endophenotype candidates in schizophrenia (Cermolacce, Micoulaud-Franchi, Faugere, Naudin, Besson & Vion-Dury, 2013; Li, Xia, Bertisch, Branch & DeLisi, 2012; Shin et al., 2008), an analogous use of these parameters in the context of complex, pragmatic language processing is doubtful in light of inconsistent results from both ERP and fMRI research. Studies combining neural (i.e. electrophysiological) and haemodynamic measures of pragmatic language processing may help to elucidate the so far heterogeneous findings on figurative language comprehension in patients with schizophrenia by providing a more holistic view on respective (dys-)functions. Because simultaneous EEG-fMRI measurements are linked to a number of technical and practical obstacles, combined EEG-fNIRS (functional near-infrared spectroscopy) measurements may be particularly useful, especially when sensitive groups of participants (such as psychiatric patients) are to be assessed. In fact, such measurements have been proposed to be especially useful in language studies (Dieler et al., 2012; Horovitz & Gore, 2004; Wallois et al., 2012).

To this end, the present study aims at investigating neurophysiological markers (P200/N400 potentials, IFG and/or STG activation) of non-literal (here: metaphoric) language processing using combined EEG-fNIRS measurements in patients with schizophrenia. With respect to electrophysiology, the study shall 1) clarify the so far conflicting N400 findings for metaphoric language comprehension in schizophrenia and 2) target early neural markers of language processing (P200) that have not yet been addressed in this context. Regarding cerebral haemodynamics, the present investigation shall clarify prefrontal and posterior-temporal activation patterns in schizophrenia patients as compared to healthy controls.

3.2.3 Materials and Methods

3.2.3.1 Subjects

22 healthy subjects (10 male, mean age: 30±12 years) and 22 patients diagnosed with schizophrenia (15 male, mean age: 35±12 years), were enrolled in the study. All participants gave written informed consent after the study had been elaborately explained. Permission for the study was obtained from the local Ethics Committee of the medical faculty, University of Tuebingen, prior to the recruitment phase, and all study procedures were in line with the latest version of the Declaration of Helsinki.

Healthy subjects were recruited at the Department of Psychology and the University Clinic Tuebingen. Two thirds of the healthy control subjects were adopted from our previous study (Schneider, Rapp et al., 2014). Patients (21 inpatients, one outpatient) were recruited at the Department of Psychiatry and Psychotherapy, University Hospital Tuebingen and were diagnosed with paranoid ($n=17$), disorganised ($n=2$), or catatonic schizophrenia ($n=1$), or brief psychotic disorder ($n=2$) by an experienced psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders, version 4 (American Psychiatric Association, 2000). Groups did not differ with respect to sex ($\chi^2=1.28$, $p>.20$), age, years of education, and working memory ability measured via the digit span test

($0.79<t<1.55$, $p>.10$). General exclusion criteria were sinistrality (as assessed by the dinburgh Handedness Inventory (EHI; Oldfield, 1971)), pregnancy, and current, chronic as well as untreated severe somatic or neurological conditions. Additional exclusion criteria for the control subjects were present psychiatric illnesses, while schizophrenic patients were excluded if they had one or more of the following severe comorbid psychiatric disorders: obsessive-compulsive disorders, eating disorders, severe major depression, bipolar affective disorders, or a borderline personality disorder.

3.2.3.2 Material

The stimulus set consisted of three different sentence categories: (1) literal and meaningful, (2) metaphoric and meaningful, and (3) meaningless, with each sentence type comprising 40 sentences. Literal, metaphoric and meaningless sentences differed only in their endings, including the last one to three words (critical word(s); CW) of a sentence (see Figure 2 for example sentences). Sentence categories were matched for grammar, tense, syntactic structure, as well as number of words, CW length, and CW frequency (each $F(2,78)<1$, n.s.). Notably, all metaphoric stimuli were novel and therefore non-salient. Stimulus novelty was confirmed by the linguistic corpus DEREKO and the web platform COSMASII web corpus (2014).

3.2.3.3 Experimental Task

Measurements took place in a sound-attenuated, electrically shielded room at the Psychiatric University Clinic Tuebingen. Participants were seated approximately 80 cm in front of a computer screen. They were instructed to read all sentences attentively and silently and judge whether a presented phrase made sense or not. Sentences were presented in white color on a black background word-by-word in randomised order (word presentation time: 400 ms; interstimulus interval: 500 ms; jittered interphrase interval: 4000-7000 ms (see, e.g., Richter et al., 2009; Schneider, Christensen, Haeussinger, Fallgatter, Giese & Ehlis, 2014; Tupak et al., 2013)). Following each sentence (and a subsequent blank screen of 750 ms) a question mark on the screen centre indicated that meaningfulness judgements should be given via button press with the right index finger and middle finger, respectively (with key assignment counterbalanced across participants). 6 sentences (two per category) which were not presented during the main experiment were used as practice trials. The main experiment consisted of 40 trials per sentence category, leading to a total number of 120 sentences and an experimental duration of approximately 25 minutes (one break included).

3.2.3.4 Neurophysiological Assessment and Metaphor Comprehension

Prior to the actual experiment, all subjects performed two neuropsychological tests, the "Digit Span" (Wechsler, 1997) to assess working memory capacity and the "MWT-B" ("Mehrfachwahl-Wortschatz-Test", version B; Lehrl et al. 1995) to measure verbal intelligence.

To measure general ability to correctly interpret common German proverbs that include metaphoric expressions, a multiple choice proverb-metaphor test (Barth & Küfferle, 2001) was applied comprising 15 metaphoric proverbs, with five different interpretational choices provided for each proverb (response type I: abstract and meaningful (correct); type II: meaningful but partly concrete; type III: meaningful and entirely concrete; type IV: meaningless and concrete; type V: meaningless and abstract). The frequency of a given response type provides the basis for further statistical analyses (see statistics section).

In the patient sample, current psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein & Opler, 1987).

3.2.3.5 Electrophysiological Recordings

EEG was recorded from 21 scalp electrodes embedded in an elastic cap (Easycap GmbH, Munich, Germany) and placed according to the International 10/20-System (Jasper, 1958; see Figure 18B). The ground electrode was placed on the forehead and FCz was used as recording reference. To identify eye movement artifacts, EOG activity was recorded from three additional electrodes, one placed below the right eye, two placed at the lateral canthi of both eyes. Two mastoid electrodes were applied for subsequent offline re-referencing. Electrode impedances were kept below 5 kΩ. All physiological data were digitalised at a rate of 1000 Hz and filtered online at 0.1-100 Hz.

3.2.3.6 Near-Infrared Spectroscopy (NIRS)

NIRS measurements were conducted with the ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) using two separate 22-channel arrays of optodes (8 sources/emitters, 7 detectors per array; 30 mm source-detector distances) covering fronto-temporo-parietal areas on the left and right side of the head. NIRS channels are located in the middle between each source-detector pair. Sources emitted near-infrared light of two wavelengths (695 and 830 nm). Optodes were attached to the subject’s head by plastic optode holders that were integrated in the elastic EEG cap (Figure 18A). This procedure guaranteed a stable NIRS channel placement across recordings according to the international 10/20 system on heads with average occipitofrontal head circumferences of 54-58 cm. The first channel of the bottom row (located in between the first two optodes of that row) was located over F7/F8 on the left and right side of the head, respectively (see Figure 18A & 18C).

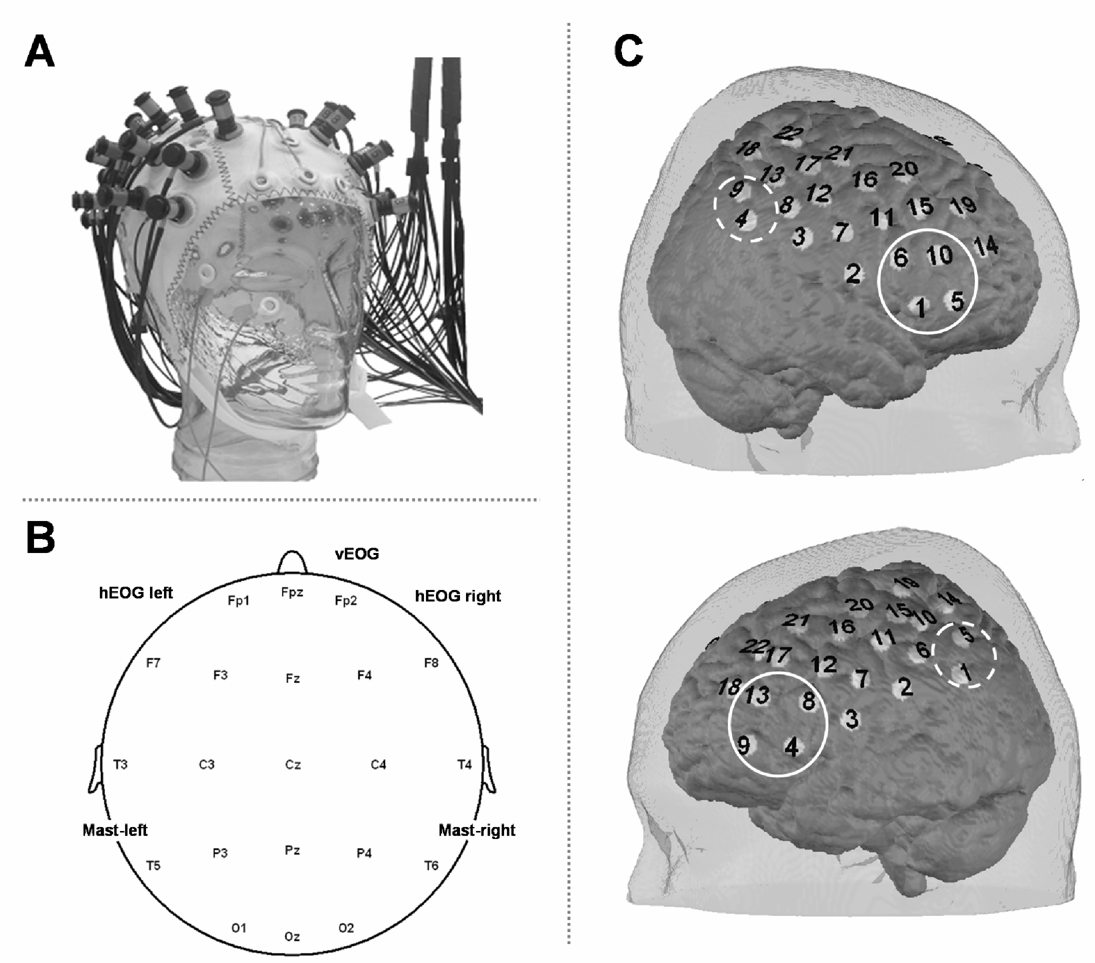

Figure 18. (A) Picture of the combined EEG-NIRS cap used in the present experiment (prototype provided by Hitachi Medical Co., Japan). (B) Placement of the EEG-electrodes according to the international 10/20 system (Jasper, 1958). Mast=mastoide channels; vEOG=vertical electroocologram; hEOG=horizontal electroocologram. (C) Illustration of NIRS channel positions on the human cortex according to the results of the neuronavigation procedure. Solid circles indicate the channels forming the left and right frontal region of interest (ROI); dashed circles show the channels that formed the left and right posterior ROI, respectively.

3.2.3.7 Data Analysis

After visual inspection of the EEG, data were band pass filtered at 0.1-40 Hz (24 db/oct). Eye movement artifact correction was performed (Gratton et al., 1989) and data were re-referenced to linked mastoids. Stimulus-locked epochs beginning 150 ms before and extending 1000 ms beyond the CW of each sentence were then created separately for the three sentence conditions (literal/metaphoric/meaningless). Only trials with correct meaningfulness judgements were analysed (minimum correct trial number/category: 15). After artifact rectification (excluding segments containing either amplitudes >±70 µV, voltage-steps >70 µV/ms, or slow amplitude changes <0.1 µV/100 ms) and averaging of the stimulus-locked segments per category, baseline correction within 150 ms prior to stimulus onset was performed. For the P200, peaks were individually determined at frontal (F3/Fz/F4) and central (C3/Cz/C4) electrode positions within defined time-windows that were derived from both previous literature and visual inspection of the present datasets (170–270 ms). In line with N400 literature (Duncan et al., 2009), mean amplitude values within a predefined time window (280-500 ms) were exported for frontal (F3/Fz/F4), central (C3/Cz/C4), and parietal (P3/Pz/P4) sites. Because the present ERP data, especially within the patients group, revealed a "double-peak pattern", N400 amplitudes were analysed within an early (280-380 ms) and a late (380-500 ms) time window, as also described in previous literature (Chwilla & Kolk, 2003; de Grauwe et al., 2010; Lai et al., 2009; Yang & Xue, 2011).

With the ETG-4000, changes in the concentration of oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb) were continuously recorded from a 10 s starting baseline throughout the language paradigm (sampling rate: 10 Hz). Signals were analysed and transformed according to their wavelength and location, resulting in values for the changes in O_2Hb and HHb concentration per channel.

Following band pass filtering (.008-.25 Hz), 16 s segments of each of the three conditions were averaged and corrected with respect to a 2 s pre-stimulus baseline using MATLAB (The MathWorks Inc., Natick, USA). Like in our previous study (Schneider, Rapp et al., 2014), maximum positive and negative peak values of the haemodynamic responses within 4-10 seconds following the CW were detected and subsequently analysed. For hypotheses-driven data analyses, haemodynamic responses within two a priori defined clusters of NIRS channels (regions of interest [ROIs]) were analysed, with one prefrontal (anterior channels #4, 8, 9, 13 left, channels #1, 5, 6, 10 right) corresponding to Broca's area and one posterior ROI (channels #1, 5, left, channels #4, 9 right) corresponding to Wernicke's area (see Figure 18C). These ROIs were chosen based on the results of a neuronavigation procedure [LOCALITE GmbH, St. Augustin, Germany] as previously described (Schneider, Christensen et al., 2014; Schneider, Rapp et al., 2014).

3.2.3.8 Statistics

First, experimental groups were compared regarding their verbal IQ using students *t*-tests general ability to comprehend metaphoric proverbs as measured by the multiple choice proverb test using nonparametric testing (Mann-Whitney-U). 3x2 ANOVAs for repeated measures comprising the within-subject factor sentence type (literal, metaphoric, meaningless) and the between-subjects factor group (controls vs. schizophrenics) were performed to analyse behavioural data (response accuracy and reaction times).

In order to analyse ERP components, 3x2x3x2 and 3x3x3x2 ANOVAs for repeated measures were conducted for the P200 and relative N400 values, respectively. ANOVAs comprised the within-subject factors sentence type (literal, metaphoric, meaningless), region (P200: frontal, central; N400: frontal, central, parietal) and hemisphere (left, midline, right) as well as the between-subjects variable group. Partial eta squares (η^2) are provided as a measure of effect size. In case of significant interaction effects, subsequent ANOVAs were calculated separately for each sentence type, region, hemisphere, or group, respectively. The Huynh-Feldt procedure was used to correct the degrees of freedom whenever Mauchly's test of sphericity revealed significant results ($p<.20$). In case of a significant main effect of sentence type, *t*-tests for paired samples were conducted comparing mean ERP values of each of the three sentence categories.

Regarding the statistical analysis of the NIRS data, only O_2Hb concentration values are reported.[22] 3x2 ANOVAs for repeated measures were conducted per ROI and hemisphere comprising the factors sentence type (within-subjects) and group (between-subjects). Mean O_2Hb peak values averaged over the respective ROI channels were used as dependent variables. If a main effect of sentence type was observed, paired *t*-tests were used to compare O_2Hb concentration changes between the three sentence conditions.

To test for relationships between electrophysiological and haemodynamic data (i.e., ERPs and O_2Hb peaks), Pearson's correlation coefficients were computed, separately for both experimental groups. For the patient group, neurophysiological data were further correlated with PANSS symptom scores. Two-sided testing procedures were used and Bonferroni-Holm correction was applied.

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[22] HHB values were in accordance with the respective O_2Hb data but were associated with lower statistical power and are, to preserve conciseness, presently unattended.

3.2.4 Results

3.2.4.1 Neuropsychology and metaphor comprehension ability

As for age, gender, or level of education (see methods section), groups did not differ regarding verbal IQ as measured by the MWT-B ($t(26)=1.76$, $p>.05$). However, groups differed significantly regarding the ability to correctly comprehend and interpret novel metaphors and metaphoric proverbs. The Mann-Whitney-U test revealed that type I responses in the multiple choice proverb test (abstract and meaningful) were more frequently chosen by control subjects than by patients ($U=103.5$, $Z=-2.91$, $p<.01$). In contrast, patients tended to give both type II (meaningful and partly concrete) and type III (meaningful and entirely concrete) responses more often ($124.5<U<147.0$, $-2.68<Z<2.51$, $p<.01$) than controls.

3.2.4.2 Behavioural Data

Analyses of a response accuracy ratio (relative frequency of correctly minus incorrectly classified sentences during the sentence classification task) revealed main effects of sentence type ($F(2,84)=101.91$, $p<.001$, $\eta^2=.71$) and group ($F(1,42)=16.92$, $p<.001$, $\eta^2=.29$). Participants responded more correctly to both literal and meaningless phrases compared to metaphoric sentences, and healthy controls showed overall more accurate responses compared to patients (see table 4). A 3x2 ANOVA conducted for RTs confirmed significant main effects of sentence type ($F(2,84)=24.62$, $p<.001$, $\eta^2=.30$) and group ($F(1,42)=6.20$, $p<.05$, $\eta^2=.13$) revealing the same pattern as for accuracy (see table 4).

Table 4. Behavioural data obtained during the sentence classification task and results of respective statistical post-hoc comparisons.

	Healthy Controls M±SD	**Schizophrenia Patients** M±SD	**group comparisons**
Accuracy ratio			
LIT	.92±.05	.78±.18	*t*(42)=4.09, *p*<.001
MET	.39±.42	.10±.36	
ML	.95±.05	.80±.25	
Sentence type comparisons	LIT vs. MET: *t*(43)=10.31, *p*<.001 LIT vs. ML: *t*(43)=-1.15, *p*=.26 MET vs. ML: *t*(43)=-10.01, *p*<.001		
Reaction times (in ms)			
LIT	363±46	479±46	*t*(23)=-2.49, *p*<.025
MET	415±71	552±250	
ML	3715±59	424±152	
Sentence type comparisons	LIT vs. MET: *t*(43)=-6.28, *p*<.001 LIT vs. ML: *t*(43)=-0.39, *p*=.70 MET vs. ML: *t*(43)=4.71, *p*<.001		

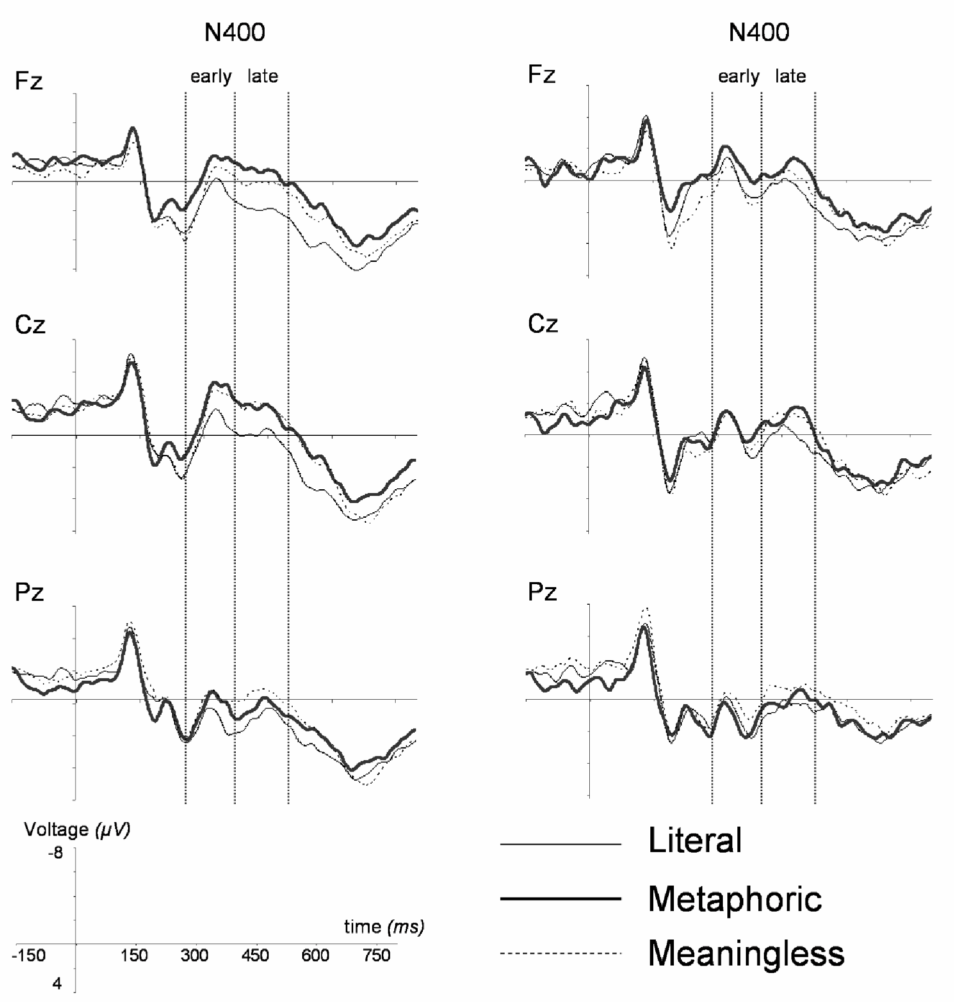
LIT: literal sentences; MET: metaphoric sentences; ML: meaningless sentences.

3.2.4.3 ERP Data

P200. The 2x3x3x2 ANOVA revealed a main effect of sentence type (*F*(2,86)=7.21, *p*<.01, η^2=.14) and a significant region x hemisphere interaction (*F*(2,86)=4.29, *p*<.05, η^2=.09). P200 peaks were lower for metaphoric (*M*=5.19±4.1 µV) compared to both literal (*M*=6.32±4.3 µV, *t*(43)=-3.54, *p*<.01) and meaningless (M=6.30±4.8µV, *t*(43)=-2.93, *p*<.01) sentences. Post-hoc analyses indicated that, while P200 values were equally high at all three positions of the frontal row (F3/Fz/F4; F(2,86)<1, n.s.), there was an effect of electrode at the central line ($F(2,86)=4.38$, $p<.05$, $\eta^2=.09$) with higher P200 peak values at Cz compared to C3 ($t(43)=3.14$, $p<.01$).

N400. For the early time window, the 3x3x3x2 ANOVA revealed significant main effects of sentence type ($F(2,84)=8.02$, $p<.01$, $\eta^2=.16$), region ($F(1,51)=14.72$, $p<.001$, $\eta^2=.26$), and hemisphere ($F(2,84)=18.23$, $p<.001$, $\eta^2=.30$). Moreover, significant interactions sentence type x group ($F(2,84)=4.30$, $p<.025$, $\eta^2=.10$) and region x hemisphere ($F(3,133)=4.86$, $p<.01$, $\eta^2=.11$) were observed. Post-hoc ANOVAs indicated a significant main effect of sentence type on mean N400 peaks solely for controls ($F(2,36)=11.66$, $p<.001$, $\eta^2=.36$), but not for patients ($F(2,38)=1.76$, $p=.20$). For healthy controls, N400 values were more negative for both meaningless (M=1.73±3.38 µV) and metaphoric (M=1.58±3.32 µV) compared to literal (M=2.94±2.95 µV) phrases ($3.61<t<4.54$, $p<.01$), while metaphors and meaningless sentences did not differ ($t(21)=0.56$, $p=.58$). Post-hoc analyses of the region x hemisphere interaction revealed a left-fronto-central pronunciation of the N400 ($5.96<F<15.02$, $p<.01$, $.12<\eta^2<.26$): While the N400 was most negative at central positions across all three (frontal, central, parietal) rows ($1.96<t<6.67$, $p<.05$), N400 values showed a left-central accentuation only at the frontal row ($t_{Fz\text{-}F4}(43)=-4.15$, $p<.001$, $t_{Fz\text{-}F3}(43)=-1.33$, $p=.19$).

For the late time window, main effects of sentence type ($F(2,84)=15.58$, $p<.001$, $\eta^2=.27$) and region ($F(1,58)=7.34$, $p<.01$, $\eta^2=.15$) were found. This time, only the region*hemisphere but not the group*sentence type interaction was significant. For the central and parietal row, N400 amplitudes were most negative at central electrode positions ($2.01<t<3.5$, $p<.05$) while for the frontal row amplitudes were approximately equal at left, central, and right sights ($F(2,86)=1.70$, $p=.19$; cf. Figure 19). Post-hoc t-tests comparing N400 amplitudes after literal, metaphoric, and meaningless phrases revealed that – across groups – N400 values for metaphors and meaningless sentences were both more negative than after literal sentences ($4.70<t<5.19$, $p<.001$) but did not differ between each other ($t(43)=0.05$, $p=.96$).



LIT: The old man is a *doter*. **MET**: The old man is an *oak*.
ML: The old man is a *traffic light*.

Figure 19. Time-locked ERPs at midline with respect to the final sentence word and 150 ms pre-stimulus baseline. Vertical dashed lines indicate the early (280-400 ms) and late (400-500 ms) time window. Exemplary sentences used in the sentence classification task are depicted below the plots (LIT: literal sentences; MET: metaphoric sentences; ML: meaningless sentences).

3.2.4.4 NIRS Data

3x2 ANOVAs for repeated measures revealed a significant effect of sentence type in left Broca's ($F(2,84)=6.95$, $p<.01$, $\eta^2=.14$) and left Wernicke's area ($F(2,84)=3.16$, $p<.05$, $\eta^2=.07$). In addition, significant group effects were observed for left Broca's ($F(1,42)=8.35$, $p<.01$, $\eta^2=.17$), left Wernicke's ($F(1,42)=4.50$, $p<.05$, $\eta^2=.10$) and, in terms of a statistical trend, right Broca's area ($F(1,42)=3.35$, $p=.07$, $\eta^2=.07$), with generally higher O_2Hb peak values in healthy controls (0.011<M<0.017 Mm*mm) compared to patients (0.006<M<0.010 Mm*mm). Post-hoc tests indicated that within left Broca's area, metaphoric sentences were associated with higher O_2Hb values compared to both literal ($t(43)=2.50$, $p<.025$) and meaningless phrases ($t(43)=3.48$, $p<.01$), while for left Wernicke's area lowest O_2Hb peaks were observed for meaningless sentences ($t(43)=2.28$, $p<.05$). Figure 20 displays the haemodynamic response pattern for the contrasts literal vs. meaningless, metaphoric vs. meaningless, and metaphoric vs. literal separately for both experimental groups. No sentence type x group interactions were observed.

3.2.4.5 Correlation Analyses

While, for all sentence types, early as well as late N400 amplitudes tended to correlate with O_2Hb peak values only in Wernicke's area ($-.47<r<-.44$, $p<.05$, uncorrected), we found negative correlations between P200 amplitudes and O_2Hb peak values in both Wernicke's and Broca's area for metaphors ($-.46<r<-.64$, $.0042<p<.05$, BH-corrected) in the control group only (schizophrenia group: $r\leq.43$; $p>.04$ uncorrected).

With respect to psychopathology, O_2Hb peak values (Broca's & Wernicke's area) after meaningless sentences tended to correlate negatively with the subscale "positive symptoms" of the PANSS interview (Broca: $r=-.47$, $p<.05$, Wernicke: $r=-.45$, $p<.05$, both uncorrected). Interestingly, PANSS item P2 which measures formal thought disorders slightly correlated with P200 values after reading metaphors ($r=-.44$, $p<.05$, uncorrected).

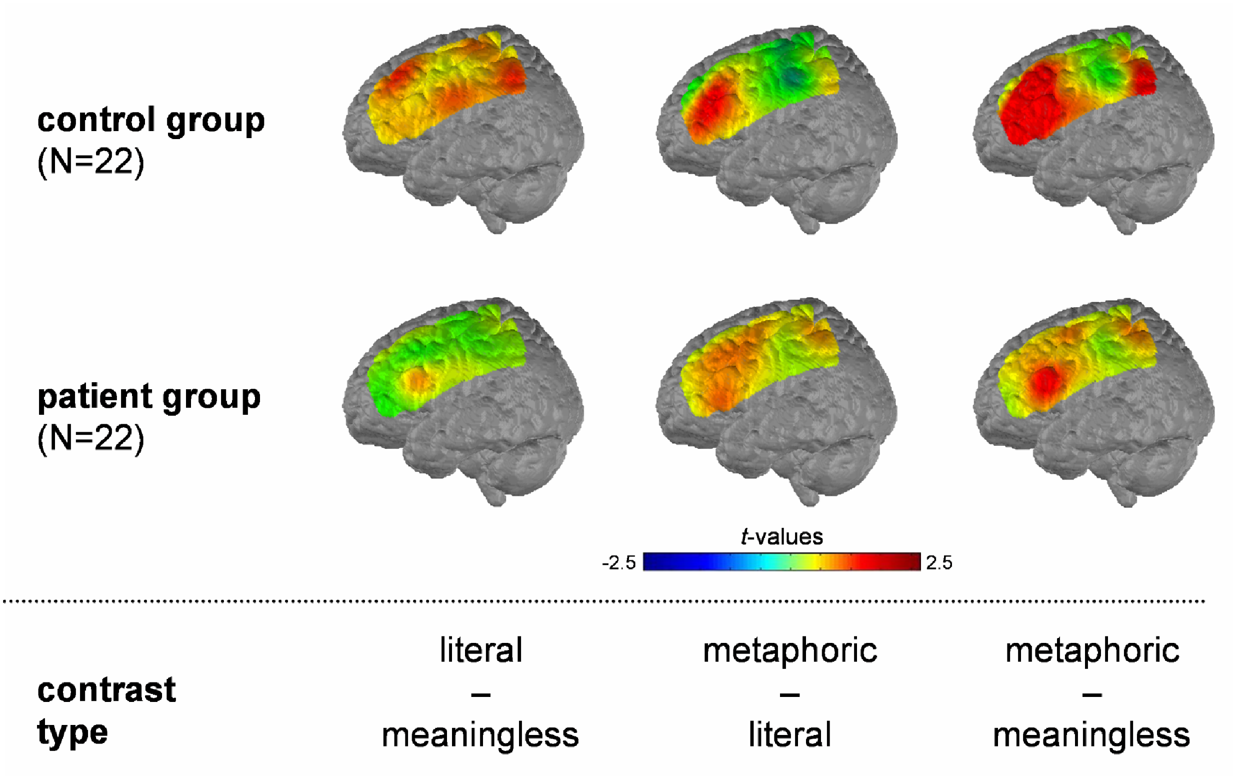


Figure 20. Contrast maps indicating relative O_2HB concentration increases for the following comparisons: literal vs. meaningless phrases (first column), metaphoric vs. literal phrases (second column), and metaphoric vs. meaningless phrases (third column).

3.2.5 Discussion

The present study assessed neurophysiological markers of pragmatic language perception in schizophrenia by means of simultaneous NIRS/EEG measurements during a sentence comprehension task.

Regarding sentence meaningfulness classifications, accuracy decreases and RT increases found in patients appeared most strongly pronounced for metaphoric sentences. However, respective interaction effects did not reach significance. Therefore, the present findings do not particularly support that schizophrenia patients show distinct difficulties in establishing meaning in figurative language (Kircher, Leube et al., 2007; Mitchell and Crow, 2005; Rapp, 2009; Tavano et al., 2008; Titone et al., 2002).

Regarding the ERP data, two basic effects were found: First, a sentence type effect was observed across groups, reflected in reduced P200 amplitudes for metaphoric compared to both literal and meaningless phrases. Second, analyses revealed a significant sentence type x group effect for the early N400, with an N400 effect being evident solely in the control group, whereas in patients N400 peaks were not at all qualified by sentence type. Like in our previous study (Schneider, Rapp et al., 2014), the P200 effect is interpreted in terms of an ambiguity effect on rough sentence meaningfulness classification. Semantic ambiguity, a prominent feature of novel metaphors, may aggravate the meaningfulness judgement, and the resulting difficulty to initially classify a phrase as senseless or not may be reflected in decreased P200 peaks for metaphors. Because patients and healthy controls show a very similar P200 effect, we conclude that patients do not differ from healthy subjects concerning this early processing of semantic ambiguity. The N400, which is in contrast associated with the mapping and integration of a word's meaning into a given linguistic (here: sentence) context (Coulson & Van Petten, 2002; Kutas & Federmeier, 2011), showed a significant group x sentence type interaction effect within the early time window: The N400 amplitude modulation by sentence type found in controls, with meaningless=metaphoric>literal N400 amplitudes, was missing in patients, indicating that mapping of semantic relations may be altered in patients with schizophrenia. A behavioural manifestation of aggravated semantic-contextual integration in schizophrenia patients was found in overall slower and less accurate responses in the meaningfulness judgement task (for corresponding results, see Condray, Steinhauer, Cohen, van Kammen & Kasparek, 1999; Iakimova et al., 2005; Kuperberg, McGuire & David, 1998; Strandburg et al., 1997). The lacking early N400 modulation by sentence type in the patient group is in line with Strandburg et al. (1997) who demonstrated that schizophrenia patients showed no N400 differences between meaningful-literal compared to idiomatic and meaningless word pairs. The authors concluded that the predictive value of the preceding linguistic context is reduced in schizophrenia. Considering these highly similar results despite different stimulus material (word pairs vs. complete sentences), this finding appears to be independent of context magnitude, as long as it contains *novel* expressions. In Iakimova et al. (2005), common literal sentences and highly familiar metaphoric expressions were presented. Therefore, the contrary findings between Iakimova et al. (2005) and the present study can be ascribed to differences in content novelty, which is regarded as a core characteristic influencing metaphor comprehension (Cardillo, Watson, Schmidt, Kranjec & Chatterjee, 2012; Giora, 1997; Giora, 2003; Giora et al., 2012). Our interpretation of the N400 results in terms of schizophrenia-related difficulties in integrating upcoming meanings into a preceding context is further supported by earlier ERP studies indicating reduced N400 effects for semantically congruent versus incongruent expressions in schizophrenia patients (Grillon, Ameli & Glazer, 1991; Mitchell, Andrews, Fox, Catts, Ward & McConaghy, 1991) and healthy subjects with enhanced schizotypal personality scores (Kiang, Prugh & Kutas, 2010), even though some studies also reported on preserved N400 effects in schizophrenia (e.g. Andrews, Shelley, Ward, Fox, Catts & McConaghy, 1993; Kuperberg et al., 2006; Ruchsow, Trippel, Groen, Spitzer & Kiefer, 2003). Indeed, regarding the later N400 time window, we found similar N400 modulations (meaningless=metaphoric>literal) for patients and controls. We infer that, after contextual mapping difficulties during earlier stages of sentence comprehension, patients reach normalised mapping processes at a later perceptual stage. This delayed normalisation of processes may reflect an adaptive mechanism that helps patients to compensate language perception deficits in daily life situations. In fact, the rather quick normalisation of neural disturbances in such a within-trial timescale may imply that the detected disturbances could reflect only small to intermediate neurophysiological anomalies in schizophrenia.

Regarding haemodynamic response patterns, language-type independent differences between control subjects and schizophrenia patients became evident. Within both left IFG/Broca's area and left Wernicke's area – regions playing a key role in language comprehension – patients showed reduced haemodynamic activity during sentence processing. Hereby, both groups exhibited the same cerebral activation pattern: Whereas within left Wernicke's area both literal and metaphoric sentences were associated with O_2Hb concentration increases, left Broca's area showed highest activity specifically for metaphoric compared to literal and meaningless phrases. The latter result is in accordance with findings from previous fMRI studies on figurative language processing in healthy subjects (e.g. Diaz & Hogstrom, 2011; Eviatar & Just, 2006; Mashal et al., 2007; Rapp et al., 2004; see Rapp et al., 2012 for an overview; Shibata et al., 2007; Stringaris, Medford, Giampietro, Brammer & David, 2007). Such a similar recruitment of frontal areas for metaphoric contents in healthy subjects and schizophrenia patients was also demonstrated by Kircher and colleagues (Kircher, Leube, et al., 2007), however, with a slightly more dorsally located focus of metaphor-related brain activity in patients. The present data revealed a general reduction in cerebral activation within left Broca's, left Wernicke's, and, tendentially, right Broca's area in patients. Hypo-activation during language comprehension in patients with schizophrenia, especially of the IFG, has also been confirmed by imaging studies using fMRI (Dollfus et al., 2005; Jeong, Wible, Hashimoto & Kubicki, 2009; Kubicki et al., 2003). However, Mashal et al. (2013) reported on increased left IFG activation in schizophrenia patients when metaphoric versus literal expressions were contrasted, which the authors interpreted in terms of a recruitment of additional cognitive resources to comprehend figurative expressions. The necessity of such an additional recruitment could have been evoked by the use of poor-context word pairs, so differences in stimulus material may have contributed to these competing results. In our study, Broca's but also Wernicke's activity tended to correlate negatively with positive symptoms in patients. A similar link (Broca activation and concretism severity) has been previously reported using fMRI (Kircher, Leube et al., 2007).

Correlation analyses of the NIRS and EEG data revealed relationships of P200 amplitudes and Broca and Wernicke activity as well as between early N400 amplitudes with Wernicke activity during the comprehension of figurative speech in healthy subjects, which were not found in schizophrenia patients. This not only means that both types of neurophysiological markers represent a common process during metaphor and therefore pragmatic language processing (see also Schneider, Rapp et al., 2014), it further indicates that this connection is, at least to some extent, reduced in people with schizophrenia. The missing link between neural and haemodynamic responses during language comprehension in patients may point to possibly deficient neurovascular coupling, an aspect that has so far been scarcely considered in schizophrenia neuroimaging studies (Lindauer et al., 2010). Therefore, future research should not only focus on haemodynamic or neural anomalies, but additionally consider how the association between those two may be affected.

To sum up, considering both the early N400 results and haemodynamic activation patterns (cf. Figure 21), our results indicate rather unspecific group differences in cortical activation that were not modified by sentence type. Therefore, both markers support the view that deficient figurative language comprehension in schizophrenia may arise from rather general changes in language processing strategies. Therefore, it appears plausible that difficulties, if not selectively connected to the figurativeness of speech, may be rather associated with mentalising abilities (e.g. Bruene & Bodenstein, 2005) or basal cognitive and/or verbal or memory functions, respectively (Kazmerski, Blasko & Dessalegn, 2003; Pierce, MacLaren & Chiappe, 2010a; Schneider, Rapp et al., 2014). Hence, based on the present findings, the evaluation of N400 anomalies as potential biomarkers in patients with schizophrenia should be considered with caution, at least when non-literal language is the matter of debate, because N400 disturbances in patients normalised within a relatively short time period. Attenuated left fronto-temporal cortex activation might be of interest for future biomarker assessments in schizophrenia (but see also Mashal et al., 2013). However, such alterations may not be exclusively related to figurative language processing deficits, but rather represent general impairments in the processing of complex language. While the very early neural parameter (the P200), which is potentially associated with the detection of semantic ambiguity, showed the same effects in healthy subjects and schizophrenia patients, correlation analyses showed that this neural parameter was related to haemodynamic markers in healthy subjects but unrelated in patients with schizophrenia, indicating deficient cerebral organization or even impaired neuro-vascular coupling in patients. Because such a decoupling of neural and vascular parameters of brain activation during language processing has not been shown before, future studies preferably including larger samples will need to clarify the nature of this anomaly and its potential as a putative biomarker in schizophrenia research. The fast, easy, and economic applicability of combined EEG/NIRS measurements simultaneously providing high benefit (both, neural activity and regional haemodynamic changes can be assessed with high ecological validity) supports the usability of both methods to further investigate the here-reported alterations and their ability to serve as potential neurobiological markers for pragmatic language deficits in schizophrenia patients. It is now in the hand of future research to transfer the present outcomes onto this step.

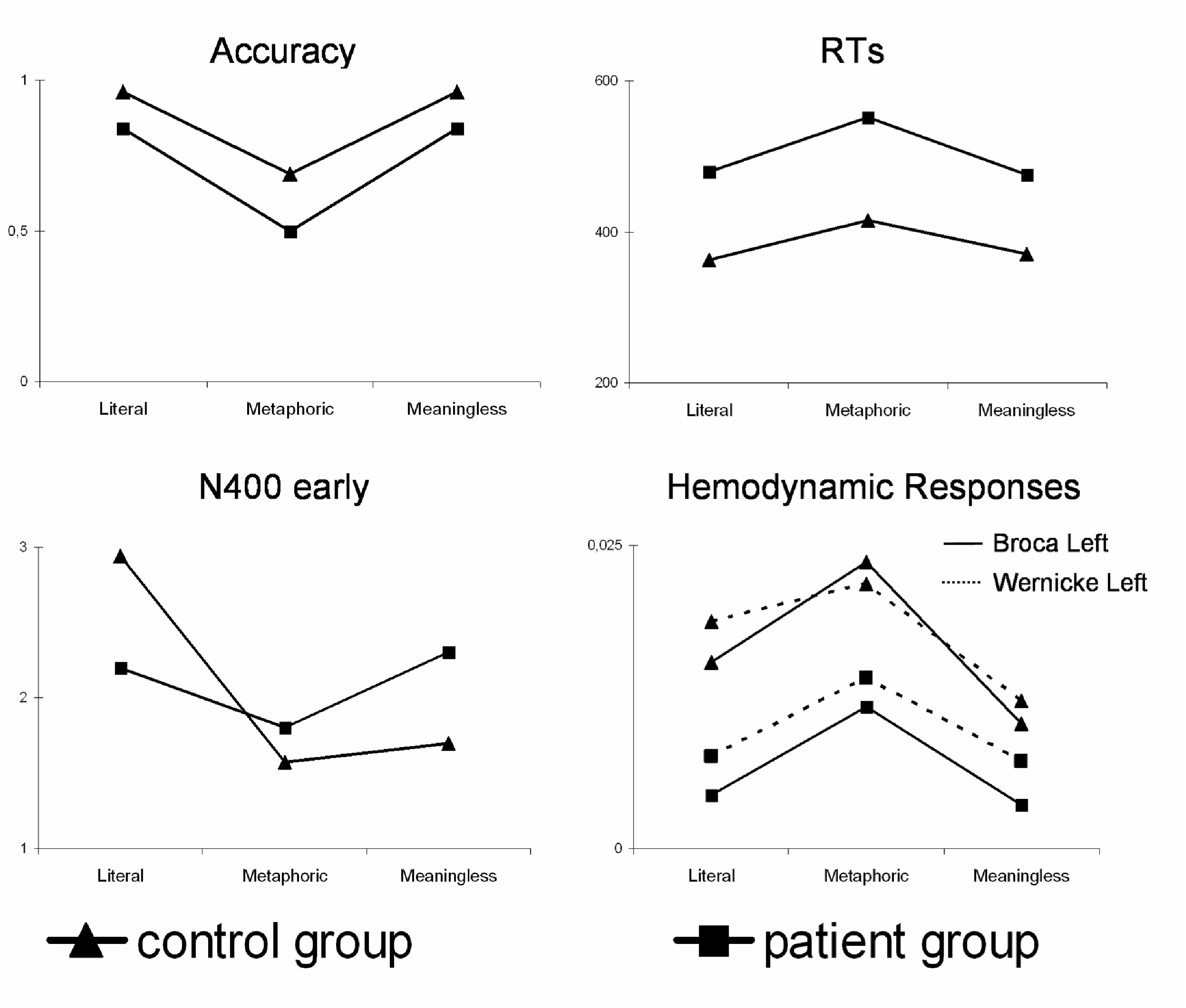


Figure 21. Illustration of the main behavioural (mean response accuracy and mean reaction times [RTs]) and neurophysiological (mean N400 amplitudes and mean O_2Hb peak values in left Broca's area and left Wernicke's area) results for healthy controls and schizophrenic patients. Mean RTs are given in milliseconds (ms), N400 amplitude values are given in µV, and mean O_2Hb peak values are scaled in mM*mm.

4. Nonverbal communication in schizophrenia: Deficient perception of emotional body language

4.1 Study 3:

Show me how you walk and I tell you how you feel — a functional near-infrared spectroscopy study on emotion perception based on human gait

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4.1.1 Abstract

The ability to recognise and adequately interpret emotional states in others plays a fundamental role in regulating social interaction. Body language presents an essential element of nonverbal communication which is often perceived prior to mimic expression. However, the neural networks that underlie the processing of emotionally expressive body movement and body posture are poorly understood. 33 healthy subjects have been investigated using the optically based imaging method functional near-infrared spectroscopy (fNIRS) during the performance of a newly developed emotion discrimination paradigm consisting of faceless avatars expressing fearful, angry, sad, happy or neutral gait patterns. Participants were instructed to judge (a) the presented emotional state (emotion task) and (b) the observed walking speed of the respective avatar (speed task). We measured increases in cortical oxygenated haemoglobin (O_2HB) in response to visual stimulation during emotion discrimination. These O_2HB concentration changes were enhanced for negative emotions in contrast to neutral gait sequences in right occipito-temporal and left temporal and temporo-parietal brain regions. Moreover, fearful and angry bodies elicited higher activation increases during the emotion task compared to the speed task. Haemodynamic responses were correlated with a number of behavioural measures, whereby a positive relationship between emotion regulation strategy preference and O_2HB concentration increases after sad walks was mediated by the ability to accurately categorise sad walks. Our results support the idea of a distributed brain network involved in the recognition of bodily emotion expression that comprises visual association areas as well as body/movement perception specific cortical regions that are also sensitive to emotion. This network is activated less when the emotion is not intentionally processed (i.e. during the speed task). Furthermore, activity of this perceptive network is, mediated by the ability to correctly recognise emotions, indirectly connected to active emotion regulation processes. We conclude that a full understanding of emotion perception and its neural substrate requires the investigation of dynamic representations and means of expression other than the face.

4.1.2 Introduction

The ability to correctly detect and recognise emotional states in others represents a fundamental requirement for adequate social interaction. It enables us to appropriately interpret social situations and to adapt our own behaviour to given conditions. Impaired emotion recognition is thus related to prominent deficits in social functioning. Accordingly, emotion recognition deficits have been observed in a variety of psychiatric syndromes, such as affective diseases (Gur, Erwin, Gur, Zwil, Heimberg & Kraemer, 1992; Mandal & Bhattacharya, 1985; Milders, Bell, Platt, Serrano & Runcie, 2010; Schaefer, Baumann, Rich, Luckenbaugh & Zarate Jr, 2010), eating disorders (Ridout, Wallis, Autwal & Sellis, 2012), and different types of personality disorders (Dickey et al., 2011; Levine, Marziali & Hood, 1997; Marissen, Deen & Franken, 2012). They are also central in schizophrenia (Chan et al., 2010; Edwards et al., 2002; Hellewell & Whittaker, 1998), and in the case of autism, they even represent the core deficit (Hobson, Ouston & Lee, 1988; Philip et al., 2010).

Over a period of several decades, emotion recognition was investigated predominantly by means of facial stimuli. Neurobiological research on facial emotion perception revealed emotion related activation increases in brain areas associated with face perception, such as the fusiform face area (FFA; Ganel, Valyear, Goshen-Gottstein & Goodale, 2005; Jacob, Kreifelts, Brueck, Erb, Hoesl & Wildgruber, 2012; Vuilleumier, Armony, Driver & Dolan, 2001; Vuilleumier & Pourtois, 2007), superior temporal sulcus (Haxby et al., 2000; Winston, Henson, Fine-Goulden & Dolan, 2004), and inferior occipital gyrus (Fusar-Poli et al., 2009). Moreover, emotional face expressions have been reported to trigger neural activation within a distributed network, including the amygdala, the insula, the cerebellum, and prefrontal as well as orbitofrontal brain regions, (see Fusar-Poli et al., 2009), whereupon regional activation increases partly depend on the respective emotion perceived.

Although facial expression plays – without question – a crucial role in human social function, there are good reasons to broaden emotion recognition research by additionally studying body language expressions. First, in a number of daily situations body language is more accessible than facial expressions, e.g. if the face is averted or a person is observed from a distance. It has further been shown that the perception of facially expressed emotions is significantly affected by whole-body expressions (Meeren, van Heijnsbergen & de Gelder, 2005; Van den Stock, Righart & de Gelder, 2007). Moreover, although traditional and widely accepted approaches assume separate processing of facial identity and emotion following an initial stage of structural encoding (Breen, Caine & Coltheart, 2000; Bruce & Young, 1986), there is some evidence that the recognition of facial expression and identity are not entirely independent (Atkinson, Tipples, Burt &

Young, 2005; Ellamil, Susskind & Anderson, 2008; Schweinberger & Soukup, 1998). While to our knowledge no studies have so far investigated interaction effects of emotion and identity for body movements, there are some studies showing that identity recognition and discrimination from moving bodies is, though possible, associated with very poor performance (Kozlowski & Cutting, 1977; Westhoff & Troje, 2007), indicating that identity is unlikely to strongly affect emotion processing from body language. Considering that facial emotion recognition, in contrast, may indeed be affected by identity, a holistic view of neural and cognitive mechanisms underlying emotion perception from body language appears even more reasonable.

Against this background, an increasing number of functional brain imaging studies have addressed the anatomical and functional substrates of emotion perception based on body expressions. Beyond face selective areas, circumscribed brain regions have been reported that are specialised in processing human body posture, body movements and/or body expressions, partially overlapping with those areas associated with the recognition of facial expressions: ventral parts of the fusiform gyrus (fusiform body area, FBA; Peelen & Downing, 2005b; Peelen & Downing, 2007; Schwarzlose et al., 2005), a region within the lateral occipitotemporal cortex (extrastriate body area, EBA; Downing et al., 2001), and the superior temporal sulcus (STS; Grossman et al., 2000; Krakowski, Ross, Snyder, Sehatpour, Kelly & Foxe, 2011). Using anatomical landmarks, a recent study further identified the inferior temporal gyrus (ITG), which is directly neighboured to the lateral fusiform cortex, as a relevant region for the perception of human bodies and limbs (Weiner & Grill-Spector, 2011). Recent studies explicitly assessing the neural processing of body expressions indicate that emotions indeed modulate brain activity within these brain regions. In addition to enhanced amygdala activity (Hadjikhani & de Gelder, 2003; Peelen et al., 2007), emotion-related increases in brain activation after the presentation of body expressions have been observed in the FBA (Hadjikhani & de Gelder, 2003; Kret et al., 2011; Pichon et al., 2008; van de Riet et al., 2009), the ITG (de Gelder, Snyder, Greve, Gerard & Hadjikhani, 2004; Prochnow et al., 2013) the EBA (Atkinson et al., 2012; see de Gelder et al., 2010 for an overview; Grèzes et al., 2007; Kret et al., 2011; Peelen et al., 2007; Pichon et al., 2008), the STS (Grèzes et al., 2007; Kret et al., 2011; Peelen, Atkinson & Vuilleumier, 2010; Van den Stock, Tamietto, Sorger, Pichon, Grézes & de Gelder, 2011), the temporo-parietal junction (TPJ; Grèzes et al., 2007; Pichon, de Gelder & Grèzes, 2009; Sinke, Sorger, Goebel & De Gelder, 2009) and frontal brain regions (de Gelder et al., 2004; Peelen et al., 2010; van de Riet et al., 2009; Van den Stock, Tamietto et al., 2011). It has to be noted, that these effects strongly depend on whether the affective state was presented by means of static vs. dynamic body expressions. Recent research indicates that activation in the STS, a region that is known for its crucial role in social information perception (Kreifelts, Ethofer, Huberle, Grodd & Wildgruber, 2010; Kreifelts, Ethofer, Shiozawa, Grodd & Wildgruber, 2009), is enhanced by emotional compared to neutral body expressions only if dynamic stimuli are presented (Grèzes et al., 2007). Moreover, emotional modulation of the EBA, in particular, is only evident in studies using dynamic, but not static, body expressions (de Gelder et al., 2010).

Human gait reflects a specific type of dynamic body motion which provides sufficient information for the perception of expressed motivational or emotional states (Karg, Kühnlenz & Buss, 2010; Montepare, Goldstein & Clausen, 1987; Montepare, Koff, Zaitchik & Albert, 1999; Roether, Omlor, Christensen & Giese, 2009; Roether, Omlor & Giese, 2009). Using biological motion stimuli in terms of animated point-light displays, previous studies showed that emotions from point-light walkers can be reliably discriminated (Atkinson et al., 2004; Clarke et al., 2005; Dittrich et al., 1996) and, moreover, it has been demonstrated that emotional content facilitates gait identification (Chouchourelou et al., 2006; Ikeda & Watanabe, 2009). Up till now, only very few brain imaging studies on the neuro-functional substrates of the perception of dynamic body expressions from gait patterns exist. Heberlein et al. (2004) used dynamic point-light stimuli that were based on walking actors expressing four different emotions (happiness, anger, fear, and sadness) to determine cortical regions that are involved in emotion recognition in healthy subjects and patients with brain damage. Their findings suggest a crucial role of the right parietal cortex in emotion recognition from point-light walkers (Heberlein et al., 2004). Using similar stimulus material, Atkinson et al. (2007) reported a case in which a patient showed normal emotion discrimination during the spot-light walkers paradigm despite complete bilateral amygdala lesion that was accompanied by strong impairments in recognising emotions from facial expressions (Atkinson et al., 2007), indicating that additional cerebral areas, such as cortical structures, may be crucially involved in emotion perception from point-light walkers.

Unlike in studies using point-light stimuli, many previous studies addressing the emotional modulation of body selective brain activity often drew on visual stimuli that were either restricted with respect to external validity (e.g., headless bodies were presented) or confounded with information other than bodily emotion perception (e.g. age, gender, or even facial expression). In order to counteract such confounding factors, the present study used whole body avatars that were established by Roether et al. (2009). They recorded 25 individuals expressing different emotional states during walking by motion capture. Resulting recordings were computationally transformed into three-dimensional avatars using (*see methods section*). The appearance of these avatars does not unveil information about the representative's age, sex, ethnicity, or facial expression while validly displaying the recorded emotional gait pattern and, by being more "human-like", reflecting higher ecological validity compared to point-light walkers.

During the last decade, near-infrared spectroscopy (NIRS) has been proven to reliably depict cortical activation changes based on vascular responses in a broad range of emotion perception tasks (Herrmann, Ehlis & Fallgatter, 2003; Herrmann et al., 2008; Köchel et al., 2011; Minati, Jones, Gray, Medford, Harrison & Critchley, 2009; Nakato, Otsuka, Kanazawa, Yamaguchi & Kakigi, 2011). In a recent study, for example, Köchel et al. (2011) reported emotional modulation of oxygenation changes in the left occipital cortex: Both the perception as well as the imagery of happy and disgusting pictures were associated with stronger increases in oxygenated haemoglobin (O_2Hb) compared to neutral stimuli.

In order to investigate neurophysiological correlates of emotion recognition from gait patterns expressed by avatars, we conducted 52-channel near-infrared spectroscopy (NIRS) measurements in a group of healthy subjects. Due to its frequently quoted advantages (Ernst et al., 2012; Fallgatter, Ehlis, Wagener, Michel & Herrmann, 2004), especially its quick and easy applicability in a noise-free, highly naturalistic setting, NIRS offers the opportunity to assess a large number of different subject groups characterised by certain needs or limitations, such as children or patients suffering from psychiatric diseases. While some fMRI studies already targeted cerebral processing of dynamic body expressions (see above), developmental aspects or pathologic alterations of brain activity in this context are rather unexplored so far. As NIRS can be a useful tool in order to examine this new research field, we plan to investigate potential alterations within the bodily emotion perception cortical network, focussing on their classificational and predictive potency in different psychiatric syndromes (Major Depression, Schizophrenia, and Anxiety Disorders). In order to have a solid basis that is fundamental for these large-scale NIRS investigations, the core aim of the present study is to investigate whether emotion specific cortical activation patterns related to human gait perception can be reliably detected using NIRS measurements. Based on recent literature on the cortical representation of dynamic body expressions and emotion modulation of cortical haemodynamic responses (see above), we hypothesise that avatars displaying emotional (i.e. fearful, sad, angry, or happy) gait patterns provoke higher O_2Hb increases compared to neutral gait within the EBA, the ITG , the STS, and the TPJ. The posterior part of the ITG, specifically, has been chosen because it has been associated with body perception and it is directly adjacent to the Fusiform Gyrus (FFG). The FG as a typical region of interest in emotional body perception studies is, in turn, located on the ventral surface of the temporal lobe and the central/medial FFG is hence unlikely to be directly assessable using fNIRS. Therefore, the present study will focus on peripheral areas of the FBA together with the neighboured posterior ITG. We also expect emotion discrimination accuracy as well as self-rated discriminability to correlate with cortical activation measured with near-infrared spectroscopy.

4.1.3 Materials and Methods

4.1.3.1 Subjects

A total of 31 Caucasian and 2 Asian subjects (10 males, 23 females) were enrolled in the present study. Participants were recruited via email announcements and postings at the Departments of Psychology and General Psychiatry at the University of Tuebingen. Mean age was 28.9 (range: 18–51) years. All participants were right handed, as assessed by means of the Edinburgh Handedness Inventory (Oldfield, 1971) and did not exhibit current or past psychiatric illness. Further exclusion criteria were severe neurological disease (e.g., epilepsy, encephalitis), untreated diabetes or instable/untreated hypertension. Permission for the study was obtained from the local Ethics Committee of the University of Tuebingen; all study procedures were in line with the Declaration of Helsinki in its latest version. After complete description of the study to the participants, written informed consent was obtained.

4.1.3.2 Stimuli

The dynamic body stimuli used in the present study were provided by the Section of Computational Sensomotorics (Head: Prof. Martin A. Giese) at the Hertie Institute for Clinical Brain Research Tuebingen, Germany (Roether et al., 2008, 2009a,b). Avatar videos were created in three steps: First, gait sequences of 13 lay theatre actors were recorded using a VICON optical motion capture system (VICON, Oxford, UK) with eight cameras which can be utilised to track and record bodies in motion based on infrared camera recordings. The actors were instructed to walk straight within a proscribed area of approximately 5 m in length, during neutral walking and emotionally expressive walking (anger, sadness, fear, and happiness), and they were explicitly encouraged to avoid gestures that would have interrupted their rhythmic walking pattern. The actors' involvement in each affective state was ensured using a mood induction paradigm based on the imagination of sentimental past life events. In order to capture neutral walking sequences that were speed matched to the – by nature – slower (e.g., sad walk) or faster (e.g., angry walk) emotionally expressive gait patterns, some actors were required to express neutral walk of three different speeds: At first, they were instructed to move at their customary walking speed followed by walking sequences of increased (instruction: "Walk faster than normal.") or decreased (instruction: "Walk slower than normal.") walking speed, respectively.

The motion captured walking data was animated using custom build software. The resulting video clips showed grey, volumetric avatars that walked as on a treadmill. Walking direction was either slightly to the left or to the right (about 22°) to provide the observer with a more lateral view on the avatar which has been shown to be beneficial for emotion perception. Video clip duration was 3 s (see Supplementary material [Figures 28 & 29] for example videos).

4.1.3.3 Experimental procedure

The emotion discrimination paradigm consisted of two tasks: In one-half of the experiment, participants had to identify the emotion expressed by the respective avatar (neutral, anger, sadness, fear, and happiness), whereas in a second task, the moving speed of each presented avatar had to be judged on a five-point scale (from "very slow" up to "very fast") in order to achieve common scaling for both tasks. The latter task was implemented in order to investigate possible attention effects, i.e. the influence of task/perceptual state (intended emotion discrimination vs. unattended emotion perception during speed judgements) on the cortical processing of the different emotion categories. Therefore, the same video stimuli were presented in both task blocks and task order was counterbalanced across subjects. For each task, subjects had to judge 120 video trials, with 24 videos per emotion category (neutral, anger, sadness, fear, and happiness). Hereby, each emotion category consisted of three different actor videos, of which each was presented in two different movement directions (avatar walking from left to right and from right to left) and was repeated four times, leading to 24 trials per stimulus category. To account for the fact that emotions expressed through gait patterns are usually confounded with speed (i.e., some emotions, such as sadness, are typically associated with slow walking speed, whereas others [e.g. anger] are linked to fast speeds), neutral walks were speed matched to the emotional walks by subdividing the neutral category into three different walking speeds (slow neutral walk, medium neutral walk, fast neutral walk).

Participants were seated comfortably in a sound-attenuated room approximately 75 cm in front of a computer screen. They were instructed to watch all videos attentively and to either judge the expressed emotion (emotion task) or the respective walking speed of the avatar (speed task) via button press. The letters "Q", "W", "P", "Ü" and the space-button on a German keyboard served as response buttons and key assignment was counterbalanced across participants. Each trial started with a fixation cross that was presented in the centre of the screen for 500 ms. After another 100 ms of blank screen, an avatar video was presented for 3000 ms. The video trial was again followed by a gap (blank screen) for 100 ms. After this gap, a response screen appeared that displayed the response options and their respective key assignment. This response screen remained until the key response was provided, whereby the maximal response time as set to 2000 ms in order to limit total experiment duration. Hence, each trial had a minimum duration of 3700 ms and a maximum duration of 5700 ms and there was a jittered inter-trial interval (ITI) of 4000–7000 ms which has been shown as a proper interval in previous NIRS studies (Telkemeyer, Rossi, Nierhaus, Steinbrink, Obrig & Wartenburger, 2011; Tupak et al., 2013) while even much shorter stimulus-onset intervals (SOAs) have been reported recently (Heilbronner and Muente, 2013). At the beginning of each task, a practice block comprising 10 video trials (two per emotion category) was carried out. The maximum total duration of the experiment came up to 48 min without breaks, but the actual duration was usually shorter due to average response times of 490 ± 165 ms instead of 2000 ms. Breaks were implemented at three fixed time points throughout the experiment and their duration could be determined by the participant.

Right after the experiment, participants were asked to rate the experimental material concerning its emotional content, emotion recognisability, and perceived arousal during stimulus perception. To this end, 30 videos (six per category) from the main experiment were presented again, and after each video subjects had to provide their judgements on a five-point Likert-scale for emotional content (1 = not at all; 5 = very, for sad, fearful, angry, and happy, respectively) as well as for recognisability (1 = not at all recognisable; 5 = very easily recognisable), and arousal (1 = not arousing; 5 = very arousing).

Several psychometric scales were additionally applied in order to assess subject's current emotional state (Beck Depression Inventory [BDI], Positive and Negative Affect Schedule [PANAS], and the State version of the State-Trait Anxiety Inventory [STAI]). The trait version of the STAI was used to further gather information about personality variations concerning anxiety. To assess interindividual preferences regarding emotion regulation strategies, the Emotion Regulation Questionnaire (ERQ) was also completed by each subject.

4.1.3.4 Near-infrared spectroscopy

NIRS measurements were conducted with the ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) using a 52-channel array of optodes (17 light sources/emitters and 16 detectors) covering posterior (corresponding to occipital–parietal–temporal cortex regions) areas on the head. Emitter-detector distance was 30 mm for contiguous optodes and near-infrared light of two wavelengths (695 and 830 nm, respectively) was used. NIRS optodes were attached to the subject's head using a plastic array of optode holders in a rectangular shape that was placed on the occiput with respect to the international 10/20 system (Jasper, 1958) in such a way that channel 37 (the middle channel in the lowest of five channel rows) corresponded to the location of Oz (see Figure 22), and the anterior NIRS channels 43 (left side) and 52 (right side) were equivalent to the temporal electrode positions T3 (T7) and T4 (T8), respectively.

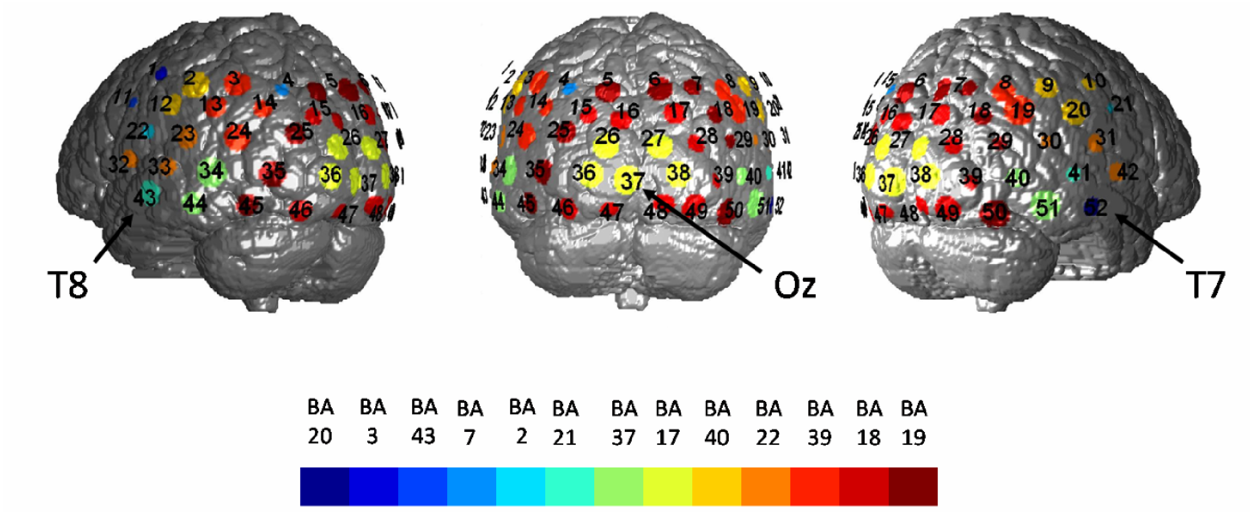

Figure 22. 3D illustration of NIRS channel arrangement over the brain resulting from the neuronavigation procedure as described in the methods section Colours indicate the respectively assigned Brodmann Area (BA). Blob size is associated with the probability of the respective channel-BA assignment.

To obtain anatomic channel assignment the plastic optode holder array was placed on a volunteer's head and respective optode positions were determined using a neuronavigation system [LOCALITE GmbH, St. Augustin, Germany]. The resulting optode coordinates were transferred from the volunteer's native MRI space to the standard MNI space by applying normalization routines from Statistic Parametric Mapping (SPM) 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The normalised coordinates were projected on a brain template in order to calculate estimates that indicate which brain region is most probably located below a certain channel. Figure 22 displays the so estimated cortical projection points of the NIRS channels and their probabilistic assignment to respective Brodmann Areas (Brodmann, 1909).

4.1.3.5 Data analyses

With the ETG-4000, changes in the concentration of oxygenated haemoglobin (O_2Hb) and deoxygenated haemoglobin (HHb) were recorded from a 10 s starting baseline continuously throughout the entire paradigm. Signals obtained from the 52 NIRS channels were measured with a sampling rate of 10 Hz, and analysed and transformed according to their wavelength and location, resulting in values for the changes in the concentration of oxygenated and deoxygenated haemoglobin for each channel. Haemoglobin quantity is scaled in mmol∗mm, implying that all concentration changes depend on the path length of the NIR light in the brain. Subsequent analyses of the recorded data were performed using MATLAB 7.9.0 (The MathWorks Inc., Natick, USA) and IBM SPSS Statistics (Armonk, NY, USA). Firstly, data was filtered using a .008–.25 Hz band pass. The pre-processed data was then assessed by applying a General Linear Model (GLM) approach to the NIRS data time series (see Plichta, Heinzel, Ehlis, Pauli & Fallgatter, 2007). Hence, functional data can be modelled as:

$$Y = X * \beta + \varepsilon \, ,$$

with Y as a time × channel matrix consisting of the entire functional NIRS time series, whereas X constitutes the design matrix containing the respective modelled effects, further including β as the parameter matrix comprising the beta weights to be estimated and the error term ε. More precisely, the design matrix X of the type time × number of modelled effects comprises the predicted haemodynamic response function (stick function) for each experimental condition over time, with stimulus (i.e. avatar video) onset as starting point. This GLM based assessment represents a common analysis approach for fMRI data (Friston et al., 1995) and has also been increasingly described for NIRS data assessment (see Plichta et al., 2007; Plichta et al., 2006; Schroeter et al., 2004). The hypothesised stick function was a Gaussian curve with a modelled peak time (PT) of 9 s after stimulus onset (corresponds to 6 s after stimulus offset, compare Figure 23, upper panel) due to previous data showing that event-related haemodynamic response function (HRF) in striate areas peaks at around 6 s after an event (Aguirre, Zarahn & D'Esposito, 1998; Buckner et al., 1996). As visual inspection of the averaged event-related haemodynamic responses revealed that actual PTs were delayed in a number of (particularly lateral) channels (see Figure 23, lower panel), we decided to test a second model with a hypothesised PT of 11 s after stimulus onset. In both cases, beta weights were estimated using the method of least squares indicating the amplitude of brain activation. In order to identify channels with significant O_2Hb increases after stimulation, we performed separate one sample t-tests (contrast value: 0) for each condition and channel on the estimated beta weights. For the first GLM analyses (PT = 9 s), t-tests revealed significant O_2Hb activation increases, indicated by significantly positive beta weights, in channels 25, 28, 36, and 38 ($2.87 < 4.13, 2.40 * e^{-4} < p < .007$, Bonferroni–Holm corrected) after neutral walks. Activation patterns for the four emotion categories were highly similar. Overall, the channels with significant and marginally significant (t>2.0, p<.05) activation increases were restricted to occipital areas. In contrast, the second GLM analyses revealed significant increases of O_2Hb in channels 1–14, 16, 19–21, 23, 30–31, 33–34, 41, 43–44, 48, and 51–52 ($3.70 < 5.51$, $4.5 * e^{-6} < p < 7.98 * e^{-4}$, Bonferroni–Holm corrected), whereby these channels are located over visual association areas instead of the occipital pole/V1. This finding implies that different perceptual processes were assessed depending on the respectively modelled HRF peak time.

To account for (1) this variability in peak latencies between different brain regions (posterior-occipital vs. lateral/temporo-parietal) and (2) the fact that in some predominantly laterally located channels the O_2Hb time course seemed too complex to be modelled by a Gaussian haemodynamic response function (see Figure 23, lower panel), an additional model-free analysis that abandons fixed unimodal HRF peak times was performed. This strategy enabled us to investigate the effects of emotional content on body movement perception instead of assessing different particular sub-processes within the complex mechanism of emotion perception and recognition. Hereby, data were analysed in an event-related fashion, i.e., NIRS data segments were created according to each of the five stimulus emotion categories (neutral, sad, angry, fearful, and happy). Segments started 2 s prior to video presentation (baseline) and lasted until 20 s following the stimulus (stimulation period). Amplitude averages of the haemodynamic response functions (HRFs) of O_2Hb within a 6–14 s segment following the onset of the presented avatar video were calculated per subject per condition. Analogously, an automatic peak detection determining maximum values of the respective HRFs was performed within this time window. Visual data inspection confirmed that HRF amplitudes and peaks were identifiable within this time window (see Figure 23). Exact peak values as well as mean amplitude values were exported in order to perform subsequent statistical analysis. To reduce complexity, only mean amplitude results are presented here. However, it is important to note that resulting activation patterns were quite similar for peak values and mean amplitudes.

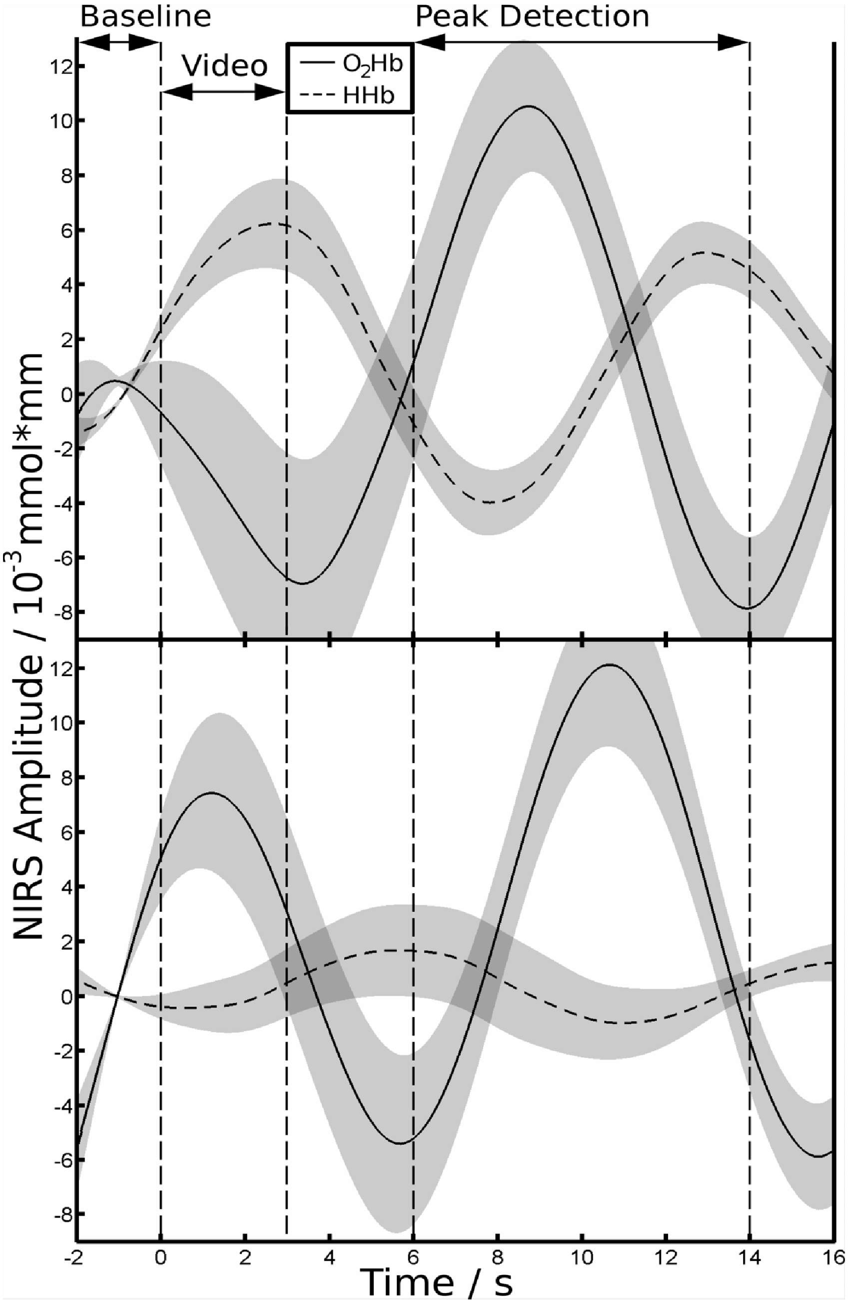

Figure 23. Typical course of the haemodynamic response function (HRF) in the occipital pole (upper panel) and an exemplary ROI (left TPJ; lower panel) averaged over subjects (n=33). Dashed vertical lines mark baseline period of the segment, avatar video onset and offset as well as the pre-defined peak-detection interval. Solid curve: oxygenated haemoglobin, dashed curve: deoxygenated haemoglobin. Greyed out thick lines in the time course indicate HRF standard deviations.

4.1.3.6 Regions of interest (ROI) definition

In order to perform hypotheses-based data analyses, certain cortical regions of interest (ROIs) were defined a priori according to recent findings from bodily emotion expression studies. According to state of the art research, at least four cortical regions are distinguishable that seem to be critically involved in the perception of bodily emotion expression: (1) the posterior part of the ITG (Brodmann Area 37) including the lateral–peripheral part of the FBA; (2) the EBA (Grèzes et al., 2007; Sinke et al., 2010), located at the junction of the visual association cortex (Brodmann Area 18) and the posterior angular gyrus (Brodmann Area 39); (3) The inferior part of the supramarginal gyrus (Brodmann Area 40), including the TPJ (e.g. Pichon et al., 2009); and (4) the posterior STS (e.g. Peelen et al., 2010). Table 5 contains the channels that formed each particular ROI with the respective MNI (Montreal Neurologic Institute) coordinates as determined by the neuro-navigation procedure (see Figure 22).

Table 5. NIRS channel assignment to the present regions of interest (ROIs) and respective MNI coordinates.

Left Hemisphere			**Right Hemisphere**		
ROI	**Channels**	**MNI coordinates (x, y, z)**	**ROI**	**Channels**	**MNI coordinates (x, y, z)**
EBA	14	-79, 41, 36	**EBA**	18	-82, -43, 32
	24	-69, 54, 21		29	-78, -50, 18
ITG	34	-60, 62, 3	**ITG**	40	-71, -57, 1
	44	-52, 67, -12		51	-58, -63, -14
pSTS	23	-47, 65, 22	**pSTS**	30	-58, -63, 20
	33	-38, 70, 6		41	-46, -70, 3
TPJ	12	-34, 64, 36	**TPJ**	19	-67, -55, 34
	13	-57, 58, 36		20	-42, -66, 35
	22	-23, 66, 25		31	-8, 65, 5

EBA – extrastriate body area; ITG – inferior temporal gyrus; pSTS – posterior superior temporal sulcus; TPJ – temporo-parietal junction.

4.1.3.7 Statistics

Behavioural data (accuracy and reaction times, recognition and arousal ratings) were analysed by means of repeated measures analyses of variance (RM-ANOVAs) for repeated measures with the within-subject factors task (emotion vs. speed) and emotion (neutral, sad, fearful, angry, and happy). Ratings concerning emotional content were further analysed performing univariate ANOVAs for repeated measures comprising the within-subject variable category which further considered different walking speeds of the avatars (neutral slow, neutral medium, neutral fast, sad, fearful, angry, and happy). Paired t-tests (with Bonferroni–Holm correction applied) were computed as post-hoc analyses whenever an ANOVA revealed significant effects.

Mean O_2Hb amplitudes were analysed with 2×5 RM-ANOVAs comprising the within-subject variables task and emotion for each ROI. In order to verify whether potential effects of condition occur specifically within the pre-defined ROIs, mean O_2Hb amplitude values for all channels not included in one of the ROIs were computed and a final ANOVA for repeated measures (again including the factors task and emotion) on non-ROI channels was performed. Bonferroni–Holm (BH) correction procedure was used to correct for multiple analyses caused by the investigation of four different ROIs per hemisphere. Separate RM-ANOVAs for both tasks including the factor emotion, and paired one-sided t-tests, respectively, were performed whenever main or interaction effects were significant in any of the computed ANOVAs. Once again, BH-correction was performed to adjust respective alpha levels, leading to adjusted alpha levels of .0125<.05.

With respect to the psychometric data, a sum score was calculated for the BDI. Regarding the STAI, PANAS and ERQ, sum scores were created for the respective subscales. The STAI thus consisted of a state score and a trait score, the PANAS of a positive and a negative affect score, and the ERQ of the components "emotion suppression" and "re-evaluation of the situation/context". Eventually, Pearson's correlation coefficients were calculated between the ascertained psychometric scores and the emotion-dependent haemodynamic brain activation parameters (i.e., mean amplitudes of O_2Hb) within ROIs that previously revealed emotion category effects on mean O_2Hb amplitudes. We further correlated the haemodynamic parameters with emotion discrimination performance (accuracy and RTs in the emotion identification task), and subjective stimulus ratings (emotion recognisability and subjective arousal that was evoked by a certain stimulus condition) within each emotion category. For the sake of conciseness, only haemodynamic parameters from the relevant emotion discrimination task block were used for these correlation analyses. Hereby, two-sided testing procedures and Bonferroni–Holm correction were used, leading to a corrected alpha of .003–.05 for r(O_2Hb mean amplitudes, psychometric scales), and 0.125–.05 for correlations between O_2Hb mean amplitudes and behavioural performance (accuracy, RTs) as well as subjective ratings (emotion recognisability, subjectively elicited arousal) per emotion category.

4.1.4 Results

4.1.4.1 Behavioural data

Table 6 contains arithmetic means and standard deviations (SDs) for accuracy and RTs during the emotion and the speed task blocks for each emotion category. With respect to response accuracy, the RM-ANOVA revealed significant main effects of emotion ($F(4,128)=39.60$, $p<.001$, $\eta^2=.55$) and task ($F(1,32)=135.40$, $p<.001$, $\eta^2=.81$) as well as a significant interaction of both factors ($F(4,128)=15.68$, $p<.001$, $\eta^2=.33$). Post-hoc *t*-tests showed that response accuracy was similar in both tasks for fearful avatars ($t(32)=0.20$; $p=.85$) whereas task performance differed with respect to the other emotion categories ($-9.36<t<-2.87$, $p<.05$; BH-corrected): Within the emotion discrimination task, emotion recognition accuracy was highest for sad and fearful, followed by angry and happy avatars ($-11.53<t<6.28$, $p<.05$; BH-corrected), while accuracy for neutral avatars was lowest ($-10.19<t_{\text{neutral-others}}<-4.10$, $p<.05$; BH-corrected). For the speed judgements, response accuracy was highest for sad and happy ($t(32)=-1.20$; $p=.24$), followed by all other categories ($1.90<t<4.92$, $p<.05$; $p<.05$; BH-corrected). Regarding RTs for trials with correctly identified emotions, there were significant main effects for both task ($F(1,32)=9.48$, $p<.01$, $\eta^2=.23$) and emotion ($F(4,128)=4.75$, $p<.01$, $\eta^2=.13$). Responses were provided faster in the speed judgement than in the emotion discrimination task ($p<.01$). Post-hoc t-tests investigating the emotion effect revealed fastest reaction times for angry followed by neutral, sad, and happy walks ($2.16<t<4.37$, $p<.05$; BH-corrected) and slowest responses overall for fearful walks ($2.42<t<4.37$, $p<.05$; BH-corrected).

Table 6. Arithmetic mean values and standard deviations (SD) for accuracy and reaction times (RTs) within the emotion task block and the speed task block, respectively. Accuracy reflects the relative frequency of correct responses.

	Emotion task block				**Speed task block**			
	accuracy		**reaction rimes (RTs) in ms**		**accuracy**		**reaction rimes (RTs) in ms**	
	mean	SD	mean	SD	mean	SD	mean	SD
neutral	.60	.14	555	203	.84	.16	433	141
sad	.92	.11	542	225	.98	.04	430	135
angry	.73	.08	496	192	.91	.10	419	157
fearful	.92	.08	540	199	.92	.17	484	161
happy	.74	.14	525	203	.97	.05	437	150

Stimulus rating analyses revealed significant main effects of emotion category with respect to subjective emotion recognisability ($F(6,192)=23.14$, $p<.001$, $\eta^2=.42$), perceived arousal ($F(6,192)=9.26$, $p<.001$, $\eta^2=.22$), and each of the emotional content ratings ($82.41<F_{ratings}<263.43$). Further analyses indicated that sad walks were most easily recognisable (M=4.19±.54), followed by angry walks (M=3.90±.41; $t_{sad-angry}=3.06$, $p<.05$; BH-corrected), followed by fearful (M=3.66±.55; $t_{angry-fearful}=2.31$; p<.05; BH-corrected) and happy (M=3.51±.57; $t_{angry-happy}=4.23$, $p<.05$; BH-corrected) walks, and with lowest recognisability rates for all types of neutral walks ($M_{neutral-slow}=3.04±0.73$; $M_{neutral-medium}=2.82±0.68$; $M_{neutral-fast}=3.14±0.92$, $-8.56<t_{neutral-sad/angry/fear/happy}<-2.50$, $p<.05$; BH-corrected). While arousal ratings were generally low, highest arousal was elicited by sad walks (M=1.77±.65) followed by fearful (M=1.53±.67; $t_{sad-fearful}=3.02$, $p<.05$; BH-corrected), angry (M=1.45±.65; $t_{sad-fearful}=3.12$, $p<.05$; BH-corrected) and slow neutral walks (M=1.46±.67; $t_{sad-fearful}=3.33$, $p<.05$; BH-corrected); medium speed (M=1.23±.37) and fast neutral (M=1.17±.39) as well as happy (M=1.32±.54) walks were associated with lowest arousal rates.

4.1.4.2 Neurophysiological data

The 2×5 RM-ANOVAs revealed BH-corrected significant main effects of emotion for the right EBA ($F(4,128)=3.00$, $p<.0167$, $\eta^2=.10$), the right ITG ($F(4,128)=2.67$, $p<.025$, $\eta^2=.08$), the left TPJ ($F(4,128)=3.00$, $p<.0167$, $\eta^2=.09$), and the left posterior STS (pSTS, $F(4,128)=3.03$, $p<.01$, $\eta^2=.10$). A significant main effect of task was only found in the right EBA with overall higher activation increases during the emotion discrimination compared to the speed judgement task ($F(4,128)=4.27$, $p<.025$, $\eta^2=.12$). Moreover, with respect to the right EBA and the left TPJ there was a significant $task \times emotion$ interaction ($2.27<F<2.81$, $p<.05$). Therefore, separate RM-ANOVAs for the emotion discrimination and the speed judgement task were conducted. Respective results showed that a main effect of emotion was only apparent in the emotion discrimination task ($3.88<F<4.08$, $p<.01$) but not in the speed judgement task ($1.19<F<1.60$, $p>.10$) within the EBA and TPJ. During the emotion task block, both right EBA and left TPJ activity was enhanced for sad, fearful, and angry compared to neutral walks ($2.35<t<3.36$, $p<.05$; BH-corrected) while there was no difference between the happy and neutral condition ($t_{EBA}(32)=0.84$, $p=.41$, $t_{TPJ}(32)=0.96$, $p=.35$). To further analyse the main effect of emotion regarding the right ITG and the left STS, subsequently calculated paired t-tests showed that mean amplitudes of O_2Hb concentration changes in the right ITG were generally higher for sad, fearful, and angry vs. neutral walks ($2.35<t<3.36$, $p<.05$; BH-corrected). With respect to the left pSTS, increased O_2Hb peak values were observed for sad and fearful as compared to neutral stimuli ($2.14<t<3.22$, $p<.05$; BH-corrected). Again, there was no O_2Hb concentration difference between the neutral and happy category ($t(32)=1.85$, $p=.08$).

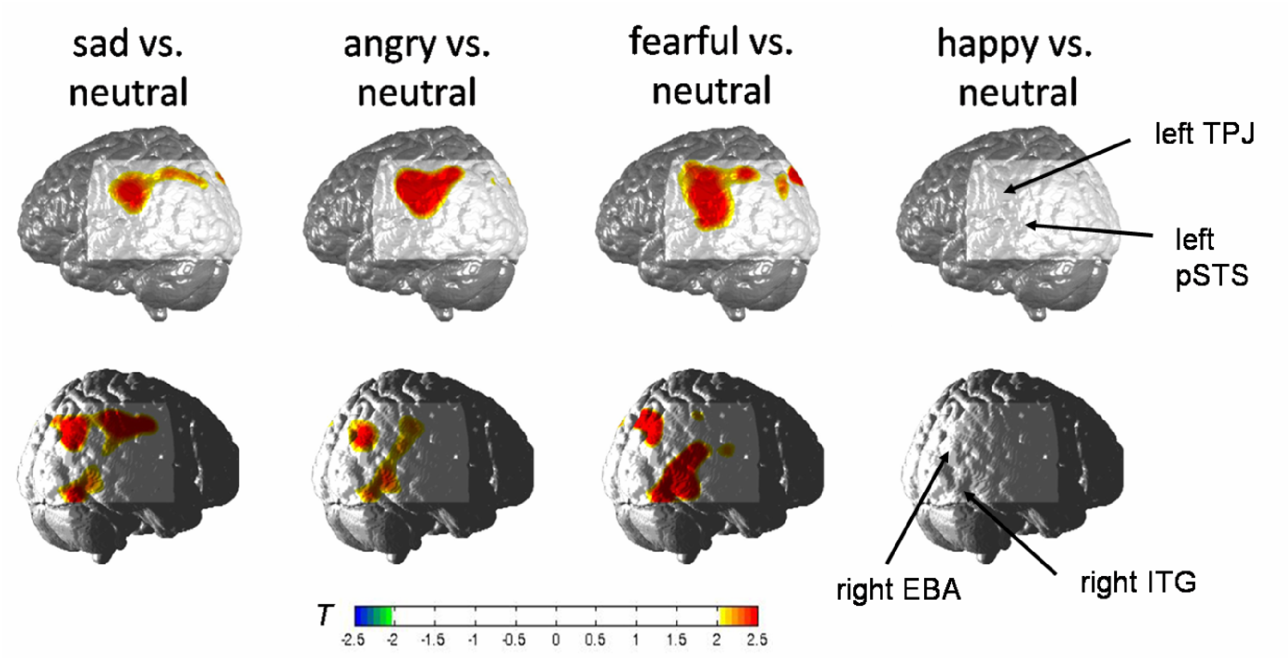

Figure 24. Contrast maps illustrating the differential O_2HB concentration changes for sad, angry, fearful, and happy walks, each contrasted to the control condition (neutral walks). T-values for the respective differences in O_2HB amplitude values (emotional - neutral) are depicted. For reasons of simplification, only T-values > ±2 are displayed. Arrows indicate the location of the following regions of interest (ROIs): left TPJ, left posterior STS (pSTS), right EBA, and right ITG. Contrast maps were created using MATLAB (The MathWorks Inc.).

Eventually, 2×5 RM-ANOVAs for the mean activation of all non-ROI channels did not reveal any significant main or interaction effects ($0.8<F<3.9$, $p>.05$). Figure 24 displays differential O_2HB concentration changes for sad, angry, fearful, and happy walks as contrasted to the neutral walks (control condition).

4.1.4.3 Relationship of Neurophysiological data, behavioural, and subjective measures

There were significant positive correlations between the preference for a favourable emotion regulation strategy (re-evaluation of the situation) and haemodynamic responses within the left posterior STS after angry walks ($r=.42$, $p<.0167$) and the left TPJ after angry ($r=.51$, $p<.0125$) or sad avatars ($r=.35$, $p<.05$) were presented. None of the other psychometric measures correlated significantly with NIRS activation within one of the ROIs. Interestingly, however, explorative calculations revealed that emotion regulation further correlated positively with sadness identification accuracy ($r=.49$, $p<.0125$). Sadness identification accuracy, again, was strongly correlated with O_2Hb concentration changes within the right ITG ($r=.43$, $p<.0125$), marginally significant within the EBA ($r=.33$, $p=.058$), and highly significant regarding the left posterior STS, and left TPJ (both: $r=.53$, $p<.01$) after viewing sad avatars. Hence, in order to clarify whether the above reported correlation between left temporal brain activation and emotion regulation strategy preference was mediated by emotion recognition accuracy, the partial correlation coefficient $r_{X,Y.Z}$ was correlated, with X = emotion regulation strategy preference, Y = O_2Hb concentration increases after sad walks in the left TPJ, and Z = sadness identification accuracy. Keeping Z constant, the relation between emotion regulation and cortical activation vanished ($r=.11$, n.s.; see Figure 25).

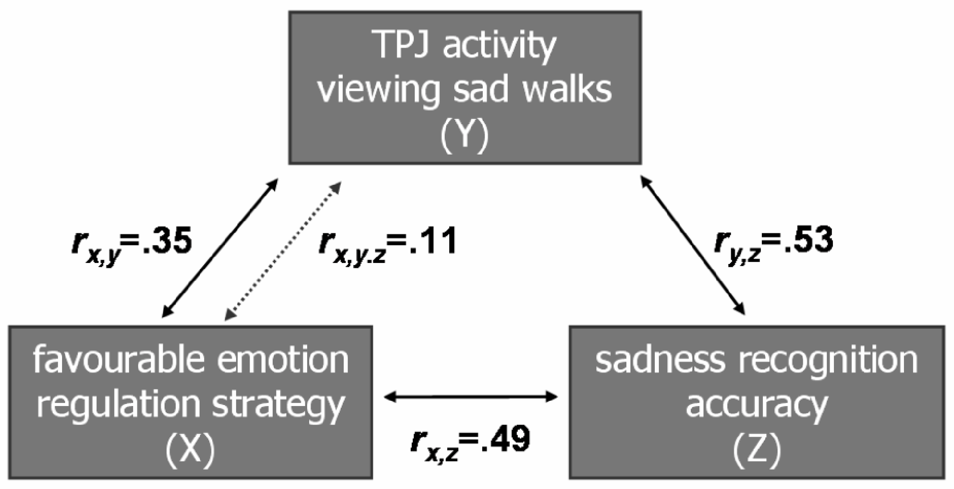

Figure 25. Graphical illustration of the relationship between O_2HB amplitudes in the left TPJ after sad walks, emotion recognition accuracy after sad walks, and preference of favourable emotion regulation. Pearson correlation coefficients ($r_{x,y}$/ $r_{x,z}$/ $r_{y,z}$) and the partial correlation coefficient $r_{x.,y.z}$ are provided.

Analogue to the accuracy-brain response correlations, we found significantly negative correlations between RTs and cortical activation parameters for sad avatars: $r_{\text{RT,left TPJ}}=-.46$, $p<.01$; $r_{\text{RT,left STS}}=-.40$, $p=.019$. There was also a trend for such a negative correlation in the angry condition ($r_{\text{RT,left TPJ}}=-.41$, $p=.018$) that did, however, not meet Bonferroni-Holm significance level correction. For sad avatars, subjective recognisability tended to correlate positively with haemodynamic responses ($r_{\text{Recogn,left TPJ}}$=.40, p=.02; $r_{\text{Recogn,left STS}}$=.33, p=.05).

4.1.5 Discussion

The present study addressed the question whether fNIRS is a reliable method for depicting activity changes in cortical regions that are associated with emotion perception from human body movements. As fNIRS is known for its great advantages in the field of psychiatry research (Ehlis et al., 2014), the NIRS paradigm investigated and presented in the present study will be the method of choice for future applications within big samples of psychiatric patients suffering from different psychological syndromes. In order to elucidate the method’s potential to investigate the activity of a distributed brain network involved in bodily emotion expression, the present study investigated the effects of emotion modulation on cortical haemodynamic responses elicited by the perception of dynamic human gait patterns and assessed via fNIRS. This study constitutes the first approach using functional NIRS in combination with newly developed dynamic body stimuli that are characterised by high ecologic validity and simultaneously allow to control for a number of possibly confounding factors (such as walking speed or actor's gender). Our results suggest that activation within a cortical network, involving right and left occipito-temporo-parietal areas, is enhanced when negative emotional gaits (sad, fearful or angry) are observed. There was no such effect for positive emotions (i.e. happy walks).

In more detail, significant activation increases were observed for sad, angry, and fearful gait patterns within the right EBA, the right ITG, and the left TPJ during the emotion task. Angry and fearful walks further elicited brain activation increases in the left posterior STS. We interpret this finding in terms of emotion recognition processes. Viewing the body movements already enhances O_2 metabolism, as indicated by increases in O_2HB concentration that also occurred when neutral walks were observed. However, differentially pronounced O_2HB concentration increases for sad, angry, and fearful compared to neutral gait patterns suggest that functional activity within these cortical areas is linked to the perception of negative emotions. This interpretation is particularly supported by the finding that mean O_2HB concentration increases in all non-ROI channels did not differ between emotional and neutral body movements, implying that activity in these non-ROI cortical areas was not modulated by emotional expressions. As the neutral avatar videos were speed matched to the emotional stimuli, we conclude that the observed brain activation pattern reflects neurophysiological processes that are specific for the emotional content of the gait pattern rather than speed sensitive. In sum, we could show that emotional modulation of cerebral activation in body sensitive cortical areas can be (1) demonstrated for basic types of body movements (gait) and (2) depicted using NIRS measurements. Interestingly, the present study further indicated that for NIRS paradigms involving videos of emotional body movements such as the one implemented in the present experiment, different analysis strategies may lead to very different outcomes and therefore need to be considered carefully. In detail, model-based (GLM) NIRS data analyses were found to be less appropriate to assess our haemodynamic data for two main reasons: First, while model-based topographical analyses require one specific peak-time that will be equally modelled for all channels, a relatively high variability in peak latencies between different brain regions of interest (occipital vs. temporo-parietal) was observed here. Second, event-related averages of the haemodynamic responses further showed that, especially within laterally located channels, the O_2Hb time course was too complex to be simulated by a Gaussian haemodynamic response function (see lower panel of Figure 23) which, therefore, would have been rather inappropriate to model the HRF in the present data. This complex time course of O_2Hb, in some channels already apparent during the baseline period, may be attributed to the occurrence of complex evaluative processes that are involved in the perception of (especially emotional) body movements. This interpretation is further supported by the fact that a rather pure NIRS signal (no baseline signal change, only one clear HRF peak) can be observed in primary visual areas associated with rather basic encoding of visual input. However, an alternative explanation for the complex O_2Hb course observed in some temporo-parietal channels that cannot be entirely ruled out refers to the somewhat short ITI used in the present study which may have led to an affection of a given HRF by the respectively proceeding trial. Although similar ITIs have been reported in previous NIRS studies (Telkemeyer et al., 2011; Tupak et al., 2013), it cannot be conclusively clarified whether video triggered HRFs could have somewhat influenced the subsequent trial. Further studies using a smaller number of experimental conditions but extended ITIs may help to elucidate this question.

Consistent with the present results, previous studies addressing the anatomic and functional correlates of emotion perception from whole body movements identified different cortical brain regions that may be involved, such as the EBA, the ITG/FBA, the STS, and the TPJ (e.g., Grèzes et al., 2007, Kret et al., 2011; see also introduction). Especially for fearful and angry body movements, brain activation increases have been reported in these areas (e.g., Kret at al., 2011; Pichon et al., 2009). Although certain deeper brain regions (Amygdala, Insula) have been shown to be also sensitive for emotion expressed in bodies and/or body movements (Hadjikhani & de Gelder, 2003; Peelen et al., 2007), by now the majority of studies focus on the main cortical regions, such as the EBA, FBA, or the STS. Enhanced cortical haemodynamic responses, however, were observed only for negative but not positive (i.e. happy) emotional walks in the present study. This finding may a) reflect a valence effect of emotional stimulation on regional brain activation patterns or b) be attributed to restricted expressiveness of the specific type of stimulation material (avatar gait patterns) for positive emotions.

Although findings from other neuroimaging studies could help to clarify the background of this lacking effect for happy walks, the neurophysiological response to happy whole body movements has been poorly investigated so far, as most experiments used stimuli of negative valence. Peelen et al. (2007) and Atkinson et al. (2012) reported enhanced activity in the EBA and FBA for both angry and happy body movements compared to neutral stimuli. These studies suggest that body sensitive cortical regions such as the EBA or the FBA are sensitive for both negative and positive emotion categories. In contrast to the present experiment, these studies used point-light instead of full-light stimuli showing typical emotional gestures instead of emotional walks. Moreover, analyses of the stimulus ratings revealed that happy walks were most difficult to identify by our subjects. The positive correlation between emotion recognition accuracy and activation in the right ITG, left TPJ, left posterior STS, and, to a lesser degree, in the right EBA, suggests that easier and better emotion recognition was associated with higher cortical activation within respective areas. Emotion recognition accuracy, in turn, is related to the emotional expressiveness of a given stimulus. We therefore conclude that happy avatar walks in particular may have lacked emotional expressiveness and were thus not associated with a significant increase in cortical brain activation in contrast to the negative emotion categories.

Moreover, there is another feature in which happy walks may differ from the other three emotional gait patterns, that is related to emotional and behavioural implications of the perceived emotional body expression for the observer. Whereas sad and also fearful body expressions may trigger secondary emotional reactions, such as empathy, in the observer, threatening (i.e. angry) walks may be associated with an activation of our internal defence or avoidance system. In both cases, the perceived emotion has relevant implications for the observer. A number of theories emphasise the communicative function of emotional expressions and postulate a direct link between perceiving other's emotional states and own motivational and action tendencies, including approach and avoidance behaviour (see for example Fischer & Manstead, 2008; Frijda, 2010; Lang & Bradley, 2010; Niedenthal & Brauer, 2012; Reis & Gray, 2009). In contrast to sad, fearful and angry body movements, the observation of happy walks may initiate less personal involvement due to their, compared with negative walks, reduced personal relevance and implications for the observer's behaviour. Whereas happy faces have been shown to induce approach behaviour during behavioural studies (Rotteveel & Phaf, 2004; Seidel, Habel, Kirschner, Gur & Derntl, 2010; Stins, Roelofs, Villan, Kooijman, Hagenaars & Beek, 2012), we propose that happy walking patterns may be less crucial for indicating reward and thus trigger appetitive behaviour to a lesser extent than happy, smiling faces. This could, at least in part, explain the missing haemodynamic effect of happy avatar walks in the present study. This interpretation is strongly supported by a behavioural study conducted by Ikeda and Watanabe (2009), who investigated emotion recognition in point-light walkers using neutral, angry and happy biological motion stimuli that were embedded in dynamic noise (moving dots). Participants had to a) judge whether moving dot stimuli contained biological motion (gait identification task) and b) identify the expressed emotion in these trials containing biological motion (emotion recognition task). Results revealed that emotion detection performance was higher for angry compared to happy walks and correlation analyses revealed that only for angry – but not for happy – biological motion emotion recognition performance was clearly linked to gait detection performance. The authors suggest that it may be more crucial for the observer to identify walks of aggressive rather than happy persons. Our present results support this hypothesis.

A detailed review of the recent literature concerning neurobiological emotion perception from whole-body movements revealed emotion-specific brain activation increases in cortical regions that are associated with body perception during various different task designs and paradigms. In some studies, subjects had to explicitly name the observed emotion (Pichon et al., 2009; Sinke et al., 2009; van de Riet, Grèzes et al., 2009), whereas other investigations used oddball paradigms containing up-right and inverted body stimuli (Grèzes et al., 2007; Kret et al., 2011; Pichon et al., 2008). Again other studies had participants provide intensity ratings for each seen emotion (Peelen et al., 2007; Peelen et al., 2010). Brain activation patterns in respective brain regions, such as the EBA, FBA, TPJ, and the STS, therefore appear to be independent of task type. Taking the factor task block into account, our statistical analyses revealed mixed results: Although we found similar O_2HB concentration increases within the pre-defined ROIs after viewing emotional vs. neutral avatars, significant task-by-emotion interactions for the right EBA and the left TPJ indicated that for these two areas, emotion related signal increases were significant only for the emotion discrimination task. Hence, additional processes of conscious emotion recognition occurring during the emotion task block may have reinforced the emotion specific cortical activation within the EBA and the TPJ. With respect to the STS and ITG, however, emotion triggered brain activation increases took place even when the emotional content is perceived unintentionally. This finding is well-consistent with the observation made by de Gelder and Hadjikhani (2006) in a patient with unilateral striate cortex damage: presentation of happy vs. neutral body images to the patient's blind hemifield triggered activation increases within the STS and the inferior temporal sulcus, pointing towards possible implicit bodily emotion perception in those areas.

In order to investigate certain relationships between the observed cerebral activation patterns and behavioural outcomes, additional correlation analyses were computed. Hereby, a crucial role of particularly the sad avatars was reflected in the various correlations that were found for O_2HB concentration increases and emotion recognition performance, subjective recognisability and personal emotion regulation strategies. Whereby high positive correlations between O_2HB amplitudes and emotion regulation were also observed for angry avatars, we found an interesting threefold relationship between cortical haemodynamic responses, emotion recognition performance, and emotion regulation preferences only for sad walks (see Figure 25): High preference for functional emotion regulation strategies (trying to re-evaluate a situation whenever bad feelings occur in order to cheer up) was associated with better recognition performance and higher brain activation increases, which were themselves positively correlated with emotion recognition performance. The computation of partial correlation coefficients showed that the relationship between emotion regulation behaviour and brain activation in the TPJ after sad avatars was entirely mediated by the ability to correctly recognise sad walks. This correlation pattern illustrates the connection between interindividual differences concerning the ability to recognise sadness from pure gait and personal emotion regulation tendencies as well as the neurophysiological counterpart of sadness recognition. This leads us to the hypothesis that certain populations showing dysfunctional emotion regulation strategies – such as, e.g., psychiatric patients – may show impaired sadness recognition from gait patterns and may thus be linked to accordingly lowered cortical responses to sad body movements. Future studies investigating respective patient groups are needed to further investigate this hypothesis.

Despite these interesting findings that leave much room for interpretation and raise possible future research questions, there are some limitations in this study that need to be kept in mind. An important restriction is the limitation of neurophysiological data acquisition to temporo-parietal and occipital areas. Different studies have reported an involvement of frontal brain areas, especially the inferior frontal gyrus (IFG) and premotor cortex (PMC), in emotion processing from whole-body movements (Grèzes et al., 2007; Pichon et al., 2009; Sinke et al., 2009). Amoruso, Couto and Ibanez (2011) proposed a model of an integrative brain network, including the prefrontal cortex, that might be critical for contextual emotion recognition from human action. The present investigation primarily focussed on posterior regions of interest, for which the most robust effects have been reported in previous research. In future studies, however, another probeset arrangement or even the simultaneous use of two NIRS systems (in order to double the number of assessable channels) should be considered.

4.1.6 Conclusions

The present study provides a new and innovative approach to investigate neurophysiological correlates of emotion recognition from human gait. For both stimulation material (computer-animated avatar videos that were created from motion-captured actors) and neurophysiological assessments (NIRS measurements), methods of particularly high ecological validity were used. We showed that negative emotional gait patterns, but not happy walks, were associated with brain activation increases in the right EBA, right ITG, left TPJ and left STS, cortical regions that have been consistently shown to respond to dynamic body expressions (other than gait) in previous studies using different stimuli and imaging techniques. Our results further indicate that these cortical activation patterns were confirmed for sad gait patterns even if the emotional content was unattended, and that they are related to emotion recognition performance and, at least indirectly, to emotion regulation tendencies. We conclude that fNIRS is now ready for further applications to assess functional alterations in the here reported cortical activation patterns in people suffering from psychiatric diseases. Future studies should therefore explore cortical activity in different neuropsychiatric disorders linked to alterations in affective processing. NIRS has been proven to be a useful tool aiming at these perspectives.

4.1.7 Study 3 – Supplementary material

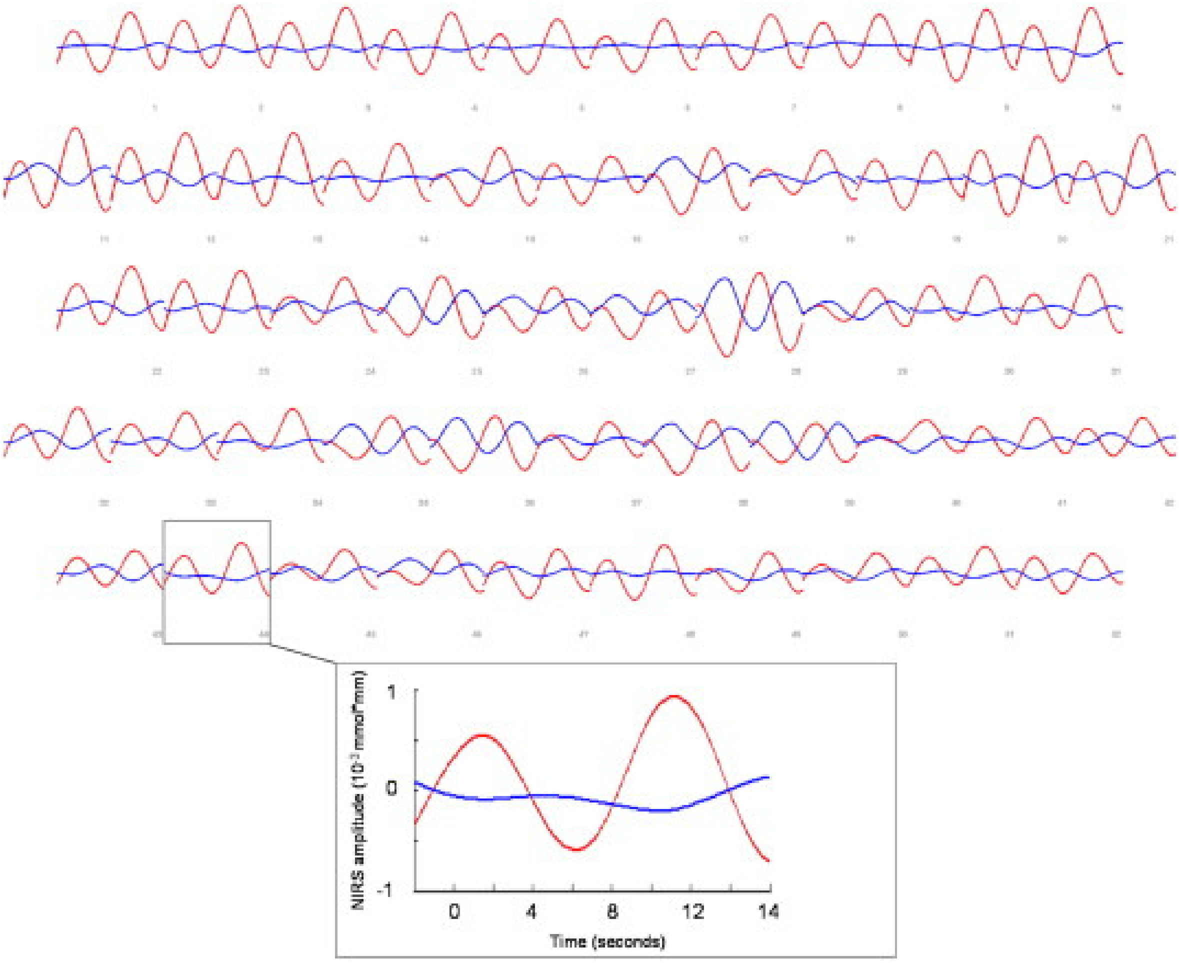

Figure 26 (suppl.). Graphical illustration of the event-related O_2HB (red line) and HHB (blue line) time courses in all 52 channels (probe set view) exemplarily for one experimental condition (fearful walks, emotion discrimination task). Numbers displayed at the bottom of each row indicate respective channel numbers.

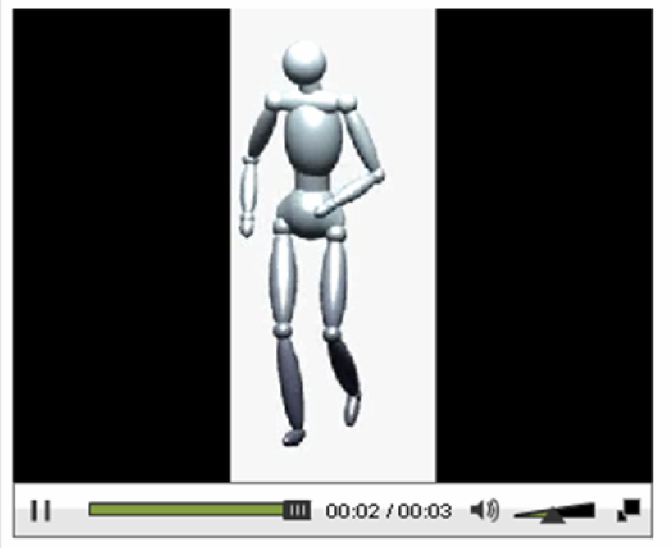

Figure 27 (suppl.). Exemplary avatar video of the angry walks category. The supplementary video file is hosted the Science Direct webpage: http://www.sciencedirect.com/science/article/pii/S1053811913008471.

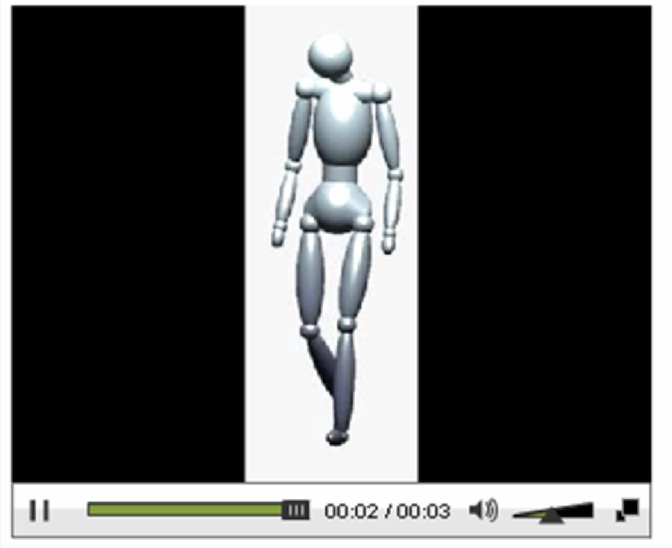

Figure 28 (suppl.). Exemplary avatar video of the sad walks category. The supplementary video file is hosted the Science Direct webpage: http://www.sciencedirect.com/science/article/pii/S1053811913008471.

4.2 Study 4:

Distinct cortical activation patterns and functional connectivity during emotional body perception in Schizophrenia and Major Depression

The contents of this chapter are currently submitted for publication at

Journal of Psychiatry and Neuroscience.

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4.2.1 Abstract

While the neurobiological basis of facial emotion processing in patients with schizophrenia has been intensively investigated, little is known about the neural background of impairments in recognising affect from body language. Both altered brain activity and/or deficient functional connectivity could account for the recently reported finding of impaired emotion recognition from body movements in schizophrenia.

Functional near-infrared spectroscopy (fNIRS) was used to investigate oxygenation patterns and activation coherence of occipito-temporal cortices in patients with schizophrenia (SZ; n=20) as compared to a matched healthy (HC; n=20) and a clinical (20 patients with major depression [MD]) control group. During fNIRS measurements, participants performed an emotion recognition paradigm presenting walking avatars that showed emotional and neutral body movements.

Only SZ patients showed impaired emotion recognition from body movements. Deviating neurophysiological responses to emotional body movements were found for both patient groups within the right extra-striate body area, and for SZ only within the left superior-temporal sulcus (STS), and the primary visual cortex. Functional connectivity between occipito-temporal cortices was reduced in both patient groups with a more pronounced decrease in SZ. STS hyper-activation and disconnection was associated with positive symptoms in schizophrenia.

Using fNIRS, we can detect functional differences between different psychiatric diagnoses that may be associated with impaired bodily emotion recognition. Because such impairments are frequently linked to severe deficits in social functioning, future studies will have to clarify how these activation patterns evolve in the course of the disorder and how they change with therapeutic interventions.

4.2.2 Introduction

The neurophysiological processing of human body movements and body expressions represents a relatively young, but recently expanding research topic within the field of psychological neuroscience. In healthy subjects, several brain regions have been determined including, beyond subcortical structures such as the amygdale (e.g. Bonda et al., 1996), a distributed cortical body perception network, which is partly overlapping with face-selective areas. It comprises at least the visual association cortices including the extrastriate body area (e.g. Atkinson et al., 2012; Downing et al., 2001), body-selective parts of the fusiform cortex (Peelen & Downing, 2005b; Schwarzlose et al., 2005), together with regions associated with biological motion and social information perception, especially the superior temporal sulcus (STS) region (e.g. Allison, Puce & McCarthy, 2000; Atkinson et al., 2012; van de Riet et al., 2009). These aforementioned regions have been further reported to selectively respond to body cues expressing emotional states, (e.g. Grèzes, Adenis, Pouga & Armony, 2013; Hadjikhani & de Gelder, 2003; Peelen et al., 2007; Schneider, Christensen et al., 2014; Sinke et al., 2010; Van den Stock, Tamietto et al., 2011). In addition, other areas that are closely related to emotional processes (e.g. orbitofrontal cortex [OFC] and inferior frontal gyrus [IFG]) or motor control (premotor cortex and supplementary motor area), have also been shown to be selectively activated by emotional versus neutral body expressions (de Gelder et al., 2004; Grèzes et al., 2013; Sinke et al., 2010; Van den Stock, Tamietto et al., 2011).

Only very recently, the processing of emotional body cues has started to be investigated among people suffering from psychological or psychiatric illness such as schizophrenia. However, functional imaging studies are sparse. In Bigelow et al. (2006), deficits in patients with schizophrenia were found when the emotional content of still body postures had to be judged. However, valence or emotion specificity of these deficits was not analysed in this work. Couture et al. (2010) used a point-light displays (PLD) test among other tasks testing social-cognitive skills in patients with schizophrenia and autism. Both groups performed more poorly in the PLD test than controls, independent of emotional valence. Van den Stock, de Jong, et al. (2011) presented static pictures of emotional body postures to healthy subjects and patients with schizophrenia or non-schizophrenic psychosis. Schizophrenia patients were significantly impaired in recognising body expressions, but again, these deficits were not emotion specific. The ability of schizophrenia patients to recognise emotional states from human gait patterns has been recently investigated by Peterman et al. (2014) who presented a set of volumetric, faceless avatars expressing either a neutral, happy, or angry state while walking. Discrimination sensitivity was reduced in patients regarding both emotion and gender recognition, suggesting that disease-related deficits in extracting social information from human gait were not limited to emotions. However, it is not clear how schizophrenia patients would perform if more emotional choices were presented. Moreover, because so far no neuroimaging study has been published, nothing is known about functional brain alterations that may underlie the reported emotion recognition deficits from body movements. Therefore, the generation of reasonable hypotheses may be supported by the wealth body of research findings regarding emotion processing from faces in schizophrenia. Recent meta-analyses suggest that facial emotion recognition impairments in schizophrenia are severe (Chan et al., 2010; Kohler et al., 2010), and may be even more pronounced than deficits in facial perception per se (Chan et al., 2010). Different imaging studies have reported reduced activation within subcortical (amygdala and parahippocampus) and cortical (e.g. fusiform cortex, STS) regions during the perception of affective versus neutral faces (see Delvecchio et al., 2013; Li et al., 2010). In recent years, these findings have been relatively mutually attributed to elevated responses of these cerebral structures to neutral faces in schizophrenia patients (Anticevic, Van Snellenberg, Cohen et al., 2012; Delvecchio et al., 2013; Hall et al., 2008; Holt et al., 2006; Surguladze et al., 2006), resulting in decreased activity when the contrast emotional – neutral is regarded. Notably, facial emotion perception seems to be more strongly impaired in schizophrenia than in other clinical groups, e.g. affective disorders, although also for these diagnoses distinct emotion recognition impairments have been reported (Addington & Addington, 1998; Feinberg et al., 1986; Gaebel & Woelwer, 1992). Therefore, patients with depression may serve as a suitable clinical control group also when body-based emotion recognition is addressed.

Functional near-infrared spectroscopy (fNIRS) is a relatively new neuroimaging method which has been increasingly applied in psychiatric research. Despite some limitations compared to other techniques (e.g., functional magnetic resonance imaging [fMRI] or positron emission tomography [PET]) – comparably low spatial resolution (10–30 mm) and limited coverage of more deeply located brain structures –, fNIRS applications in psychiatry have been rapidly progressing in recent years (Ehlis et al., 2014) because they assess brain activity in naturalistic positions quickly, easily and non-invasively. NIRS measurements are not tied to the invasive use of radioactive agents or noisy and tight, possibly fear-evoking measurement settings. They are quite insensitive to distal muscle activity/body movements, which may be relevant in measurements of brain activity in psychiatric patients, especially if they show acathisia or extrapyramidal symptoms. In recent years, analysis strategies of fNIRS data have strongly developed and methodologically improved. Beyond event-related analyses of concentration changes of (de)oxygenated haemoglobin, functional connectivity between, for example, different fNIRS channels is becoming increasingly investigated in fNIRS studies. Such studies particularly emphasise the promising translation/integration of elaborate data analysis strategies that are already established for more "conventional" neuroimaging methods (such as EEG or fMRI) into more recently established fNIRS measurements with their specific advantages in psychiatric neuroscience.

The present study uses this advantageous combination to investigate both event-related cortical activity and functional connectivity during emotion processing from whole-body movements in patients suffering from psychiatric disorders. Hereby, the following unanswered questions shall be investigated: Do patients with Schizophrenia show altered cortical activity – compared to healthy controls – during the perception of emotional body movements? Are there differences in contrast to a clinical control group (patients with Major Depression [MD])? Do patients and healthy subjects show differences in functional connectivity during the perception of bodily expressed emotions and, if so, how may these differences be related to psychopathology and/or emotion recognition impairments? The use of a clinical control group (MD patients) shall help to elucidate the diagnostic specificity of potential anomalies in recognising emotions from bodies in Schizophrenia.

4.2.3 Materials and Methods

4.2.3.1 Subjects

A total of 64 participants were initially enrolled in the study (20 healthy subjects, 20 patients with major depression, 24 patients with schizophrenia). Healthy subjects were recruited at the Department of Psychology, SZ and MD inpatients from a ward of the University Clinic of Psychiatry and Psychotherapy in Tuebingen. Outpatients were recruited via online advertising. After complete description of the study, written informed consent was obtained. The study was approved by the Ethics Committee of the University of Tuebingen; all study procedures were in line with the Declaration of Helsinki in its latest version.

Table 7. Demography of experimental groups and pharmacological treatment of the patient groups (SZ and MD).

	HC	**MD**	**SZ[1]**
N (male/female)	20 (12/8)	20 (12/8)	20 (14/6)
Number of inpatients	--	14	19
Mean Age (SD) in years	32.1 (11.7)	33.9 (13.9)	32.6 (7.7)
Median educational level (range)*	4 (1-5)	4 (1-5)	4 (1-5)
Smoking habits**	1.95 (5.39)	4.65 (7.62)	8.20 (11.03)
Drinking habits**	2.42 (2.61)	1.50 (2.76)	0.63 (1.22)
Psycho-pharmacological treatment (substance groups)	--	SSRI (n=7), SSNRI (n=6), SGA (n=5)[a], none (n=5), BZ (n=3), TCA (n=1), Lithium (n=1), MAOI (n=1), NDRI (n=1), AC (n=2)[b]	FGA (n=1), SGA (n=19), SSRI (n=3), SSNRI (n=2), Lithium (n=2), none (n=1)
Exclusion criteria	present or past psychiatric disorders (exceptions: specific phobia, past single depressive episode)	obsessive-compulsive disorders, eating disorders, bipolar disorder, borderline personality disorder, schizophrenia	obsessive-compulsive disorders, eating disorders, bipolar disorder, borderline personality disorder, major depression

AC = Anticonvulsants; BZ = Benzodiazepines; FGA = First-generation antipsychotics, NDRI = Noradrenalin-dopamine reuptake inhibitor; SGA = Second-generation antipsychotics, SSNRI =

Selective serotonin-noradrenalin reuptake inhibitor; SSRI = Selective serotonin reuptake inhibitor; TCA = Tricyclic antidepressants.

[1] Four datasets (all SZ group) were excluded because they showed an insufficient trial number of correctly identified emotions throughout the emotion recognition paradigm (threshold: 66 percent correctly recognised trials per emotion category).

* Educational level ranged form 1 (no school qualifications) to 5 (college/university graduation).

** Average number of cigarettes/ day or alcoholic drinks/ week, respectively.

[a] SGA doses were far beyond the antipsychotic action spectrum (max. 150 mg)

[b] Amlodipin and Lyrica were administered to reduce depressive or anxiety symptoms, respectively.

Patients were diagnosed based on the German version of the Structured Clinical Interview for *DSM–IV* (Wittchen, Zaudig & Frydrinch, 1997). Groups did not differ with respect to age ($F(2,57)<1$, $p=.86$), sex ($\chi^2(2)=0.57$, $p=.75$), educational degree ($\chi^2(2)=0.57$, $p=.90$), or handedness ($\chi^2(2)=1.03$, $p=.60$). Group differences were found for nicotine ($\chi^2(2)=3.87$, $p<.20$) and alcohol consumption ($\chi^2(2)=6.43$, $p<.20$). Table 7 provides an overview over the exclusion criteria and demographic features of all three groups as well as the pharmacological treatment in the patient samples.

4.2.3.2 Stimuli

A detailed description of the creation of the dynamic body stimuli that were used in the present study can be found in (Roether, Omlor, Christensen et al., 2009; Roether, Omlor & Giese, 2008; Roether, Omlor & Giese, 2009). Here, we used video clips (duration: 3 seconds) showing grey, volumetric avatars that walked across the screen as on a treadmill. Walking direction was either slightly to the left or to the right (about 22°) and the avatars' walking patterns expressed either a neutral mood or one of the following emotions: sadness, anger, fear, or joy. Neutral walking sequences were speed matched to the – by nature – slower (e.g., sad walk) or faster (e.g., angry walk) emotionally expressive gait patterns. For two exemplary videos, please see the supplementary files of (Schneider, Christensen et al., 2014).

4.2.3.3 Experimental Procedure

Participants were seated in a sound-attenuated room approximately 75 cm in front of a computer screen. During the emotion recognition paradigm (please see Schneider, Christensen et al., 2014 for detailed descriptions) participants viewed 3 s video trials, with 24 videos per emotion category (neutral, anger, sadness, fear, and joy). Subjects were asked to identify the emotion expressed by an avatar via button press. In a second task (with counterbalanced task sequences), participants judged the walking speed of the same videos used in the emotion recognition task on a 5-point scale (very slow – very fast).

The current state of psychopathology in the patient samples was assessed by the Positive and Negative Symptoms Scale (Kay et al., 1987) including its subscales measuring positive (PANSS-pos), negative (PANSS-neg), or global (PANSS-g) symptom severity or General Depression Scale (GDS; Hautzinger, Bailer, Hofmeister & Keller, 2012).

4.2.3.4 Near-infrared Spectroscopy

NIRS measurements were conducted with the ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan) using a 52-channel array of optodes (17 light sources/emitters, 16 detectors, emitter-detector distance: 30 mm) covering posterior (occipital-parietal-temporal cortex regions) areas on the head. Near-infrared light of two wavelengths (695 and 830nm, respectively) was used. NIRS optodes were attached to the subject’s head using a plastic array of optode holders in a rectangular shape that was placed on the occiput with respect to the international 10/20 system (Jasper, 1958) with the middle channel in the lowest fNIRS channel row corresponding to Oz and the most anterior NIRS channels of that bottom row corresponding to T3 (T7) and T4 (T8), respectively (see Figure 29).

To obtain anatomic channel assignment to corresponding cortical brain regions located beneath the NIRS probeset, we performed the spatial registration method of NIRS channels introduced by Cutini et al. (2011). Figure 29 displays the so-estimated cortical projection points of the NIRS channels. Notably, the resulting NIRS channel projection points were highly similar to those obtained by means of a single subject spatial registration approach that was used in our previous study (Schneider, Christensen et al., 2014). Based on the channel results, two cortical regions of interest (ROIs) which have been most frequently associated with emotion perception from dynamic body stimuli (see de Gelder et al., 2010) were defined according to our previous study (Schneider, Christensen et al., 2014; see Figure 29): (1) the bilateral EBA (at the junction of Brodmann Areas 18, 19, and 39), and (2) the bilateral posterior STS (pSTS). In order to investigate whether possible neurophysiological differences between groups occur already on an early perceptual stage, an additional ROI comprised the primary visual cortex (V1 area).

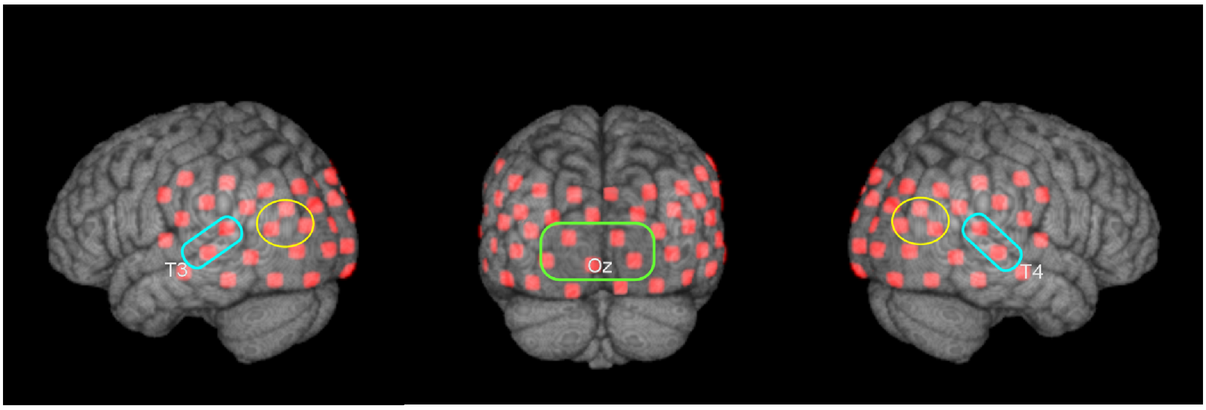

Figure 29. 3D illustration of NIRS channel arrangement over the cortex. To obtain these channel-cortex assignments, the NIRS probe holder array was placed on a physical head model that corresponds to the anatomical data of the International Consortium for Brain Mapping-(ICBM)-152 brain template provided by the McConnel Brain Imaging Centre of the Montreal Neurological Institute (MNI), McGill University. Coordinates of respective NIRS optodes and channels were obtained by applying a neuronavigation procedure (for a detailed description of the anatomic registration procedure, please see Cutini et al, 2011). Light red squares represent fNIRS channel projection points on the cortex. Electrode positions (T3, T4 and Oz) according to which the probe holder was placed on the head are provided in grey. Channels forming a region of interest (ROI) are highlighted as follows: yellow – EBA; green – V1; blue – pSTS.

4.2.3.5 Data Analyses

Changes in the concentration of oxygenated (O_2Hb) and deoxygenated (HHb) haemoglobin were recorded from a 10 s starting baseline continuously throughout the emotion discrimination paradigm (sampling rate: 10 Hz). Signal changes from 52 NIRS channels were measured, providing values for the changes in the concentration of O_2Hb and HHb for each channel (with haemoglobin quantity being scaled in Mm*mm).

Subsequent analyses of the recorded data were performed using MATLAB 7.9.0 (The MathWorks Inc., Natick, USA) and IBM SPSS Statistics (Armonk, USA). After data filtering (.008-.25 Hz band pass), event-related O_2Hb and HHb time courses were created according to each of the five stimulus categories (neutral, sadness, anger, fear, and joy). Segment length was 18 s including a 2 s pre-stimulus baseline. Amplitude averages of the haemodynamic response functions (HRFs) of O_2Hb and HHb within a 4-16 s segment following video onset were calculated per subject per condition. As in our previous study (Schneider, Christensen et al., 2014), mean amplitude values of event-related O_2Hb curves were exported in order to perform subsequent statistical analysis.

4.2.3.6 Statistics

To preserve conciseness, all analyses will be restricted to the emotion recognition task except for the behavioural data (accuracy [relative number of correct responses] and reaction times [RTs]), as *emotion* recognition from body movements is the actual focus of the present study. In order to find out whether emotion identification in particular or rather the global perception of body movement features (such as velocity) is impaired in SZ, behavioural task performance in both tasks will be compared. For the interested reader, we provide the results of fNIRS data analyses for the speed judgement task as supplementary data (see table 9 (suppl.)).

Main dependent variables, including (1) behavioural data (accuracy and RTs, recognition and arousal ratings) and (2) mean O_2Hb amplitudes per ROI, were analysed by means of 3 x 5 repeated measures analyses of variance (RM-ANOVAs) with the within-subject factor emotion (neutral, sadness, fear, anger, and joy) and the between-subject factor group (HC, SZ, MD). Bonferroni-Holm (BH) correction procedure was used to correct for multiple analyses caused by the investigation of five different ROIs, leading to corrected alpha levels of .01-.05 (the term "p<.05, BH corrected" will be used subsequently instead of quoting the exact corrected value each time). Whenever a main effect was significant, paired *t*-tests (main effect emotion) or two-sample t-tests (main effect group), respectively, were. In the event of significant interaction effects, separate two-sample *t*-tests were performed for each emotion category. For each level of the independent variables, Kolmogorov-Smirnov (K-S) tests were initially computed to confirm Gaussian distribution and Levene-tests were carried out to test for equality of variances for all group comparisons. Whenever both Levene-test and K-S-test revealed significant results ($p<.20$), t-tests were substituted by nonparametric tests (Mann-Whitney-U-test).

The emotion-dependent haemodynamic brain activation parameters per ROI (i.e., mean amplitudes of O_2Hb) were correlated with objective (accuracy, RTs) measures of emotion recognition performance separately for each group. For both patient groups, additional correlations were calculated between mean O_2Hb amplitudes within each ROI and respective psychopathology measures (SZ: PANSS subscales scores; MD: GDS sum score). For normally distributed variables, Pearson's correlation coefficients (r) were computed; otherwise nonparametric correlation measures (Spearman's ρ) were used. Hereby, two-sided testing procedures were used and p-values were Bonferroni-Holm corrected for emotion category (i.e. divided by 5).

Similar to recent studies applying functional connectivity analyses in event-related fNIRS studies (see, for example, Medvedev, Kainerstorfer, Borisov & VanMeter, 2011), functional coherence measures were based on coefficients of correlations between the O_2Hb time courses of different fNIRS channels (here: ROIs). Hereby, event-related O_2Hb time courses of a 16 s segment (starting point of each segment: beginning of a video trial showing a walking avatar) were correlated emotion- and subject-wise using Pearson's correlation coefficients between the following regions of interest: primary visual (V1), EBA & STS separately for both hemispheres (i.e. a 16 s O_2Hb time course [after neutral walks] of the V1 area was correlated with the respective time course of the right EBA in subject 1, subject 2, and so on). Because Pearson's correlation coefficients are not interval scaled (Bortz, 2005, p. 219), Fisher's z-transformations were applied to each correlation coefficient in order to compute average correlation values for each experimental group. Finally, these transformed correlations were statistically compared between groups using z-significance-tests which were Bonferroni-Holm-corrected (three group comparisons, leading to $.0167<\alpha<.05$ / $1.96<z_{krit}<2.39$). The z-scores were further used to calculate correlations between the coherence measures and emotion recognition performance as well as symptom severity (as measured by PANSS scales and the GDS score) in patients.

4.2.4 Results

4.2.4.1 Behavioural Data

For descriptive values of response accuracy and RTs in both the emotion recognition and the speed judgement task for three experimental groups, please see table 8.

Table 8. Overview over accuracy (relative frequency of correct responses) and reaction times (RTs in milliseconds) in the emotion recognition task and the walking speed judgement task.

	Emotion Recognition			**Speed Judgement**		
	HC	MD	SZ	HC	MD	SZ
Accuracy	**M±SD**	**M±SD**	**M±SD**	**M±SD**	**M±SD**	**M±SD**
Neutral	.65±.08	.66±.18	.63±.13	.91±.14	.99±.02	.97±.04
Sadness	.90±.12	.89±.12	.81±.13	.98±.04	.93±.09	.93±.07
Fear	.89±.11	.85±.13	.81±.19	.84±.25	.84±.19	.81±.20
Anger	.71±.07	.64±.13	.65±.14	.91±.10	.91±.11	.89±.08
Joy	.70±.16	.64±.22	.56±.18	.97±.05	.98±.03	.92±.11
mean	*.77±.06*	*.74±.11*	*.69±.10*[a]	*.92±.12*	*.93±.09*	*.90±.10*
RTs	**M±SD**	**M±SD**	**M±SD**	**M±SD**	**M±SD**	**M±SD**
Neutral	559±212	500±222	617±207	421±126	439±160	580±171
Sadness	541±208	509±224	658±197	425±138	480±192	645±231
Fear	539±207	543±165	697±240	459±153	496±204	694±265
Anger	506±193	519±264	624±169	414±138	452±206	659±211
Joy	525±194	498±176	663±229	412±133	414±138	571±178
mean	*534±182*	*514±186*	*652±185*[a,b]	*426±126*	*456±175*	*629±195*[a,b]

M = arithmetic mean, SD = standard deviation.

[a] SZ differed significantly ($p<.05$) from HC;

[b] SZ differed significantly ($p<.05$) from MD.

Emotion recognition task. RM-ANOVAs revealed significant main effects of emotion ($F(4,228)=50.29$, $p<.001$) and group ($F(2,57)=3.31$, $p<.05$) on emotion recognition accuracy. Accuracy was highest for both sad and fearful walks ($t(59)=0.86$, $p=.40$)

compared to all other emotion categories ($8.09<t<12.08$, $p<.001$) and that the SZ group responded less accurately than HCs ($t(38)=2.79$, $p<.01$). Regarding RTs, RM-ANOVAs indicated a main effect of group ($F(2,57)=3.27$, $p<.05$), with slowest RTs for SZ compared to both the HC group ($t(38)=2.03$, $p<.05$) and the MD group ($t(38)=2.36$, $p<.05$).

Speed judgement task. For walking speed judgements, we found a main effect of emotion ($F(4,121)=11.58$, $p<.001$) on accuracy and a main effect of group ($F(2,57)=8.53$, $p<.001$) on RTs. Across groups, speed recognition was poorest for fearful walks ($2.27<t<4.56$, $p<.05$). Post-hoc tests on RTs showed overall delayed reactions in the SZ group compared to both HC ($t(32)=3.91$, $p<.001$) and MD ($t(38)=2.95$, $p<.01$), who did not differ ($t(38)=0.62$, $p=.54$).

4.2.4.2 Neurophysiological Data

RM-ANOVAS revealed a significant main effect of group for the left pSTS ($F(2,57)=5.39$, $p<.05$ BH-corrected) as well as a significant group*emotion interaction for the right EBA ($F(8,228)=2.40$, $p<.05$ BH-corrected). Moreover, there was a trend for a group*emotion interaction within the V1 area ($F(5,228)=2.10$, $p=.06$). Further analyses of the pSTS group effect, which is illustrated in Figure 30A, showed that mean O_2Hb amplitudes within the pSTS were much higher for SZ compared to MD ($t(30)=3.46$, $p<.01$) and somewhat higher for SZ compared to HC ($t(38)=2.01$, $p=.05$), while HC and MD did not differ ($t(30)=0.97$, $p=.34$). Investigating the group*emotion interaction within the EBA, we found that both SZ and MD patients had higher mean O_2Hb amplitudes as compared to HC in response to neutral walks (MD-HC: $U=85.0$, $Z=3.11$, $p<.001$; SZ-HC: $U=123.0$, $Z=2.08$, $p<.05$), while in response to joyful walks only MD patients showed higher amplitudes then HCs ($U=114.0$, $Z=2.33$, $p<.05$, see Figure 31).

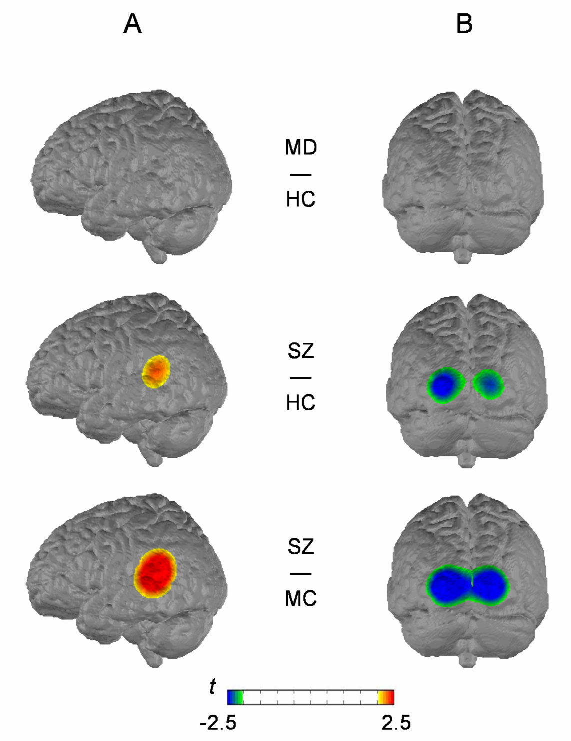

Figure 30. Illustration of A) the main effect of group for the left pSTS and B) the effect of group in the angry walks category as revealed by post-hoc comparisons that were performed to assess the group*emotion interaction in V1. Contrast maps between two groups are provided as follows: MD-HC: Patients with depression vs. healthy controls. SZ-HC: patients with schizophrenia vs. healthy controls; SZ-MD: patients with schizophrenia vs. patients with depression.

Trends towards slightly higher O_2Hb amplitudes for patients compared to controls were observed for the angry walks condition (MD-HC: U=136.0, Z=1.73, p=.08; SZ-HC: U=141.0, Z=1.60, p=.11). In addition, the two patient groups differed between each other: SZ showed higher mean amplitude values than MD with respect to sad (U=126.0, Z=2.00, p<.05) and, marginally, fearful (U=128.0, Z=-1.95, p=.05) avatars. Within the V1 area, our analyses revealed group differences as follows: In response to angry walks, SZ patients showed decreased O_2Hb amplitudes (see Figure 30B) compared to MD patients (t(36)=3.19, p<.01) and HCs (t(37)=2.31, p<.05).

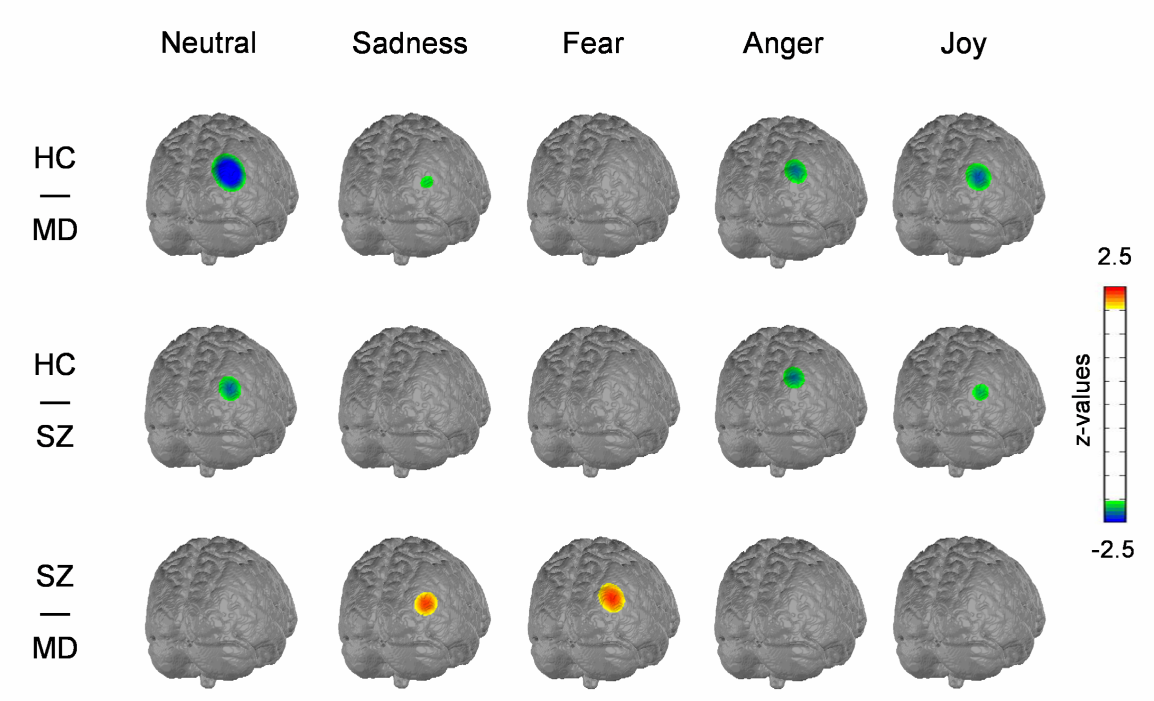

Figure 31. Contrast maps illustrating the group*emotion interaction found in the right EBA. *Z*-scores for comparing mean O_2HB amplitudes between the experimental groups separately for neutral, sad, angry, fearful, and happy walks are presented. HC – healthy controls; MD – patients with major depression; SZ – patients with schizophrenia.

4.2.4.3 Relationship of cortical haemodynamics, behavioural data and psychopathology

In the HC group, emotion recognition accuracy correlated with emotion-related O_2Hb amplitudes within the V1 area ($r_{Acc\_sad,O2Hb\_sad}=.49$, $p<.05$; $r_{Acc\_fear,O2Hb\_fear}=.48$, $p<.05$), the right EBA ($r_{Acc\_fear,O2Hb\_fear}=.44$, $p=.05$), and the left pSTS ($r_{Acc\_sad,O2Hb\_sad}=.60$, $p<.05$ BH-corrected). In SZ patients, only one analogue correlation has been found: Within the EBA, task performance was positively related to mean O_2Hb amplitudes ($r_{Acc\_joy,O2Hb\_joy}=.65$, $p<.05$ BH-corrected). The equivalent correlation in the MD group did not reach significance ($r_{Acc\_joy,O2Hb\_joy}=.39$, $p=.09$).

Regarding psychopathology, no correlations between mean O_2Hb amplitudes in any of the ROIs and depressive symptom severity were found in the MD group. For the SZ group, the subscale PANSS-pos correlated positively with O_2Hb amplitudes in the left pSTS

(ρ=.49, p=.04) and negatively with O_2Hb amplitudes in the V1 area (r=-.58, p=.01). However, both correlations only met the uncorrected significance level (p<.05).

4.2.4.4 Functional coherence analyses

Figure 32 shows Fisher's z-transformed correlation coefficients between haemodynamic time courses of V1, EBA, and STS per emotion category. Separate plots are provided for each experimental group and hemisphere. Z-tests indicated the following group differences of correlation coefficients: For the right hemisphere, functional coherence was decreased in both patient groups (MD and SZ) between V1 and the EBA as well as V1 and pSTS in the sad walks condition (V1-EBA: $2.43<z<4.18$, $p<.0167$; V1-pSTS: $1.97<z<2.55$, $.0167<p<.05$). In addition, SZ showed decreased coherence measures between V1 and EBA with respect to fearful walks (z=2.70, p<.0167). Regarding the left hemisphere, a similar pattern was observed (see Figure 32, left column), but BH-corrected z-Tests did not reveal any significant group differences.

Correlation analyses between z-scores reflecting functional coherence between the cortical regions of interest and behavioural performance measures (emotion recognition accuracy) did not reveal any significant relationships. However, in the SZ group, significant negative correlations between PANSS-pos scores and coherence between the pSTS and V1 area (right hemisphere, Figure 33) as well as coherence between the pSTS and the EBA (left hemisphere) emerged: $-.58<r<-.78$; p<.05 BH-corrected.

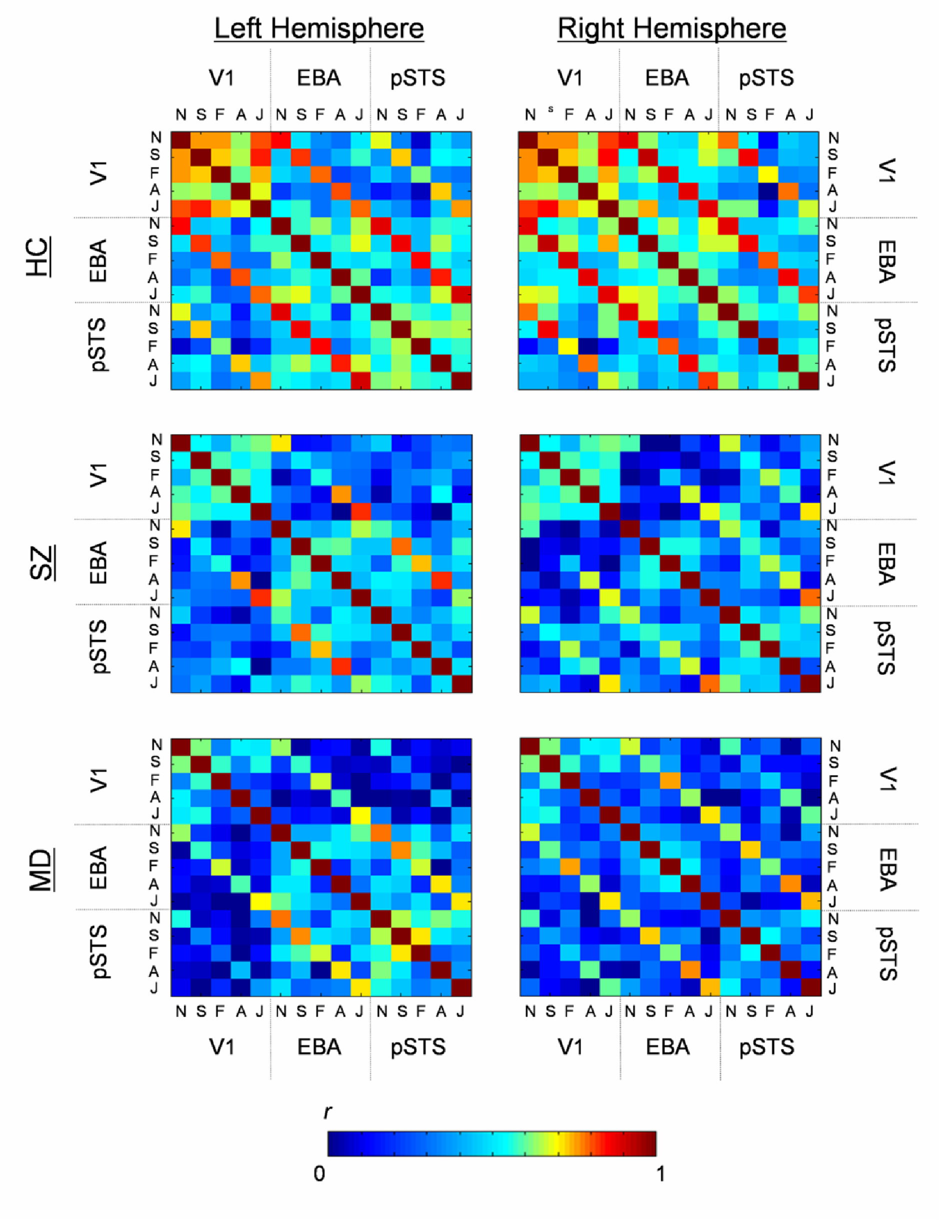

Figure 32. Illustration of functional coherence analyses for the three experimental groups between the V1, right & left EBA, and right & left pSTS, respectively. N = neutral walks; S = sad walks; F = fearful walks; A = angry walks, J = joyful walks. HC = healthy controls; MD = major depression; SZ = schizophrenia. Average correlations (per group) computed from back-transformed Fisher's z-scores are displayed.

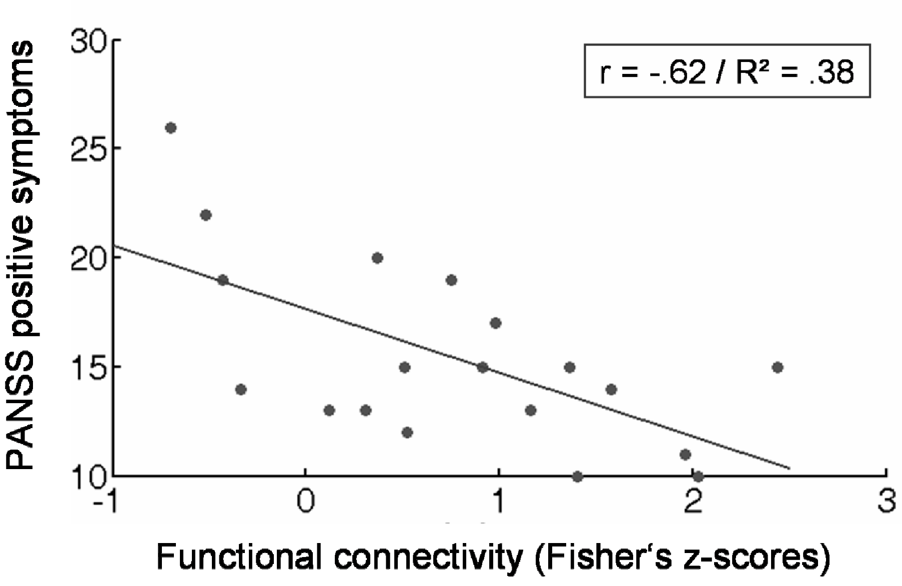

Figure 33. Correlation between functional coherence between the V1 and right pSTS (during angry walks processing) and total scores on the PANSS subscale "positive symptoms". The solid line represents the linear function of these data based on least mean squares.

4.2.5 Discussion

The present study investigated functional deficits in emotional body perception along with their neurophysiological correlates in schizophrenia as compared to a clinical (MD patients) and a non-clinical (HC) control group. FNIRS measurements were conducted while participants identified emotional states from walking avatars to investigate cortical haemodynamic activity as well as functional connectivity of cortical regions involved in the perception of emotional body language.

Recent behavioural studies have indicated that not only body perception (Soria Bauser et al., 2012), but also emotion identification from body movements (e.g. Peterman et al., 2014; Van den Stock, de Jong et al., 2011) may be impaired in schizophrenia. The present behavioural results of support this idea: In the emotion recognition paradigm, SZ patients performed less accurately than HCs and more slowly compared to both, HC and MD. In contrast, response accuracy in SZ was not impaired when other features than emotion had to be identified from the dynamic body cues (i.e. walking speed), suggesting a specific rather than a general deficit of schizophrenia patients in processing human body movements, at least for socially relevant (e.g. emotion, but also gender, cf. Peterman et al., 2014) as compared to socially less or even irrelevant information (i.e., walking speed). The lack of a significant interaction of group and emotion for the behavioural data reveals a valence-independent emotion recognition deficit from body movements which is in line with findings from recent studies using body (Couture et al., 2010; Peterman et al., 2014; Van den Stock, de Jong et al., 2011) or face stimuli (Kucharska-Pietura et al., 2005; Turetsky, Kohler et al., 2007). In addition, we could show for the first time that such impairments appear to be diagnostically dissociable: Only the SZ group but not the MD group showed reduced emotion recognition accuracy compared to HC.

Investigating the neurobiological background of schizophrenia related deficits in emotion recognition from faces, the majority of studies demonstrated that brain activation decreases in the contrast of emotional versus neutral faces are predominantly driven by enhanced neural responses to neutral stimuli in SZ (Anticevic, Van Snellenberg, Cohen et al., 2012; Delvecchio et al., 2013; Holt et al., 2006; Surguladze et al., 2006). In line with this view, the present results indicate an elevated cortical response (within the right EBA) to neutral stimuli in patients with schizophrenia when bodies were perceived. An increased response to neutral stimuli was also observed in the MD group, a pattern that has just started receive increasing attention (Oliveira, Ladouceur, Phillips, Brammer & Mourao-Miranda, 2013), suggesting that this neurophysiological pattern may show only limited diagnostic specificity. In contrast, when emotion-related EBA-responses were compared directly between both patient groups, SZ patients showed higher cortical responses to sad and, tendentially, fearful body movements. To sum up, neurophysiological response patterns within the right EBA suggest an elevated responsiveness to neutral body movements for both, patients suffering from schizophrenia and patients with depression, whereas altered EBA activity for certain emotional movements appeared to reflect distinct features of the respective patient group. The only study that we are aware of having investigated EBA activity in schizophrenic patients so far showed overall decreased EBA activity in SZ patients during the observation of video clips displaying basketball related (context congruent) vs. unrelated (context incongruent) body movements (Takahashi et al., 2010). However, EBA activity was not diminished when only context incongruent body movements were regarded, indicating that a context processing deficit rather than a perceptual deficit for body movements had been detected in that study.

Results obtained for the pSTS region suggest that SZ patients may also show generally increased cortical activity during body movement perception: In the left pSTS, a main effect of group indicated emotion-independent increases in cortical haemodynamic activity for SZ as compared to both control groups (MD & HC). The pSTS can be described as the cortical region that is most prominently associated with human body movement processing (Blake & Shiffrar, 2007; Grossman & Blake, 2002; Krakowski et al., 2011). Therefore, one might conclude that pSTS activity increases observed in the SZ group are related to hyperprocessing of human movements. However, Kim et al. (2011) who directly investigated the detection of biological motion in dynamic PLD could not find an increase of pSTS activity in schizophrenic patients. Therefore, we suggest that enhanced pSTS recruitment in the emotion recognition task may have been related to the detection of socially relevant features, as the pSTS has also been linked to social cognition (Allison et al., 2000). Against the background of general performance deficits during the emotion recognition paradigm, this increased cortical recruitment may be compensatory. Interestingly, activity in the left pSTS tended to correlate positively with positive symptoms measured by the PANSS, indicating that pSTS hyperactivation in SZ patients may be particularly related to the degree of positive symptoms. Unfortunately, it is difficult to relate the pSTS activation increases found here in SZ patients to findings from previous studies, as pSTS activity during the perception of emotional human motion has not yet been investigated in patients with schizophrenia.

In terms of a statistical trend, V1 activity was attenuated in SZ patients (as compared to both control groups) when angrily walking avatars were presented. As a possible influence of emotional valence to primary visual stimulus processing has been previously demonstrated (Herrmann et al., 2008) and there is evidence that people with schizophrenia are often impaired on early stages of visual perception and fundamental elements of face processing (Kerr & Neale, 1993; Li et al., 2010), this result could reflect a combined impairment of these two aspects.

Beyond assessing event-related cortical haemodynamic responses to emotional body movements, another core aim was to investigate functional connectivity between cortical areas that are crucial for visual perception and emotional body processing. So far, few studies have investigated functional brain connectivity during (emotional) face perception in patients with schizophrenia (Bleich-Cohen et al., 2009; Fakra, Salgado-Pineda, Delaveau, Hariri & Blin, 2008; Leitman et al., 2008; Popov, Rockstroh, Popova, Carolus & Miller, 2013), but for emotional body processing the question of functional connectivity has been, up to now, entirely disregarded. In the present study, both SZ and MD patients had significantly lower within-emotion correlation values between V1, right EBA, and right pSTS, indicating that functional connectivity between the V1 area and the higher order visual areas was decreased in SZ and MD patients, with a more strongly pronounced decrease in the SZ group. A decrease of functional connectivity between brain regions is in line with findings from facial expressions experiments, for example Leitman et al. (2008) as well as Fakra et al. (2008) reported decreased subcortico-cortico connectivity in schizophrenia. Presenting gestures executed by an actor, Straube, Green, Strass and Kircher (in press) found that in SZ patients, the STS was relatively disconnected from frontal, parietal, and temporal cortex regions when metaphoric body gestures had to be processed. In line with this, our present results suggest that the STS and also the EBA may be more weakly connected to primary visual areas in schizophrenia but also, to a lesser extent, in major depression. In addition, the functional disconnection of the STS was associated with the severity of positive symptoms in patients with schizophrenia. We interpret these findings in terms of an impaired integration of basal visual features of moving bodies and more complex aspects, such as emotional content, that is closely related to positive symptoms, such as hallucinations and delusions, with more severe symptoms being linked to a higher degree of STS disconnection. This might, in combination with cortical activation anomalies that were more strongly pronounced in the SZ sample, account for the deficient emotion recognition performance from human bodies in patients with schizophrenia. Our findings, indicating STS hyper activation, disconnection, and a relationship of both anomalies with positive symptoms, emphasise that aberrant functioning of this region that is most prominently linked to social cognition (cf., e.g., Blake & Shiffar, 2007) is critically linked with clinical state in schizophrenia.

Although we tried to control for many possibly confounding factors, the present study certainly has its limitations. Due to the restricted depth resolution of fNIRS measurements, our analyses had to be restricted to cortical areas. Particularly in emotion perception paradigms, different subcortical structures, such as the amygdala or thalamic nuclei, may also be of interest. However, we chose this method for the present study as we preferred to investigate cortical emotion processing from human bodies in a much more natural setting, which is, in our opinion, a crucial factor in social-cognitive paradigms. An additional research question was to assess the usefulness of fNIRS to measure cortical anomalies during body-based emotion perception in psychiatric disorders, because in the long run fNIRS could be advantageous for repeated measurements in intervention studies or might be a useful therapeutic tool itself (e.g. for neurofeedback training). Hereby, the well-accepted method among psychiatric patients allowed us to assess two groups of mostly hospitalised, severely ill patients during a manageable period.

A certain drawback is the lacking assessment of prefrontal cortex areas, such as the medial frontal gyrus or the OFC which is thought to represent an interface between emotion perception and cognition and is therefore involved in motivational action (Rolls, 2004). As the present study exclusively targeted occipito-temporal regions that have been associated with human body/biological motion perception in most studies, and because the number of available fNIRS channels of our system was limited to 52, follow-up studies will have to endorse the assessment of PFC activity in body-based emotion recognition paradigms.

Another frequent problem in studies investigating differences between schizophrenia patients and healthy subjects or other psychiatric samples is linked to the high heterogeneity of patients. For example, although correlations between positive symptom scores and pSTS and V1 activity may point to some impact of paranoid symptoms on emotion perception from body movements, the design of the present study does not allow for unequivocal conclusions regarding the impact of different schizophrenic symptom facets, such as paranoia, catatonia, or disorganization (see Huang, Hsiao, Hwu & Howng, 2013 for a study on differences in facial expression recognition between paranoid and non-paranoid schizophrenia patients).

Finally, future studies could more deeply investigate the relationship between (deficient) emotion perception from body cues and practically relevant outcome measures such as quality of life or general social functioning. While for facial emotion recognition such a relationship has been emphasised, it will be important to know if this can be transferred to other aspects of social cognition, such as body language recognition, particularly with regard to the improvement of specialised treatment approaches.

4.2.6 Study 4 – Supplementary material

Table 9 (suppl.). Results of the statistical analyses of mean O_2Hb amplitudes obtained during the speed judgement task.

	ME emotion	**ME group**	**IA group*emotion**	**Post hoc comparisons**
Left EBA	*F*(4,212)=1.17; *p*=.33	*F*(2,56)<1; *p*=.73	*F*(8,211)=1.10; *p*=.36	--
Right EBA	*F*(4,224)=1.04; *p*=.39	*F*(2,56)<1; *p*=.92	*F*(8,224)=2.37; *p*=.018*	*Neutral:* MD > HC *Sad*: SZ > MD *Joyful*: MD > HC
Left pSTS	*F*(3,194)=1.36; *p*=.25	*F*(2,56)=4.28; *p*=.019*	*F*(7,194)<1; *p*=.86	SZ > MD = HC
Right pSTS	*F*(3,187)<1; *p*=.77	*F*(2,56)=1.98; *p*=.15	*F*(7,187)<1; *p*=.73	--
V1	*F*(3,151)<1.91; *p*=.14	*F*(2,56)=1.98; *p*=.15	*F*(5,151)=2.00; *p*=.07$^+$	*Angry:* SZ < HC & SZ < MD

5. General Discussion

5.1 Summary and conclusions

The present dissertation has been dedicated to the investigation of neurophysiological correlates of verbal and nonverbal processing skills that are of high relevance for everyday social functioning in patients with schizophrenia. Hereby, an important aim was to investigate both verbal-cognitive and nonverbal-affective facets of putative schizophrenic communication impairments and respective neurophysiological correlates using practically relevant and innovative experimental paradigms and functional brain imaging methods that are particularly suitable for investigating psychiatric patients. Verbal communication functions have been assessed using a pragmatic language comprehension paradigm and simultaneously applied EEG-NIRS measurements. Nonverbal communication functions have been investigated by means of an emotion labelling task involving dynamic human body movements, while fNIRS measurements were carried out to assess cortical oxygenation patterns. In general, the studies revealed 1) that fNIRS measurements – either unimodally applied or combined with EEG – are useful to detect cortical activation associated with these processes and 2) patients with schizophrenia show significant alterations in these neurophysiological processes along with impaired recognition of pragmatic language and emotional body language.

5.1.1 Verbal language comprehension in schizophrenia

In study 1, comprehension of novel metaphors was investigated for the first time by means of combined EEG-fNIRS measurements to obtain effects of figurative language on electrophysiological markers and cortical haemodynamic responses. This investigation pursued the following major issue formulated in section 2.3:

1. *(Basic question):* Can simultaneous EEG/NIRS measurements of metaphor processing help to elucidate the linkage of neural and haemodynamic substrates underlying pragmatic language comprehension?

Based on the results obtained in study 1, this question can be generally affirmed. Hereby, study 1 revealed differentiable neural mechanisms for metaphor processing, related to a broad and unspecific appraisal of semantic meaning (P200) and conceptual mapping of incoming semantics to build up more detailed sentence meanings (N400). The major fNIRS finding pointed to the strongest relevance of the left IFG for the processing of figurative meanings, replicating previous findings from fMRI studies. Interestingly, neural parameters and cortical haemodynamic responses were significantly correlated, offering a functional interpretation of haemodynamic activation patterns, which can in turn be assessed for schizophrenia patients in a second step.

Among the models on non-literal language processing (cf. section 2.1.2.1), the neurophysiological data of study 1 provide the best fit for the Lakoff's contemporary theory (Lakoff, 1993) and, likewise, the *graded salience theory* (Giora, 1997), as both frameworks make similar predictions that would be relevant for the present study. Specifically, both models predict processing costs for novel non-literal (e.g. metaphoric) as compared to literal expressions.[23] The neurocogntive processing costs arising from the novel (and therefore non-salient) metaphoric expressions used in the current projects have been reflected in enhanced N400 amplitudes and IFG activation in response to these sentences. No evidence have been found for the coarse semantic coding approach that suggests a critical involvement of right-hemisphere areas to the processing of figurative speech (Beeman, 1998), as only left hemispheric fronto-temporal regions showed activation modulations by sentence type.

In study 2, the psycholinguistic paradigm and the combined EEG-fNIRS measurements were adopted by a clinical study measuring patients with schizophrenia, in order to address the following major questions (cf. section 2.3):

2. *(General clinical question):* Are these measurements promising tools to assess potential neurobiological markers (N400 and/or left fronto-temporal activity anomalies) of semantic-pragmatic impairments in patients with schizophrenia?

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[23] Notably, a direct testing of both hypothesis could not be achieved by study 1, because commonly known figurative expressions, which would be assumed to be comprehended as fast as their literal counterparts, have not been used.

Possible functional alterations of the cerebral activation patterns during pragmatic language comprehension revealed by study 1 were finally tested in a sample of schizophrenia patients in study 2. In that study, distinct patterns of neural and cortical haemodynamic patterns were found in schizophrenia patients, suggesting that these markers represent useful parameters for investigating impaired verbal pragmatics in schizophrenia patients. However, although the comprehension of figurative language seemed to be most strongly impaired in schizophrenia patients, they showed a general performance deficit in the meaningfulness judgement task of study 2. Although this same general semantic performance decline in schizophrenia patients has been reported previously (Iakimova et al., 2005), the implication of this finding – pointing towards more fundamental semantic processing deficits that perhaps superimpose non-literal language comprehension – has been widely neglected so far. Likewise, the neurophysiological data obtained in study 2 did not suggest that patients show alterations in neural and haemodynamic activity that are exclusively linked to the processing of metaphors (see below).

> 3. (*Specific clinical questions*): Is metaphor processing in patients with schizophrenia accompanied by altered ERP components and, respectively, malactivation of the left fronto-temporal language network? If so, how do these alterations relate to clinical symptomatology?

Findings of study 2 suggested that only semantic mapping processes (as reflected in N400 modulations), but not unspecific meaningfulness appraisals (P200) were affected in schizophrenia patients who showed an impaired semantic meaning classification. In addition, left-hemispheric haemodynamic response decreases were observed in patients, independent of the form of language (i.e. literal versus non-literal) presented. Therefore, in the discussion section of study 2 it was concluded that at the neurophysiological level, general semantic processing disturbances are not distinguished from specific processing deficits for figurative language in particular. This, in turn, leads to the question how the present findings account for the fact that particularly figurative language comprehension (irony, sarcasm, and metaphoric language) skills seem to be frequently impaired in schizophrenia. Considering studies that have linked deficits in figurative language processing to impaired ToM and/or working memory functions (see section 2.1.3.3), I argue that fundamental disturbances within the semantic processing system contribute to impaired pragmatic language comprehension in schizophrenia patients whenever they co-occur with other functional impairments related to verbal memory, working memory, or ToM. In case of uncomplex literal speech, neurophysiological deficits within the semantic system may alone not be sufficient to produce comprehension deficits. However, whenever the complexity and/or form of language (i.e. in cases non-literal meanings need to be abstracted from figurative expressions) increase socio-cognitive demands (for example, the comprehension of irony requires contextual information such as knowledge about the speaker's intention; the comprehension of unfamiliar metaphors requires a comparison of concepts that are often not closely related), verbal language processing deficits become apparent.

Concerning the exact quality of the above described general semantic processing impairments, priming studies at word level have repeatedly suggested a loosening of semantic associations between lexical concepts stored in the human language network (Maher, 1983; Pomarol-Clotet et al., 2008). Such a semantic loosening can also often be observed in schizophrenic language production, considering that associatively loose speech is one diagnostic index for formal thought disorders. While this abnormal facilitation of the spreading activation within semantic networks may affect the correct comprehension and interpretation of pragmatic language, it has also been linked to increased levels of creativity (Duchene, Graves & Brugger, 1998; Mohr, Graves, Gianotti, Pizzagalli & Brugger, 2001). Therefore, while disturbed semantic processes may be, in some cases, favourably linked to creative thinking, together with impairments in cognitive and/or psychosocial functions it rather leads to deficient pragmatic verbal language comprehension, potentially resulting in substantial social pitfalls.

A clear strength of studies 1 and 2 was the combined EEG-fNIRS measurement, an approach that enabled us to directly investigate the relationship of neural activity and cortical oxygen metabolism and test whether this relationship is aberrant in schizophrenia. Strong correlations between ERPs and cortical haemodynamic responses (for example, P200 amplitudes and Broca and Wernicke activation to figurative sentences) may have reflected neurovascular coupling processes in healthy control subjects, which appeared to be remarkably decreased in patients with schizophrenia. On the one hand, simple correlation analyses between ERP and even-related cortical haemodynamics reflect only parts of the complex mechanisms underlying neurovascular coupling (for detailed descriptions see Buxton, Uludag, Dubowitz & Liu, 2004; Moreno, Jego, de la Cruz & Canals, 2013) and the quantitative relationship between neuronal activity and cerebral blood flow is complex (e.g., Buxton et al., 2004) and still not completely understood. For instance, the way in which subsequent (separate but partly overlapping) individual haemodynamic responses summate over time is still a matter of debate (Fabiani et al., 2014; Zhang, Liu, He & Chen, 2008). Nonetheless, the prominent decrease in neural and cortico-haemodynamic activation covariance observed for schizophrenia patients during pragmatic language comprehension may open new and interesting clinical research questions. Instead of regarding electrophysiological and haemodynamic markers of aberrant brain activation during verbal language comprehension in schizophrenia as separate entities, the findings of study 1 and 2 argue in favour of integrative investigations of these parameters. The present studies have proven the high usefulness of combined EEG-fNIRS measurements to address this issue.

5.1.2 Nonverbal social signal processing in schizophrenia

The second part of the present projects addressed the processing of emotional information from dynamic human body cues. The first aim was to implement and test a newly developed psychological paradigm to investigate the recognition of emotional states from human walking patterns, whereby a non-affective control task (walking speed recognition) was also included. The development of this method was the basis for answering the following research questions:

1. *(Basic question):* Can fNIRS measurements detect cortical activation changes that are related to emotion processing from body movements?

The ability of fNIRS to measure cortical activation patterns that are associated with the perception and processing of these emotional body movements was assessed in study 3. The results indicated that fNIRS measurements in fact produce distinct cortical activation patterns related to emotional body movement processing that are consistent with previously identified activation patterns using fMRI. Therefore, fNIRS has proven to be useful for investigating cortical responses to nonverbal social cues, the study of which may then be extended to patients with mental disorders. Moreover, study 3 showed that the neurophysiological responsiveness to emotional body movements is not limited to a voluntary processing, as similar cortical response patterns were detected even when the participant's attention had been turned to non-emotional aspects (i.e. walking speed).

2. *(General clinical question):* Are patients with schizophrenia impaired in recognising emotional states from dynamic body stimuli?

Study 4 addressed this issue investigating emotion labeling performance in a group of schizophrenia patients. This study revealed general emotion recognition deficits from human movements in schizophrenia patients, a finding that has been similarly reported in studies using static facial expressions (Chan et al., 2010; Kohler et al., 2010) and which has recently been indicated for body stimuli as well (e.g. Peterman et al., 2014). Moreover, this deficit appears – at least to some extent – to be diagnosis specific, as it has not been observed in a clinical control group with major depression patients.

3. *(Specific clinical questions):* Do patients with schizophrenia show distinct cortical activation patterns during body-based emotion processing that differ from those seen in healthy subjects or other psychiatric groups? If so, how do these alterations relate to clinical symptomatology?

To answer these questions, study 4 assessed the activity of two cortical regions (EBA and STS) that have been most consistently linked to emotional body movement processing and which have – among other regions – been identified in study 3 among healthy subjects. New analysis strategies were implemented to investigate functional cortical connectivity of these two regions amongst themselves and with the primary visual cortex. A healthy and a clinical control group were used to interpret respective results in terms of diagnostic specificity. STS and EBA activity were found to be significantly altered in schizophrenia patients, with a general hyperactivity of the left STS and an increased reactivity of the EBA to neutral body movements. While the former finding was diagnostic for schizophrenia patients, the latter one was also found in depressive patients. These findings on emotional body language perception in schizophrenia are well-consistent with a prominent etiological theory of the disease. According to the aberrant salience model, which has been shortly introduced in section 1.3.2, chaotic neurotransmission leads to a mal-attribution of significance to neutral events (Kapur, 2003). In case of emotional body movements, patients might misattribute the walker's intentions and motivations, resulting in erroneous recognition of emotional states from respective movements. Hereby, the misattribution seems to affect the recognition of emotional body movements in general, i.e. is not mainly restricted to neutral movements that are spuriously interpreted emotional, as suggested by the behavioural data obtained in study 4 (emotion labelling was impaired across categories in patients). Especially the EBA results would be consistent with the aberrant salience approach, as they indicate an enhanced responsively of this brain area to neutral dynamic and also slightly in response to angry body stimuli. Hereby, the increased EBA responsiveness to neutral stimuli reflects a particularly relevant finding considering recent reviews and commentaries addressing emotion perception in schizophrenia. For example, Anticevic et al. recently noted "the possibility that patients “over recruit” regions typically associated with emotion processing in response to neutral stimuli remains an open question" (Anticevic, Van Snellenberg & Barch, 2012, p. e24, right column). They have argued that it will be critical for future experimental and metaanalytic reports to fully clarify this issue. Over-recruitment of brain structures in response to actually neutral events has been reported in some experiments using facial expressions (for example see Anticevic, Van Snellenberg, Cohen et al., 2012), and it has now been confirmed for body-based emotion recognition in the present project, providing consistent insights for future research as demanded by Anticevic and colleagues.

While aberrant haemodynamic responses of the EBA to neutral and emotional body movements may confirm postulates of the aberrant salience model, altered EBA activation is unlikely to solely contribute to the deficient emotion recognition from body movement. As previously argued (see the discussion section of study 4), body-based emotion recognition impairments in schizophrenia might result from concordant activation anomalies within the EBA and the STS, together with reduced intercortical functional connectivity of these regions with each other and with primary visual perception cortices. Hereby, overall enhanced STS activity might reflect a general hyper-responsiveness of the schizophrenic brain to social stimuli, which has been proposed to be a contributing factor to delusions of reference. The disruption of STS-connections with other cortical areas may further contribute to these symptoms. Interestingly, decreased connectivity of the STS and the primary visual cortex was indeed closely related with positive symptoms, pointing to a functional clinical significance of decreases in functional connectivity of these regions (cf. section 5.3). Hence, the present project further reveals how informative functional connectivity analyses of fNIRS-based haemodynamic data can be for clinical research questions. The present results, therefore, strongly argue for a further development and more frequent implementation of respective analyses in future neuropsychiatric research.

5.2 Relationship with mentalising abilities

An important question arising from the many results obtained in the present work is whether an how the findings on neurophysiological processing anomalies of pragmatic language and emotional body movements in schizophrenia can be brought together and integrated. In other words, we can ask ourselves if there is a possibly common contributor to verbal and nonverbal language comprehension deficits. Hereby, ToM, also generally described as "mentalising ability" may represent a putative candidate.

The idea that mentalising abilities, referring to the "belief that other people have minds different from our own and to our ability to infer the beliefs, wishes, and intentions of other people in order to predict their behaviour (Frith, 1992, p. 118)", may underlie specific symptoms of schizophrenia is not new. More than twenty years ago, Frith (1992) postulated that some positive symptoms in schizophrenia, for instance delusions about the intentions of others, can be explained by impairment in mentalising. "Without mentalising, [...] communication will be abnormal because [one] will not be able to take into account the beliefs and knowledge of the person to whom he [or she] is speaking (Frith, 1992, p. 118)." This quotation illustrates the significance of ToM on both verbal and nonverbal transmission of socially relevant information. In fact, the meta-representational abilities to mentalise have been linked to the comprehension of pragmatics (Gavilan Ibánez & Ristol, 2013) as well as the recognition of socially relevant information (such as affective states) from body postures and movements (Biedermann et al., 2012; Bora et al., 2009). At the verbal communication level, particularly the ability to comprehend language that contains non-literal meanings, such as metaphors, requires context knowledge and beliefs about the speaker's motivations and intentions. As described in section 2.1.3.3, this relationship has been confirmed by studies that reported on correlations between mentalising abilities and non-literal language comprehension. Hereby, evidence is not limited to studies on schizophrenia patients, but has also been driven from children with autism spectrum disorders (ASD; see Norbury, 2005). Studies reporting on non-literal language comprehension impairments in ASD patients further reduce the strength of the thought disorders account, according to which pragmatic language comprehension is critically linked to the occurrence of schizophrenic formal thought disorders, which, however, are not inherent in ASD. Notably, while ToM impairments are repeatedly used to account for pragmatic language comprehension deficits in schizophrenia patients, intact mentalising skills in turn do not guarantee metaphor comprehension. Thus, according to Norbury (Norbury, 2005), ToM abilities represent an important factor influencing pragmatic language comprehension skills, but the influence of general semantic abilities may not be underrated. A methodologically adequate approach to investigate the quantitative significance of mentalising abilities to language comprehension skills in schizophrenia would involve a comparison of pragmatic language functions in schizophrenia patients that show deficient ToM versus patients with preserved ToM. Such studies, however, are so far lacking, leaving us behind with speculations.

Among the different accounts trying to explain pragmatic language comprehension deficits in schizophrenia introduced in section 2.1.3.3 (semantic memory impairments;. working memory impairments, general executive function deficits, or impaired ToM), deficient mentalising skills may have the greatest potential to represent a link, i.e. a common basis for both, pragmatic language comprehension and emotion recognition from human body movements. In fact, ToM is continuously used during the rapid interplay of verbally and nonverbally carried conversation, as it essentially requires the ability to equally anticipate other's thoughts and actions (Wible, 2012). Beyond the perception of emotional face and body expressions, theory of mind deficits have even been related to a lack of emotional expressiveness in schizophrenia patients (Andreasen, Calarge & O'Leary, 2009; Bruene, Abdel-Hamid, Sonntag, Lehmkaemper & Langdon, 2009).

While ToM findings for patients with schizophrenia appear relatively consistent, ToM deficits in patients with major depression are less obvious. According to Cusi, Nazarov, MacQueen, and McKinnon (2008) and Schreiter, Pijnenborg and Aan Het Rot (2013), patients with major depression show deficits in second-order, cognitively demanding ToM scenarios, whereas affective ToM might be less or even not impaired. Regarding facial expression recognition resembling basic first-order mentalising, even better performances of depressed patients as compared to healthy subjects have at least once been reported (Beck et al., 2013). On the other hand, an impaired recognition of happy body movements from PLDs in currently depressive versus both remitted major depression patients and healthy control subjects has been reported in the only study that has so far investigated emotional body perception (Loi, Vaidya & Paradiso, 2013). It is not clear whether the reduced ability to appraise positive stimuli of emotional body language reported in that study was linked to more general ToM deficits. Therefore, the discrepancy to the present finding (intact body-based emotion recognition in patients with Major Depression) might be explained by ToM differences of the samples of both studies. In study 4, no hints for impaired first-order ToM abilities, as represented by emotion recognition from body movements, have been found in patients with major depression. It is possible that differences in mentalising abilities between the schizophrenia patients and the depression patients in study 4 have contributed to the finding that only the former but not the latter patient group showed deficient emotion recognition from walking bodies.

In their recent review, Biedermann and colleagues (2012) suggested a mediation role of ToM abilities between neurophysiological anomalies and general social competence in schizophrenia. In line with this view, Couture et al. (2006) found that in 178 patients with schizophrenia, ToM partially mediated the relationship between neurocognition and social competence, with social competence being in turn related to self-reported general functioning. Although several meta-analyses and reviews have independently concluded that mentalising deficits represent rather a trait than a state marker in schizophrenia (Bora et al., 2009; Gavilan Ibanez & Garcia-Albea Ristol, 2013), state dependent changes, such as acute psychotic symptoms, significantly affect the size of ToM impairments (Bora et al., 2009).

Despite the convincing findings suggesting a critical relationship of ToM with verbal and nonverbal communication abilities in schizophrenia, one should be aware that mentalising itself constitutes a somewhat fuzzy concept, and it is hard to grasp into which single cognitive operations ToM can be decomposed. For example, ToM skills can be accessed through very different task designs, such as "false-belief tasks", "hinting tasks", or "reading the mind in the eye" - tasks. In their simplest form, false believe tasks measure the ability to understand that someone can act on the basis of beliefs that misrepresent reality (Frith & Corcoran, 1996). Hereby, false belief understanding can be measured using stories or picture sequences. Hinting tasks, in contrast, represent a measure of indirect speech, whereby participants have to understand the real intended meaning from a series of statements (Corcoran, Mercer & Frith, 1995) . Another task opportunity, named "reading the mind in the eyes test", requires participants to infer complex mental states of other people from the pictures of their eyes (Baron-Cohen, Wheelwright, Hill, Raste & Plumb, 2001). These tasks differ, for example, in their ability to test rather automatic decoding abilities as compared to reasoning abilities about others' mental states. In more detail, different ToM tasks rely on different neurocognitive processes (such as working memory, executive functions and attention) and, moreover, ToM tasks are not well standardised and their psychometric properties have been poorly studied (Bora et al., 2009). Hence, speculations about mentalising impairments being a common denominator of verbal and nonverbal communication disturbances should also be taken cautiously, as the concept of ToM is itself not perfectly determined. Nevertheless, mentalising impairments in schizophrenia have been judged to fulfill the criteria for being considered an endophenotype (Martin, Robinson, Dzafic, Reutens & Mowry, 2014) and therefore represent a promising target for social – both verbal and nonverbal – communication research in schizophrenia.

5.3 The role of the STS-TPJ region

ToM impairments, that have been discussed as a potentially common factor of deficient verbal and nonverbal communicative functions in schizophrenia within the previous section, have been linked to a number of brain regions, including medial PFC, STS, thalamus, parietal somatosensory areas and the posterior cingulate cortex (Sugranyes et al., 2011). Particularly the extended areas surrounding and including the posterior STS – also referred to as TPJ –have been increasingly addressed in studies investigating brain functions underlying ToM. For example, lesions in this area appear to impair ToM (Samson, Apperly, Chiavarino & Humphreys, 2004). In addition, recent neuroimaging studies have shown that the STS-TPJ region reveals a response profile that is more selective for theory of mind than other ToM associated regions, such as the posterior cingulate and the medial PFC (Wible, 2012). Moreover, the ability to make inferences about others' mental states, beliefs or intentions during moral judgements has been found to be impaired after TMS application to the right TPJ (Young, Cushman, Hauser & Saxe, 2007).

While being associated with ToM as a possibly shared component of verbal and nonverbal language processing, the posterior STS-TPJ region further appears to be involved when pragmatic language comprehension and body-based emotion processing are regarded separately.

In her holistic review, Price (2010) acknowledged a fundamental significance of the anterior-posterior line in the middle temporal gyrus, extending to the inferior parietal lobe and including the STS-TPJ region, for language processing at sentence level. Based on lesion analyses, Donkers and colleagues (2004) particularly named the STS as a region involved in sentence processing. In the present project (study 1), the posterior part of the left TPJ, overlapping with Wernicke's area, has been found to be associated with the processing and comprehension of meaningful (both literal and non-literal) phrases. As for the IFG, this region was generally hypoactive during sentence processing in schizophrenia patients. These results support the previously reported findings that suggest a basal association of the STS-TPJ region in language comprehension at sentence level, while, however, certain abstract language operations appear to rely more strongly on other cortical areas, particularly the left IFG.

Likewise, findings from studies on gesture and body movement perception point towards a significant role of the STS. In section 2.2.2.2 a number of studies have been cited showing that the STS consistently responds to human body motion, no matter if presented by means of point- or full-light displays (e.g. Blake & Shiffrar, 2007; Grèzes et al., 2007). Both structural lesions and repetitive TMS to the STS significantly affect biological motion perception (Billino, Braun, Boehm, Bremmer & Gegenfurtner, 2009; Grossman et al., 2005). Interestingly, activity in the STS in humans is further modulated by the perceived intentionality of the movement (Morris, Pelphrey & McCarthy, 2008) In line with previous findings provided from studies using fMRI (Atkinson et al., 2012; Sinke et al., 2010), the present fNIRS studies suggest an emotional modulation of activity within the movement-sensitive part of the STS (study 3). Because this means that STS activity is −beyond motion perception per se −crucially involved in the processing of social signals that are communicated by means of body movements, a special role of this region for nonverbal communication can be concluded. An overactivation of this region during the perception of emotional walks has been observed in the present study. Notably, this finding contrasts the results obtained in the sentence comprehension paradigm, where an underactivation oft this approximate region has been observed. Therefore, it can be concluded that STS-TPJ hypoactivation may contribute to verbal communication deficits, in terms of sentence processing, whereas STS-TPJ hyeractivation rather contributes to impairments in nonverbal communication, manifested in aberrant processing of body movements that carry socially relevant information.

The idea that the STS constitutes a common region for verbal and nonverbal facets of interpersonal communication (see Figure 34) is further augmented by studies assessing audiovisual integration. Findings from these studies suggest that the STS is not only activated by a separate analysis of verbal language and social cues, such as faces or bodies, but that this region is further critically involved in situations when verbal and nonverbal social information have to be integrated online (Puce & Perrett, 2003; Wible, 2012). Patients with schizophrenia have shown difficulties in this multimodal integration of sensory input (de Jong, Hodiamont, Van den Stock & de Gelder, 2009; Surguladze et al., 2001) and it is assumed that these problems are related to aberrant function and connectivity of the left posterior temporal lobe (see Straube, Green, Sass & Kircher, in press).

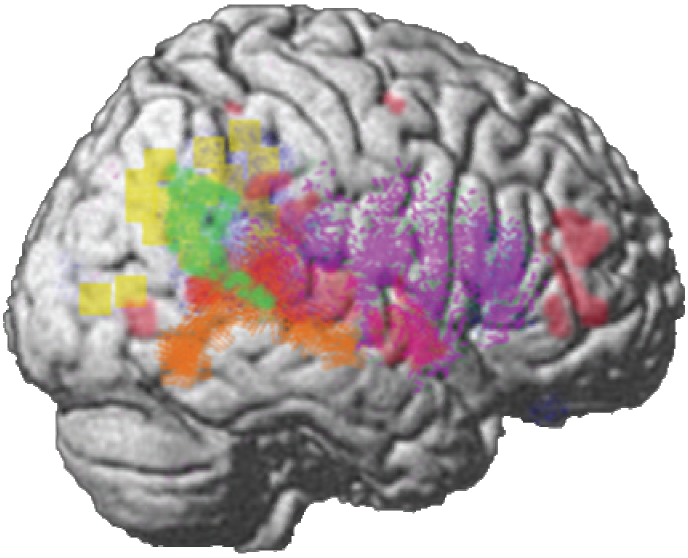

Figure 34. Illustration of the overlap of functional regions in the TPJ-STS region (IPL and pSTS; cf. Wible, 2012). Cortical representations of verbal (speech) and nonverbal (facial emotions) information processing are highlighted in orange and dark blue, respectively. In addition, functional representations eye gaze (red), self-representation (yellow), theory of mind (green), and prosody (dark blue and purple) are shown.

While these studies using audiovisual material point to possible alterations in schizophrenia during the integration of verbal and nonverbal information processing in schizophrenia, common factors of verbal and nonverbal signal processing, when regarded separately, have not yet been comprehensively regarded. The present dissertation therefore uniquely brings together verbal and nonverbal aspects of socially relevant information transmission in schizophrenia and integrates them into current neurocognitive concepts of the STS area. As a result, the findings presented within this work underpin that the STS resembles a hub within the social brain network, which appears to be unbalanced in schizophrenia, mediating both aspects of social interactions, namely verbal and nonverbal language processing and comprehension. However, both aspects have been assessed among separate samples of schizophrenia patients, and a holistic investigation of the common basis of verbal and nonverbal communication anomalies in schizophrenia will eventually require assessing these functions within the same patient group. In addition, the contributions of other areas that have been associated with social perception, such as the IFG, should also be considered, particularly as a recent study has suggested a disconnection of the STS and the IFG in schizophrenia patients during audiovisual comprehension of non-literal expressions (Straube et al., in press; see section 5.7 for details). Therefore, investigations assessing the collective response patterns reflecting the functional connectivity of the STS with other regions have been attempted in study 4 of the present projects. In this study, coherence analyses linking STS cortical responses to the activity of other striate (V1) and extrastriate (EBA) areas during the processing of emotional body movements were performed. The results of that analysis not only supported a functional disconnection of the STS with other areas involved in social perception (here, specifically, in body-based emotion perception), they further revealed a strong relationship between this disconnection and positive symptoms in schizophrenia. Therefore, abnormal STS connectivity (together with STS hyperactivation; see Blanke, Ortigue, Landis & Seeck, 2002; Penfield & Perot, 1963) might bridge the gap between aberrant social stimulus processing and the endophenotypical manifestation of certain psychotic symptoms.

To sum up, it has been pointed out that the STS-TPJ region may play a crucial part in the decoding and integration of complex social signals, therefore "enabling appropriate affective responses and social behaviour" (Puce & Perrett, 2003, p. 435). Inappropriate social behaviour has been counted among the most prominent features of schizophrenia. To this end, the STS could be hypothesised to play a critical role in the psychopathology of schizophrenia. Hereby, the development and evolving of (aberrant) functioning of the STS-TPJ region prior to the onset and during the course of the disease will be of great interest for future research (cf. section 5.7).

5.4 The endophenotype question

In section 1.2, the role of putative endophenotypes for different psychiatric disorders in current clinical neuroimaging research has been highlighted and schizophrenia has been claimed as the disorder most intensely pursued for endophenotypes (Miller & Rockstroh, 2013). Gould and Gottesman (2006) have defined endophenotypes as "quantifiable components in the genes-to-behaviours pathways, distinct from psychiatric symptoms, which make genetic and biological studies of aetiologies for disease categories more manageable" (Gould & Gottesman, 2006, p. 670, right column). The concept likely represents an important direction of future psychiatric research (cf. Figure 35), as endophenotypes may improve the power to detect genes influencing risk of illness by being genetically simpler and/or by providing added statistical power through their ability to quantitatively rank people within diagnostic categories (Glahn et al., 2014).

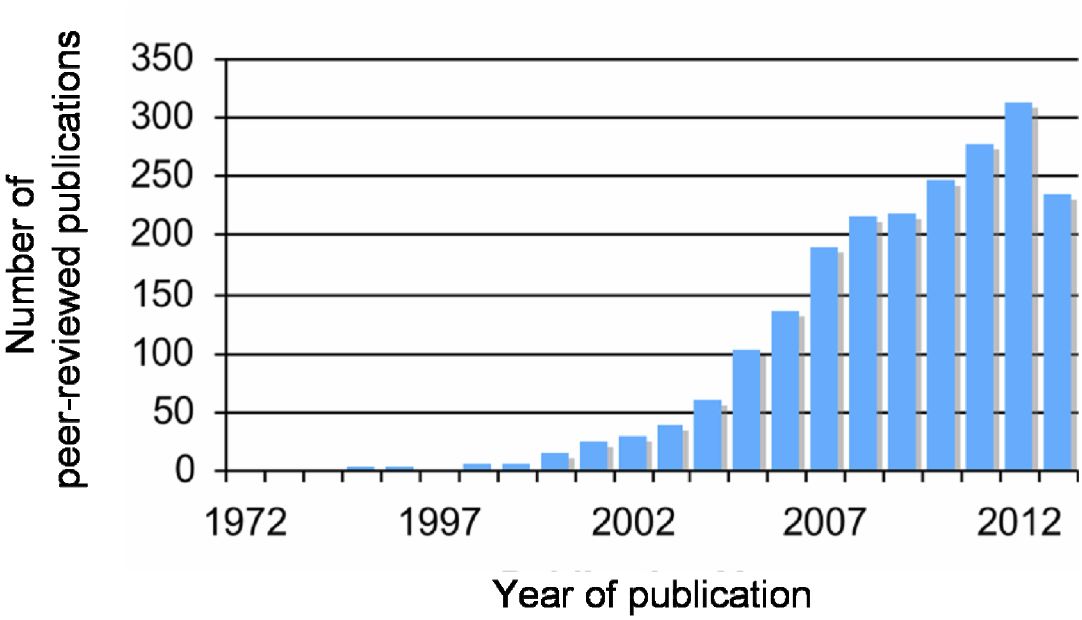

Figure 35. Number of peer-reviewed manuscripts that include the term endophenotype published between 1972 and 2012. Modified from Glahn et al. (2014).

Considering this advantage, the question arises whether verbal and nonverbal comprehension anomalies in schizophrenia patients that have been investigated and identified within the current projects might be classified as endophenotypes in schizophrenia.

According to Glahn and colleagues (2014), who reviewed the recent endophenotype literature, neuroimaging, electrophysiological, and cognitive variables represent the most frequently cited endophenotypes in psychiatric studies. Hereby, especially functions assigned to the latter category are already used increasingly as endophenotypes particularly in schizophrenia research. One of the most prominent cognitive endophenotype candidates is working memory impairment that has been described repeatedly for schizophrenia patients (Lee & Park, 2005) as well as in their healthy first-degree relatives (Glahn et al., 2003). Moreover, working-memory-related brain activation patterns have been shown to be highly heritable (Blokland et al., 2008). Similarly, ToM/mentalising skills have been discussed as another promising cognitive endophenotype in schizophrenia, being repeatable, stable, and heritable (Martin et al., 2014). Neuroimaging studies have widely confirmed that this is also true for the neurophysiological substrates of ToM deficits (e.g. de Achával et al., 2012; see also Martin et al., 2014). Considering that both working memory functions and mentalising abilities have been proposed as influential factors for pragmatic language comprehension in schizophrenia, it will be interesting to see whether pragmatic language processing deficits and their neurophysiological substrates represent a unique endophenotype, or may simply reflect a manifest expression of either ToM or working memory deficits as the basic phenotype. From the semantic domain, decreased verbal semantic fluency, altered language lateralisation and aberrant BOLD activity underlying semantic associations have been suggested as putative endophenotypes (Francis et al., 2012; Jamadar, Pearlson, O'Neil & Assaf, 2013; Szoeke, Trandafir, Dupont, Meary, Schuerhoff & Leboyer, 2008; van Veelen et al., 2011), whereas this remains purely hypothetical with respect to pragmatic language skills.

Besides verbal-cognitive deficits that have been proposed as endophenotypes for schizophrenia, the recognition of emotions from facial expressions and respective neurophysiological correlates have also been brought up for discussion (de Achával et al., 2012; Eack et al., 2010; Kohler et al., 2014; Leppänen, Niehaus, Koen, Du Toit, Schoeman & Emsley, 2008). However, it is not yet clear whether these emotion recognition impairments would represent an independent endophenotype or if they rather resemble a consequence of general face recognition deficits, which have also been demonstrated for patients with schizophrenia and their unaffected relatives (Calkins et al., 2005). However, as the present study 4 provided evidence that emotion recognition impairments in schizophrenia are probably not restricted to facial stimuli, the reduction of emotion recognition impairments to face perception deficits as the basic endophenotype seems to be less appropriate.

To sum up, the particular socio-cognitive functions investigated in the present projects – pragmatic verbal language comprehension and emotion recognition from human biological motion – have not yet actually been targeted as potential endophenotypes for schizophrenia. However, respectively related neuropsychological functions, such as semantic associations or facial emotion processing have been previously discussed as such, leading to the question whether deficits in pragmatics and body-based social cognition might constitute related or distinct endophenotypes, or whether they meet the endophenotype criteria at all.

Addressing these questions, different behavioural and neurophysiological markers of verbal and nonverbal communication deficits observed in the present projects could be adduced for testing their potential as an endophenotype. For instance, the directly accessible recognition deficits that have been found for both pragmatic language comprehension and body-based emotion recognition could be chosen. In addition, electrophysiological markers of pragmatic language processing impairments in schizophrenia patients can be used, whereby lacking N400 modulations during the early time window would be the parameter of choice, because P200 and later N400 amplitudes did not appear to be altered in patients with schizophrenia. At the cortico-haemodynamic level, hypoactivity of the IFG and temporo-parietal parts of the language network during sentence processing could be taken into account (but see also Mashal et al., 2013, for IFG hyperactivation patterns in response to metaphoric expressions). Concerning emotion recognition from body movements, we could explore whether general STS hyperactivity and/or altered EBA response patterns to specific emotions meet the criteria of endophenotypes. In addition, it would be highly interesting to assess the potential of decreased cortico-cortical connectivity during body-based emotion processing as an endophenotype. Hereby, one could argue that the relationship between STS disconnection and current psychopathology in schizophrenia indicates a state dependency of that marker, therefore not meeting one of the endophenotype criteria. However, simple correlations of do not function as "hard" evidence for state dependency. Moreover, also other putative endophenotypes (e.g. ToM) have been shown to vary with symptom severety. Longitudinal investigations or studies comparing chronic with first episode schizophrenia patients will be necessary to test for state (in)dependence of STS disconnection during bodily emotion processing.

An elaborate investigation of these research questions will therefore require to replicate the present findings – among both schizophrenia patients and family relatives – and to provide evidence supporting the heritability of respective deficits as well as their state independence. Regarding state dependency of figurative language processing deficits, few studies already exist which, however, have presented somewhat mixed results, (Herold et al., 2002; Mo et al., 2008).

The present projects actually provide a promising starting point for such investigations, as the data presented here support the liability and usability of two newly established paradigms to measure certain sub-functions of verbal and nonverbal communication in schizophrenia. The high efficacy and practicability of fNIRS measurements with or without additional electrophysiological acquisitions can now promote an intensified investigation of the endophenotypical characteristics of these functions and their neurophysiological correlates in subsequent studies.

However, despite its appeal for neuropsychiatric research, the endophenotype concept also may have its drawbacks and limitations. These need to be taken into account when arguing for or against putative endophenotypes in, for example, schizophrenia. Firstly, an endophenotype is commonly placed between genes and behaviour in terms of a simple linear-causal chain (although Gottesman and Shields, 1973, originally left room for more complex relationships). This simplification has been acknowledged to be beneficial in order to proceed with a complex concept such as endophenotypes (Miller & Rockstroh, 2013). However, it is simultaneously known that such relationships are reciprocal and recent progress in epigenetics illustrates that genes do not simply set the stage, creating a fixed biology (Goldman, 2012). Besides reciprocal epigenetic relationships, simple causal relations are, though tempting, frequently lacking "hard" evidence. Neurophysiological anomalies found in schizophrenia patients, such as the currently presented altered cortical correlates of verbal and nonverbal language comprehension, might not only represent the cause or basis of respective social communication deficits. Consequences of impaired social communication, such as social withdrawal and isolation tendencies, may in turn affect neurobiological activity in relevant brain regions. Hence, reciprocal relationships between environment/phenotypes and genes as well as between environment/phenotypes and brain functions need to be kept in mind when classifying cognitive, haemodynamic, or electrophysiological factors as endophenotypes.

In addition to the somewhat problematic causality issues, many studies on endophenotypes in psychiatry widely neglect the possibility of gene expression (i.e. transcripts) being itself an endophenotype for mental illnesses. However, gene expression is substantially affected by genetic factors and transcripts are highly relevant for the occurrence and characteristic of other, "visible" biomarkers, such as working memory or emotion recognition impairments in schizophrenia. To this end, Glahn et al. suggested that understanding the liability for mental illness "will involve combining more traditional endophenotypes with potentially complex genetic underpinnings with less genetically complex endophenotypes like […] transcripts" (Glahn et al., 2014, p. 124, right column). Therefore, future studies combining neuroimaging and molecular techniques could possibly fill the gap between genes, transcripts, and affective or cognitive endophenotypes in schizophrenia.

Finally, a rather pragmatic problem hampers the potential to *adequately* assess putative endophenotypes in schizophrenia, or psychiatric disorders in general. A thorough consideration of endophenotype criteria exceeds the capabilities of many institutional laboratories (e.g., longitudinal, multisite studies integrating molecular genetics, neuroscience, and cognitive examinations). Miller and Rockstroh (2013, p. 187) noted that "even ambitious, longitudinal studies may not allow adequate examination of the state-independence criterion, given ongoing variance in gene expression, such that many phenomena that may depend greatly on genes vary over time". Hereby, innovative imaging techniques could step in: Such methods that are characterised by a relatively effortless applicability, such as stational or even portable fNIRS, are advantageous for multiple and multiply repeated neurophysiological measurements, at least when *cortical* functions and their relations to genomic expressions shall be investigated. Combined EEG-fNIRS assessments could further represent multivariate, multilevel approaches that, according to Miller and Rockstroh (2013), could encourage a changing view of the endophenotype concept from a single causal chain to a network of complex relationships.

5.5 Schizotypal personality as a "model" for schizophrenia?

Because investigating samples of patients suffering from schizophrenia and more or less acutely experiencing psychotic symptoms is often associated with a number of pitfalls, some researchers try to access psychological functions that may be disturbed in schizophrenia using schizotypal personality traits. They argue that certain aspects of the phenomenology of schizophrenia are also traceable in the general population, beyond the diagnostic borders of the clinical classification systems (van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam, 2009), and that these subclinical, expressions of schizophrenia ranging along a continuum are represented in schizotypal signs (Ettinger et al., 2014). It has been stated that "individuals with high levels of schizotypal traits exhibit alterations in neurocognitive task performance and underlying brain function similar to the deficits seen in patients with schizophrenia" (Ettinger et al., 2014, p. 1, abstract).

Notably, schizotypy must not be equated with schizotypal personality disorders included in DSM-IV or DSM-V (though in DSM-5 changes have been made). Unlike the personality disorder, schizotypy is a rather broad concept that refers to a latent personality organization (Lenzenweger, 2010) instead of being limited to a cluster of observable signs and symptoms. Meehl (1962) suggested four fundamental signs of schizotypy: cognitive slippage (mild associative loosening), social fear, anhedonia, and ambivalence. Using factor analyses, Kerns (Kerns, 2006) identified a three factor model of schizotypal traits, including positive (e.g. magical thinking or ideas of reference), negative (e.g. flat affect), and disorganised (e.g. odd speech) traits.

A number of different psychometric methods can be used in order to assess schizotypy in the general population. An overview over the most common measures is provided in table 10. At present, self-report questionnaires, such as the Schizotypal Personality Questionnaire (SPQ), are implemented in most studies.

Table 10. Overview over commonly used scales to assess schizotypal personality.

Assessment method	**Reference**	**Type of measure**
Structured Interview for Schizotypy	(Kendler, Lieberman & Walsh, 1989)	Interview
Schizotypal Personality Scale	(Claridge & Broks, 1984)	Self-assessment
Rust Inventory of Schizotypal Cognitions	(Rust, 1988)	Self-assessment
Schizotypal Personality Questionnaire	(Raine, 1991)	Self-assessment
The Eysenck Psychoticism Scale	(Eysenck & Eysenck, 1991)	Self-assessment
Oxford–Liverpool Inventory of Feelings and Experiences	(Mason & Claridge, 2006)	Self-assessment

Regarding verbal information comprehension, Fisher, Heller and Miller (2007) reported on an impaired context maintenance during a lexical task in subclinical schizotypy. Hereby, especially positive schizotypal traits were associated with problems to maintain lexical contexts, and these deficits were further related to frontal lobe activity. Interestingly, in study 2 of the present projects, a similar relationship for the schizophrenia patients between positive symptoms and left IFG (Broca) activity was found during the sentence comprehension paradigm. Therefore, similar neurobiological mechanisms may contribute to language comprehension and potential deficits in schizophrenia and schizotypy. Moreover, studies that have directly tested pragmatic language comprehension in patients with pronounced schizotypal personality traits additionally argue for the model function of schizotypy for schizophrenic language processing. For example, Langdon and Coltheart (2004) found that adults with high-schizotypal personality traits had problems to comprehend ironical utterances and irony-related activity in the middle temporal gyrus was shown to be correlated with schizotypal personality scores. In contrast, schizotypy individuals seem not to be impaired in their ability to correctly comprehend metaphoric expressions (Humphrey et al., 2010; Langdon & Coltheart, 2004). Therefore, the suitability of schizotypy to serve as a model for schizophrenia might be restricted when the processing of metaphorical meanings in particular is regarded.

Abbott and Byrne (2013) used the three-factorial model proposed by Kerns (2006) to investigate the relationship of schizotypal personality traits and emotion recognition from dynamic social stimuli. The authors found that global schizotypy and positive schizotypal traits were associated with overall poor emotion recognition. Negative schizotypy was only linked to problems in recognising positive emotions. Abbott and Byrne thus replicated findings from studies using static facial expressions (Brown & Cohen, 2010; Poreh, Whitman, Weber & Ross, 1994) and they concluded that "poorer emotion recognition in schizotypy is not limited to single-channel stimuli, but can be seen even when multiple emotional cues are available" (Abbott & Byrne, 2013, p. 40). Shean, Bell and Cameron (2007) further demonstrated an impaired ability to correctly identify emotional postures in subjects with high SPQ scores, indicating that, like for schizophrenia patients, body-based emotion recognition might be deficient in people with schizotypal personality traits.

With respect to mentalising abilities, which have previously been suggested as a potentially linking factor between verbal and nonverbal communication deficits and impaired emotion recognition from body movements, results obtained from samples scoring high on schizotypy scales are less clear. While one study has reported that people with increased schizotypal traits also show deficits in ToM functioning (Pickup, 2006), another study has failed to replicate this finding (Jahshan & Sergi, 2007). Moreover, Pickup noted that ToM impairments found in his study were rather subtle. In addition, the study conducted by Jahshan and Sergi could not confirm that people with high schizotypy scores presented aberrant emotion perception, verbal memory, and executive functioning. Therefore, more research on the processing of verbal and nonverbal social cues in people scoring high on schizotypy, using adequate diagnostic instruments, will be necessary to figure out whether schizotypy constitutes a useful model for assessing respective functions in schizophrenia.

5.6 Methodological aspects and limitations

The present projects indented to investigate cortical correlates of the perception and comprehension of verbal and nonverbal communication signals, including pragmatic language and emotional body movements. The results obtained in four different studies brought new insights into the accessibility of these neural substrates in healthy subjects and patients with schizophrenia by means of fNIRS measurements, either implemented alone or in combination with electrophysiological assessments. Hereby, the present findings partly replicated and partly augmented previous findings from respective fMRI and EEG studies, simultaneously providing evidence for the usefulness of fNIRS and fNIRS-EEG measurements to assess pragmatic language as well as social cognition functions in psychiatric disorders.

Nonetheless, a number of limitations need to be taken into account when appraising and interpreting the results of the present projects. These limitations should be addressed in future studies in order to help clarifying ambiguous findings or remaining research questions.

Two major pitfalls of studies investigating samples that include patients with schizophrenia are associated with (1) the typically high group heterogeneity and (2) potential influences of current psychopathological state. The first issue is mostly driven by the concept of the disorder that is framed by the present nosologic systems. According to the DSM-IV which has been an important basis for diagnostic classifications in psychology and psychiatry for almost twenty years, at least four different subtypes of schizophrenia could be distinguished, (catatonic, disorganised/hebephrenic, paranoid, and undifferentiated subtypes). Hence, if these subtypes are not separately diagnosed and compared with each other, study results are always somewhat "tainted", as different psychopathologies may be pooled in a single clinical sample. For example, a schizophrenia patient predominantly suffering from paranoid symptoms exhibits a highly different clinical picture as compared to a patient with mainly disorganised symptoms and it is likely that these phenotypical differences are associated with symptom-specific differences in neurophysiological anomalies. When such a heterogeneous patient group is assessed in a neurophysiological investigation (as it has been done in the present projects), disentangling this confoundation is often difficult and problematic. Although the arguments for abandoning the subtype differentiation in the present manual published by the APA, the DSM-5, appear reasonable, the avoidance of subtypes might somewhat reinforce this methodological problem in future studies. Besides the high heterogeneity within the diagnosis of schizophrenia, some studies report on a common investigation of patients with schizophrenia and schizo-affective disorders. Although some researchers suggest a high neurophysiological similarity of these diagnoses, such a procedure increases sample heterogeneity even more and therefore might strongly hamper the external validity and interpretability of respective findings. Therefore, in the present studies we tried to only include patients that meet the schizophrenia diagnosis, whereby, however, the diagnostic dissociation from schizo-affective disorders is sometimes difficult.

In addition to general diagnostic heterogeneity, studies on schizophrenia patients frequently suffer from the fact that patients have been assessed at different stages of the disease. Although some studies achieve at least a broad limitation with respect to the onset and time-course of the disorder, for example if they distinguish first-episode schizophrenia and chronic patients, patients usually tend to differ according to their acuteness of symptoms when included into psychological studies. In the present projects, only hospitalised (except for one patient) schizophrenia patients were measured in order to keep the problematic influence of current stage of the disease minimal (i.e. to avoid an inclusion of both acute and fully remitted patients). Moreover, only subacute patients with schizophrenia have been assessed. However, even subacute patients can differ significantly, for example regarding their remission progress. On the other hand, sample variations in current psychopathology can also be very revealing, for example if psychopathology is correlated with certain neural alterations. To this end, the symptom severity was always thoroughly assessed using the PANSS interview and it correlated with different outcome measures in the present studies: In study 2, correlations between positive schizophrenia symptoms were found with IFG activation and P200 amplitudes during pragmatic language processing. In study 4, again positive symptoms were found to be related with both STS activation and functional disconnection during body-based emotion recognition. Such analyses would be limited in studies using homogeneous patient samples.

Analogously to symptom heterogeneity and state variations in clinical samples, another potentially influencing factor is related to medication. The majority of the patients assessed in the present projects received psychopharmacological treatment, and there was a high variance in the choice of administered agents. One possibility to rule out this limitating factor is the assessment of unmedicated patients. However, a number of practical problems occur when unmedicated, strongly impaired patients are exposed to complex experimental situations. Future studies should therefore explicitly address the degree of influence on present socio-communicative functions in schizophrenia patients that is exerted by antipsychotic medication.

The limited depth resolution and, to a lesser extend, limited spatial resolution of fNIRS has been already intensively discussed within the different discussion sections of the studies 1-4. Therefore, this issue shall only be briefly addressed at this point. Especially regarding the assessment of nonverbal-affective information processing fNIRS refuses information about probably relevant subcortical activity, including particularly amygdala and anterior cingulate responses to emotional stimuli. Therefore, specific hypotheses concerning activation patterns within these areas in response to emotional body language will have to be addressed in future studies using imaging methods with higher depth resolution. Regarding verbal-cognitive information processing, the limited depth resolution of fNIRS might be less problematic, as these processes are predominantly linked to cortical activity. Notably, in section 1.2 of the General Introduction, the choice of a method that is appropriate (and may be superior over other imaging techniques) to investigate a certain scientific topic should always include cost-benefit considerations. The lower depth-resolution of fNIRS measurements that might have been particularly relevant for the investigation of bodily emotion recognition in schizophrenia was accepted in light of some important benefits of fNIRS to assess this issue: high acceptance rates of fNIRS by patients with severe psychiatric disorders, easy and non-aversive measurement settings for the patients, and high ecological validity, with fNIRS setups being much closer to natural situations of social perception than fMRI measurements.

While in section 5.2, mentalising abilities have been discussed as a potential common basis of verbal and nonverbal communication deficits −at least for the specific processes of non-literal language and emotional body movement recognition −a direct link of these functions to ToM has not been tested in the present projects. Although it can be argued that in study 4, first-order ToM abilities were measured indirectly through the task design (emotion labeling), a holistic investigation of mentalising skills involving their different components, such as the affective and cognitive parts, has not been done. Moreover, the emotion labeling deficits observed in schizophrenia patients in study 4 cannot be linked to the figurative language comprehension deficits in schizophrenia patients observed in study 2, as two different patient samples were measured in the two studies. The lack of elaborate ToM data somewhat weakens the arguments for an association of ToM with verbal and nonverbal communication functions in schizophrenia that have been noted in section 5.2. However, the reason for not co-assessing mentalising skills within the present projects was a quite simple and rather pragmatic one: Due to investigation durations of about two to two and a half hours per study (not including psychopathology explorations using the PANSS interviews), we refrained from conducting any additional examinations in order not to bias the present outcomes due to an exhaustion of the patients. Notably, fNIRS and EEG-fNIRS studies had been selected for the present projects in order to provide a less discomforting and more naturalistic experimental setting for both patients and control subjects. This advantage of the methodological choice would have been compromised by an overload of psychological tasks. Nonetheless, the examination of mentalising skills would have been highly informative and might have been able to underpin the present conclusions regarding the impact of ToM deficits on the present results. Therefore, it would be beneficial for future studies to assess the respective relationships in more detail.

In section 5.3, the region including and surrounding the posterior STS has been suggested to be involved in both verbal and nonverbal language processing functions. However, it cannot be concluded that a crucial commonality of verbal and nonverbal communication is limited to this region, because a number of cortical regions could not be assessed due to channel limitations in the fNIRS measurements. For example, while in studies 1 and 2 the left IFG was found to be crucially associated with pragmatic language comprehension and respective anomalies in schizophrenia patients, this region has not been targeted in the body-based emotion recognition studies. However, previous fMRI findings have pointed towards an important role of this area for the perception of social information from body cues (van de Riet et al., 2009). Hence, a common involvement of the IFG in verbal and nonverbal processes, along with a crucial relevance of this region for social communication impairments in schizophrenia patients appears reasonable, but was not testable within the studies presented here. In both project parts, midline frontal cortex regions were left out entirely. These regions encompass the medial and the orbitofrontal cortices which have been linked to self-representation/self-awareness and social cognition in general (Wible, 2012). OFC and ventral PFC anomalies in particular have been linked to a lack of empathy and euphoria as well as to a lack of future concerns and decreased concerns for social rules (Blair & Cipolotti, 2000; Damasio, Tranel & Damasio, 1990). Hereby, Damasio and colleagues suggested that the functions of these areas are not limited to top-down processes during social cognition, as they were also related to the automatic processing of social stimuli. It will, therefore, be of interest if and how activation patterns within these areas are altered in patients with schizophrenia. It is, however, a matter of debate whether fNIRS is able to validly detect activation changes within these medial and ventral parts of the PFC due to its depth resolution limitations. On the other hand, the number of published fNIRS studies reporting on activity patterns of exactly these areas are increasing, indicating that in the future fNIRS studies with an increased number of measurement channels may complement the current findings with results from ventro-medial frontal measurements.

The use of another clinical group in study 4 can be seen as a strong advantage of this work. Clinical "control" groups may help to interpret the neurophysiological and behavioural findings and integrate them into current models and perspectives on psychopathology of specific mental disorders. For example, emotion processing difficulties from face stimuli have been reported for both, patients with schizophrenia and major depression (albeit with partly different patterns of anomalies, see Hoertnagl & Hofer, 2014). In contrast, study 4 showed that this may not be the case for body-based emotion recognition, indicating that different factors may contribute to the ability to correctly comprehend social information from faces versus bodies in both disorders. Besides patients with major depression, an additional examination of psychiatric disorders that have frequently been associated with socio-cognitive dysfunctions with schizophrenia are frequently reported, such as autism or bipolar disorders, might also have been very revealing. However, this would have exceeded the capacities available for the present projects and therefore had to be left for future investigations. Moreover, no other clinical group for diagnosis-specific comparisons was assessed in the project part that addressed non-literal language (study 2). The assessment of different clinical groups is often effortful, but it is even more informative. While such a clinical control group has been examined in only one study of the present work, both fNIRS and EEG-fNIRS measurements generally allow for the investigation of multiple clinical groups and will therefore be useful in advanced studies comparing social communication across various diagnoses.

Although the current work revealed new insights into so far rather rarely investigated areas of verbal and nonverbal communication, fundamental parts of social cognition in schizophrenia, a sustaining problem constitutes the broadness of the concept "social cognition". In fact, "a huge number of psychological constructs that vary in complexity from more elaborated ones—such as empathy, theory of mind, and self-representation—to more elementary ones such as social perception, action-monitoring, and more generally the processing of social stimuli" (Derntl & Habel, 2011, p. 145, right column). Hence, when investigating particular functions that fall within the definition of social cognition, we need to be aware that they only reflect a part of the picture. Against this background, the comparability of the present studies with other studies that address social cognition in schizophrenia can be limited, as other studies might have assessed completely different functions or processes. When drawing conclusions from studies on "social cognition in schizophrenia" this should be carefully considered, because the concept "social skills" remains unclearly defined. Improvements in the definition and sub-classification of social-communicative skills will facilitate the behavioural and neurophysiological assessment of these functions among patients with schizophrenia.

Finally, an important yet often underrated methodological issue concerns the applicability of findings obtained from group analyses to the individual. As noted in section 1.2, we need to be cautious when drawing conclusions based on group-level data and employ them on individual patients, especially because hard evidence supporting intraindividual reliability of functional imaging data is so far widely lacking. Against this background, we need to be aware that the present findings are not yet ready to be applied to individual diagnostic and/or treatment issues for patients with schizophrenia. However, in the long run, this should be a major goal of future neuropsychiatric research, in order to further improve the diagnostic and therapeutic process for the individual patient.

5.7 Remaining questions & future perspectives

The findings obtained from the four studies that have been included in this work raise further questions. In fact, the current studies were (at least to some extend), quite preliminary, assessing (1) newly established paradigms by means of (2) comparatively new and – with respect to neuropsychiatric research – innovative neuroimaging methods in a highly heterogeneous clinical sample such as patients suffering from schizophrenia. Only this way, by generating new and testable questions, ideas, and hypotheses, neuroscience research in general, and in particular within the field of psychiatry, can proceed. In this final section, possible future directions for research dealing with verbal and nonverbal communication in schizophrenia are described, first considering verbal and nonverbal language comprehension separately, and later highlighting general future perspectives for social communication studies in schizophrenia.

Within the past years, a trend in socio-cognitive neuroscience has evolved towards a stronger emphasise on nonverbal social perception using a variety of affect-laden social stimuli. A simple example shall highlight this assumption: When feeding searching the terms "language, processing, and schizophrenia" in PUBMED explicitly looking for papers published after 2000, 480 published manuscripts are listed (date of research: June 15th, 2014). When the word "language" is replaced by the term "emotion", the number increases to almost 600. As the less obvious deficit, semantic processing impairments in schizophrenia may be somewhat underrated. Nonetheless, there is need for intensive research addressing their neurophysiological background along with their impact on social communications and interactions of schizophrenia patients in general. The studies assessing pragmatic types of language processing in schizophrenia that have been reported here show that fNIRS measurements, particularly when combined with temporally resolving electrophysiological assessments (i.e. EEG), are highly informative as they provide topologic-haemodynamic and direct neural markers of language processing in schizophrenia patients which can be used to assess the complex psychopathology underlying semantic processing difficulties. Therefore, such or similar investigations could be integrated in general task compilations used to identify biomarkers of social communication deficits in schizophrenia, hereby particularly dealing with the verbal-perceptual part of social communicative functions. However, the majority of the grand initiatives providing recommendations on particular neuro-cognitive functions that should be particularly addressed in schizophrenia have so far neglected verbal-semantic processing impairments. For example, the CNTRICS initiative intends to establish a framework to characterise different facets of neurocognitive dysfunctions in schizophrenia, and recommendations and task selections for various functions have been offered, such as visual integration (Butler, Chen, Ford, Geyer, Silverstein & Green, 2012), working memory (Barch, Moore, Nee, Manoach & Luck, 2012), executive control (Carter, Minzenberg, West & Macdonald, 2012), or affect recognition (Taylor & MacDonald, 2012). Considering that the ability to correctly process, understand and interpret spoken (or written) language is highly significant for adequate social functioning, it would be beneficial to further take semantic processing skills into account.

While largely sparing verbal language comprehension that is often impaired in patients with schizophrenia (as in the present study), the CNTRCS initiative recently recommended the use of emotional walks paradigms as a standard test battery part in future research on biomarkers on social cognition and communication in schizophrenia (Taylor & MacDonald, 2012). More precisely, the "Emotional Point-light Walker" paradigm which has been developed by Heberlein and colleagues and which is based on the work of Johansson (1973), has been suggested by the CNTRICS committee. This attempt emphasises the potential future relevance of the assessment of body-based social information processing in patients with schizophrenia. However, the use of PL walkers in studies on schizophrenia is also seen controversially, as a possible confoundation with impaired visual pattern analyses (i.e. patients with schizophrenia more frequently tend to interpret randomly moving dots, which are typically used as control stimuli in PLD tasks) has been claimed (Peterman et al., 2014). So far, the study published by Peterman and colleagues and the projects presented here have consistently shown that full-light displays of schematised, walking human bodies are similarly useful to detect aberrant socio-emotional processing from biological motion in patients with schizophrenia, whereby task difficulty is reduced due to the avoidance of potentially deceptive moving dots. Moreover, the current work emphasises that the neurophysiological counterparts of these processing deficits can be investigated noninvasively, in a naturalistic and uncomplicated fashion. In addition to altered cortical responses to emotional body movements in schizophrenia patients, the EBA results of study 4 further suggest that an analogous principle might underlie body-based emotion recognition in depressive patients. These patients also showed elevated cortical responses to neutral and, additionally, to happy body movements. In future studies, this issue could be further investigated in studies exclusively addressing body-based emotion processing in subjects with depression. To this end, the present project (studies 3 and 4) has laid the foundation of more extensive research on body-based emotion processing using fNIRS in different clinical samples.

Within the present projects, pragmatic, non-literal language comprehension and the perception of socially relevant body movements have been addressed by means of two separate paradigms. However, a common, simultaneous assessment of both aspects may provide additional information on the difficulties that schizophrenia patients often experience during verbal and nonverbal communication. In a recent study, Straube and colleagues (in press) presented videos of of an actor performing iconic (concrete/literal) and metaphoric gestures together with corresponding concrete and abstract sentences, respectively, to 16 healthy subjects and 16 schizophrenia patients while cerebral haemodynamic activity was assessed by means of fMRI measurements. The major result in that study was a functional disconnectivity of the left STS with the left and right IFG during the processing of metaphoric, but not iconic-concrete, gestures. This interesting result augments findings from an earlier study conducted by the same research group, which revealed a disturbed neural integration of metaphoric gesture meaning into an abstract sentence contexts in patients with schizophrenia: While gesture-speech integration of abstract-figurative contents activated the left posterior MTG/STS and IFG in healthy subjects, schizophrenia patients showed reduced responsivity to abstract videos of the left MTG, STS/STG and an inferior part of the left IFG (Straube et al., in press). These findings suggest that difficulties in the multimodal integration of sensory input, that have repeatedly been reported for schizophrenia patients (e.g. de Jong et al., 2009; Stekelenburg, Maes, Van Gool, Sitskoorn & Vroomen, 2013), may not reflect a uniform problem, but may be emphasised for pragmatic, non-literal language forms. Taken together, the fMRI findings from both studies integrating figurative content comprehension and body language processing reveal a convincing overlap with the regions that have shown altered activation patterns in schizophrenia patients in the present projects, when both functions are regarded separately (decreased IFG and STG/STS during abstract language processing; STS hyperactivation and disconnectivity during emotional body perception).

The studies published by Straube et al. might be of particular relevance for future schizophrenia research, as unlike most studies investigating the neurophysiological basis of audiovisual integration in schizophrenia, the task developed by Straube and colleagues requires an elaborate matching of auditory and visual information that is not restricted to the face. In other words, the stimuli used in these studies appear to be relatively natural and are close to what we usually encounter in everyday situations involving other individuals. Given the usability of fNIRS to investigate the regions of interest relevant for gesture-body integration processes, future directions could involve a promising combination of such integrative language-gesture paradigms and innovative neuroimaging approaches providing an even more naturalistic assessment of the relevant socio-cognitive functions.

Due to a necessary constraint of the vast topic "verbal and nonverbal communication in schizophrenia", the current projects were entirely restricted to the perceptual domain of social cognition and communication. However, different psychiatric disorders, especially schizophrenia or major depression, have also been associated with an impaired motor expressiveness. Such anomalies have been observed for both facial and body-based emotional expressiveness (Bruene et al., 2009; Bruene et al., 2008; Kupper et al., 2010; Mandal et al., 1998; Sestito et al., 2013; Trémeau, 2006; Wolf, Mass, Lambert, Wiedemann & Naber, 2012). Hereby, lacking affective expressiveness seems to be more strongly pronounced for positive emotions (Lotzin et al., 2013). In one study, facial mimicry evoked by audiovisual stimuli depicting emotional facial expressions was investigated among healthy participants who had been compared to patients with schizophrenia (Sestito et al., 2013). Whereas the control group responded with rapid and congruent mimicry to emotional stimuli, a similar pattern was observed in patients only when exposed to negative stimuli. In contrast, schizophrenia patients exhibited a lack of an emotion-triggered muscular response to positive stimuli. Due to the sensitivity of most brain imaging methods to muscular artefacts, such studies are typically rare and they almost never assess the neurophysiological substrates of impaired affect responsivity in patients suffering from schizophrenia. While this is already true for mimicry assessments, an investigation of the effects of social-affective stimulation on *body* expressivity would be even more tainted with potential movement artefacts (in case of EEG measurements) or not possible at all (in case of fMRI). Taking advantage of the flexibility of fNIRS measurements regarding the motor domain, future studies could examine whether and how the presentation of emotional stimuli, ranging from facial expressions and body movements to audiovisual material or even scenes depicting social interactions, have impact on body posture and movement in the recipient. If, as indicated by previous studies (see above), this sort of reactive expressiveness is impaired in patients with schizophrenia, fNIRS can allow access to corresponding cortical alterations. Such investigations would uniquely combine social communication assessments from both the perceptual and the expressive domains in people with psychiatric disorders, such as schizophrenia.[24] Moreover, such studies could help to determine the contribution of impaired neural emotion processing to the reported mimicry deficits, and vice versa (see also below), by disentangling activity of areas that are more strongly associated with the sensory emotion perception versus motor expression during such whole-body mimicry tasks.

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[24] Whereby, of course, a number of psychopathologies apart from schizophrenia would be conceivable, such as autism spectrum disorders, bipolar disorders, or major depression. While for all of them the processing and recognition of socio-affective stimuli have been thoroughly investigated, almost nothing is known about face and body expressiveness in response to such stimuli, together with corresponding neurophysiological activation patterns.

Up till now, body-based mimicry of emotional stimuli has been investigated neither in schizophrenia nor, to the best of my knowledge, in healthy subjects. However, influential theories on embodied cognition (for example see Niedenthal, 2007; Zajonc & Markus, 1984) would actually argue in favour of assessments of that kind. Embodied *emotion* theories in particular suggest an engagement of sensory-motor processes in the processes of emotion perception, recognition, and understanding (cf. Figure 36). Hereby, a manipulation (inhibition or facilitation) of somatosensory resources is assumed to influence the perception and understanding of emotional stimuli. Condensing the assumptions made by embodied cognition accounts, Niedenthal postulated "a reciprocal relationship between the bodily expression of emotion and the way in which emotional information is attended to and interpreted" (Niedenthal, 2007, p.1002, middle column). Supporting this postulate, Niedenthal, Barsalou, Ric, and Krauth-Gruber (2005) reviewed empirical evidence suggesting that when individuals adopt facial expressions or make emotional gestures (1) they experience corresponding emotions and (2) their preferences and attitudes are influenced. Moreover, when motor movements are inhibited, the experience of emotion and processing of emotional information is affected. Against this background, a relationship of aberrant or deficient bodily expressiveness and bodily emotion recognition in patients with schizophrenia would be reasonable and offers an interesting area for future research. As mentioned above, the implementation of naturalistic imaging methods, such as (portable) fNIRS and EEG systems, can offer promising insights into respective neurophysiological mechanisms underlying this particular aspect of embodied social cognition.

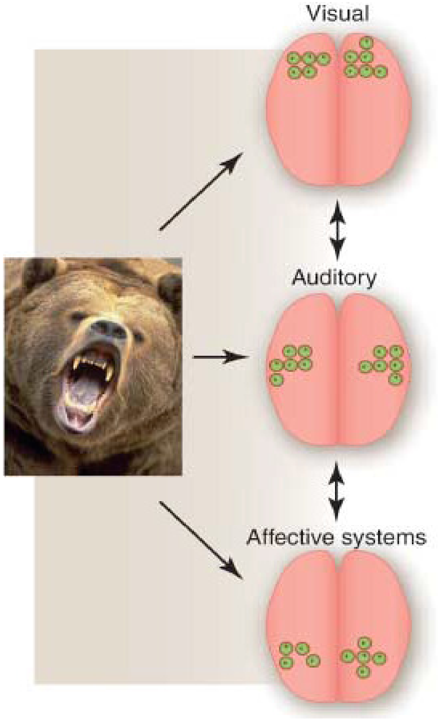

Figure 36. Schematic illustration of activated neuron populations within visual, auditory, and affective systems upon perception of a snarling bear. Modified after Niedenthal (2007).

Apart from such rather specific research opportunities that can be derived from the present work, the findings presented here can also be transferred into more fundamental parts of schizophrenia research, such as etiology and treatment research. In section 1.3.2, findings have been quoted that support a potential impact of urbanicity, which might be related to socio-cultural factors, on the risk of developing schizophrenia (Heinz et al., 2013; Kelly et al., 2010; Lewis et al., 1992). In fact, urbanicity, as indexed by population density, has been reported to be associated with a 1.5- to 4-fold increase in the incidence of schizophrenia and non-affective psychosis (Harrison, Fouskakis, Rasmussen, Tynelius, Sipos & Gunnel, 2003; Kelly et al., 2010; Kirkbride, Fearon, Morgan & et al., 2006) and there might even be variation across neighbourhoods within cities (Zammit et al., 2010). While, for a long time, the most commonly accepted explanation of this relationship was a selection of individuals into urban areas following disease onset, the majority of recent studies support the view of a risk-increasing exposure to urban environment: Several studies have independently reported that the risk of schizophrenia increases as degree of urbanization at birth or, perhaps more critically, during upbringing (for a review of respective studies see Heinz et al., 2013). As a consequence, Heinz and colleagues raised the question "of what it is in the urban environment that places more individuals at risk of non-affective psychotic disorders" (Heinz et al., 2013, p. 188, right column). To answer this question, the authors distinguished individual level and area level factors, which are also likely to interact. Among the latter category, "social deprivation" has been suggested as a potentially important factor. However, although animal experiments suggest that social defeat or social exclusion may cause dopamine deregulation, the exact mechanisms by which social factors exert their influence remain unknown (Cantor-Craae, 2007). Considering that both reduced emotion recognition and complex language comprehension have been associated with early social deprivation or hazards (Allen & Oliver, 1982; Desmarais, Roeber, Smith & Pollak, 2012; Nelson, Westerlund, McDermott, Zeanah & Fox, 2013), one could hypothesise a link between urbanicity, social deprivation during childhood, the decreased processing of verbal-semantic and nonverbal-emotional social information, and the psychopathology of schizophrenia. Considering neurophysiological mediators, it could for example be speculated that early social deprivation in some urban areas (together with individual factors) contributes to an aberrant development of relevant "social brain areas", for which altered structure and function have been shown repeatedly among patients with schizophrenia. This idea would be in line with review findings published by Akdeniz, Tost and Meyer-Lindenberg (2014) suggesting that the functional and structural architecture of neural circuits in the brain undergoes unfavourable changes in response to a continuous exposure to social stress. To specifically test such hypotheses, future etiologically oriented studies on schizophrenia could start to actually implement paradigms investigating (bodily) emotion perception or pragmatic language comprehension, such as the ones presented in this work, in children who grow up in risk areas for developing schizophrenia.[25] Such studies could further enrich the debate on whether emotional movement recognition impairments or deficient pragmatic language functions constitute

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[25] Notably, because developmental language disorders have also been proposed to increase the vulnerability for schizophrenia (Mouridsen & Hauschild, 2008), a clear distinction of area-level social factors (e.g. social deprivation) and individual factors (such as language development) would be important in such studies, especially for determining the relationship of early social environmental factors and pragmatic language comprehension abilities.

endophenotypes for schizophrenia (cf. section 5.4), shedding light on the links between adverse social factors and altered brain function in schizophrenia.

Shifting from etiological considerations to treatment perspectives, another very important research branch in the study of schizophrenia, the present studies again may provide fruitful input. For example, an integration of the present findings into cognitive models underlying CBT of schizophrenia can support a better understanding of both action mechanisms and limitations of CBT for treating socio-cognitive functions in patients with schizophrenia. One cognitive model, the aberrant salience hypothesis of psychotic symptoms, suggests a mal-attribution of significance of stimuli or events that is based on an imbalanced dopamine transmission (Kapur, 2003). The results of study 4 suggest that such a misattribution may take place when patients observe neutral and emotional body movements (generally elevated STS activation and enhanced EBA activation to neutral movements). At the verbal communication level, problems in understanding figurative meanings such as metaphors (cf. study 2), but also irony and sarcasm can lead to incorrect attributions of another person's intentions. The significance of such a cognitive bias for different facets of the schizophrenia psychopathology has recently been highlighted by Wittorf and colleagues (2012). Their study revealed a diagnosis-specific externalising bias (i.e. attending towards threat-related information and attributing negative events to external causes) in paranoid schizophrenia, distinguishing this group from patients with Anorexia Nervosa and Major Depression.[26] The knowledge about disorder-specificity of this cognitive bias is highly relevant for the development of disorder-specific cognitive models and, perhaps more critically, disorder-specific psychotherapies. Against this background, some CBT strategies in schizophrenia psychotherapy especially target these attributional biases (e.g. metacognitive training; MCT; for example see Moritz, Veckenstedt, Randjbar, Vitzthum & Woodward, 2011). While it has recently been shown that such strategies can actually ameliorate cognitive biases and delusional symptoms (Moritz et al., 2011), their effects on more specific misattributions, for instance during the observation of neutral or emotional body movements, are still unknown. Future clinical studies should therefore particularly investigate CBT treatment effects on emotion recognition abilities from body language, and try to elucidate if and how related cortical activation anomalies may be affected.

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[26] In their study, Wittorf et al. further investigated the so-called "jumping to conclusions" bias in schizophrenia for which, in contrast to the external attribution bias, the authors did not find a clear evidence of disorder-specifity.

Moreover, in future research, the paradigms and measurement techniques introduced by the present work could be further implemented in treatment studies, with the aim to either evaluate treatment efficacy regarding the respective verbal-semantic and nonverbal-emotional communicative functions, or to predict treatment responses of patients with varying impairments within these functions.

While attribution biases in schizophrenia patients are mostly investigated by means of affect recognition or ToM studies, the investigation of possible misattributions of semantic content in pragmatic language expressions could further be interesting. A recent study investigated the neurophysiological processing of positive and negative metaphoric expressions using fMRI in healthy subjects and found that activation of different cortical areas was associated with the comprehension of positive and negative non-literal meanings, respectively. Future studies could assess whether patients show similar or different cortical patterns and if they reveal altered attribution of positive versus negative meaning to figurative expressions. Such studies could clarify if misattribution of valence, as repeatedly observed in studies on emotion recognition, appears in a similar way for pragmatic linguistic material and may therefore potentially constitute another common factor of verbal and nonverbal social information processing deficits in schizophrenia.

Besides CBT, neurophysiological findings on body-based emotion processing and non-literal language comprehension in schizophrenia can be integrated into more specific therapeutic approaches, such as specialised remediation programs targeting verbal or nonverbal communicative competences. In their review, Kaneko and Keshavan (2012) found that (social) cognitive remediation programs are likely to be more successful when the skills trained closely approximate those needed in daily life. The functional significance of the ability to (1) recognise and interpret emotional states from another person's movements and (2) correctly comprehend and interpret non-literal meanings frequently occurring in our everyday language has been thoroughly emphasised already (cf. sections 1.1 and 1.4). Therefore, the paradigms and measurements introduced and tested in the present work may offer an approximation to the assessment of socio-cognitive functions that are relevant to everyday situations.

When addressing psychotherapeutic treatment of schizophrenia symptoms, we may not only focus on the pure effects of different treatment strategies. Instead, we can also be interested in the process of treatment, and how patient-therapist interactions may influence treatment response and efficacy. Such considerations are highly relevant for everyday clinical practice and shall therefore be shortly highlighted here. One parameter that can be used to operationalise the quality of patient-therapist interactions is synchrony. In a very sophisticated study on healthy participants using intersubject correlations for fMRI data, Dikker, Silbert, Hasson, and Zevin (2014) found increased speaker-listener brain-to-brain synchrony for highly (versus poorly) predictive contexts in the posterior STG, a region that has been implicated in lexical-semantic comprehension and prediction (Friederici, 2012). This finding gives interesting directions for schizophrenia research, as a decreased brain-to-brain synchrony might account for problems in language comprehension, which might be relevant for psychological interventions as well as everyday social interactions. While brain-to-brain synchrony between schizophrenia patients and therapists has so far not been investigated, a similar approach has been made with respect to nonverbal information exchange. Actigraphic data, obtained by Motion Energy Analysis (MEA, cf. Kupper et al., 2010) can be used to assess the quality of interactions, represented by the degree of nonverbal synchrony between therapist and patient. Interestingly, one preliminary study using MEA found that the degree of nonverbal (i.e. body movement) synchrony between schizophrenia patients and their therapist was reduced and varied with patients' symptoms and social cognition abilities (Tschacher, Kupper & Ramseyer, 2014; unpublished data). However, it is not yet understood whether this sort of nonverbal desynchronisation during social interactions (as well as therapeutic settings) can be detected at the level of brain-to-brain synchrony. In this context, fNIRS measurements could likely offer new and interesting research opportunities on nonverbal communication anomalies in schizophrenia and their potential significance for the therapeutic process. Hereby, further technical-methodological developments of fNIRS measurements and data analysis algorithms will be necessary in order to promote reliable results.

To close this final chapter, I will return to the usefulness and potential of combining modern methods from neuroimaging and psychiatry. As stated in the General Introduction of this work, the implementation of brain imaging methods in psychiatric research has been strongly contributing to our understanding of the pathophysiology of various mental disorders. Hereby, insights are not limited to specific alterations of brain structure and functions, as neuroimaging brought further knowledge on aberrant cerebral metabolism and neurotransmission and therefore helped to generate profound etiological models for different mental disorders, which are in turn highly important with respect to prevention and intervention. In recent years, neuroimaging studies supported the view that the human brain is organised in terms of complex networks, which may, to some extent, be imbalanced in psychiatric disorders, and the introduction of the endophenotype concept, despite its limitations, has brought additional progress to the understanding of the development of mental disorders. The present work has highlighted that problems in verbal and nonverbal communication, which are frequently experienced by patients with schizophrenia, are associated with distinct alterations in cortical activity and cortico-cortical connectivity. Hereby, emphasis was put on the use of (1) relatively novel, innovative brain imaging methods that may be beneficial for future neuropsychiatric research (fNIRS and EEG-fNIRS *combinations*) and (2) newly established paradigms to assess specific verbal and nonverbal communicative functions that so far have not or only rarely been assessed in schizophrenia. Therefore, the present work further underpins the usefulness of neuroimagning studies – particularly if they occur in naturalistic settings – in psychiatric research. Importantly, however, when implementing brain imaging research in psychiatric contexts particular attention should be given to the principle of proportionality, as for ethical reasons these comparatively effortful studies should only be performed when the issue of interest is likely to be beneficial for prospective advancements in prevention, diagnostics, and/or treatment of the disorder. Both verbal-semantic and nonverbal-emotional aspects of communication are not only highly relevant for general psycho-social outcome; respective impairments in patients with schizophrenia are also still insufficiently understood, despite the fact that they constitute a prominent phenotype that is associated with severe social impairments for schizophrenia patients. Therefore, the value of neuroimaging studies to elucidate the background of these functions and their potential as endophenotypes appears quite obvious. Knowledge on the neurobiological basis of social communication deficits in schizophrenia can help to provide an adequate, comprehensible disease model to support patients in understanding their troubles and potential social difficulties. Moreover, the neurophysiological insights on social communication disturbances in schizophrenia patients support a more holistic understanding of the neural mechanisms of action of therapeutic interventions, be it from a pharmacological, psychotherapeutic, or socio-psychiatric perspective. Against this background, the present work has tried to provide a number of potential directions for future studies investigating social communication – both deficits but also possible resources – in schizophrenia.

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7. List of Abbreviations

(f)NIRS	(functional) near-infrared spectroscopy (funktionelle) Nahinfrarot-Spektroskopie
(f/s)MRI	(functional/structural) magnetic resonance tomography
(m)PFC	(medial) prefrontal cortex
(p)STS	(posterior) superior temporal sulcus (posteriorer) superiorer temporaler Sulcus
(RM-)ANOVA(s)	(repeated measures) analysis/es of variance
ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
APA	American Psychological Association
ASD	autism spectrum disorder
BA(s)	brodmann area(s)
BDI	Beck Depression Inventory
BH (correction)	Bonferroni-Holm (correction)
BOLD	blood oxygen level dependent
BRAIN	Brain Research Through Advancing Innovative Neurotechnologies
CBT	cognitive-behavioural therapy
CNTRICS	Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia
COMT	catechol-O-methyltransferase
CT	computer tomography
CW(s)	critical word(s)
DCM	dynamic causal modelling
DNA	deoxyribonucleic acid
DOT	diffuse optical imaging
DRD2	gene for the dopamine D2 receptor
DSM(-IV/-IV-TR/-5)	diagnostic and statistical manual of mental disorders (4th edition/text revision of the 4th edition/5th edition)
DTI	diffusion tensor imaging
DTNBP1	gene for the protein dysbindin
DUI	duration of illness

EBA	extrastriate body area extrastriatales “body Areal”
EEG	electroencephalography Elektroenzephalographie
EHI	dinburgh Handedness Inventory
EKP(s)	Ereignis-korrelierte(s) Potential(e)
ELAN	early lateralized negativity
EOG	electrooculography
ERP(s)	event-related potential(s)
ERQ	Emotion Regulation Questionnaire
FBA	fusiform body area
FFG	fusiform gyrus
FGA(s)	first-generation antipsychotic(s)
GABA	gamma-aminobutyric acid
GDS	General Depression Scale
GM	grey matter
Hb	haemoglobin
HC	healthy controls
HHb	deoxygenated haemoglobin
hMT	human motion selective area
HPA (axis)	hypothalamus-pituitary adrenal (axis)
ICBM	International Consortium for Brain Mapping
ICD(-10/11)	International Classification of Diseases (version 10/11)
IFG	inferior frontal gyrus
IFL	inferior frontal lobe
INC	incongruent
IOG	inferior occipital gyrus
IPL	intraparietal lobule
IPS	intraparietal sulcus
ISI(s)	inter-stimulus interval(s)
ITG	inferior temporal gyrus
ITI(s)	inter-trial interval(s)
KOR	kinetic occipital region
K-S	Kolmogorov-Smirnov

LIT	literal
LOC	lateral occipital cortex
LRP(s)	lateralized readiness potential(s)
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MCT	metacognitive training
MD	major depression
MEA	motion energy analysis
MEG	magnetoencephalography
MET	metaphoric
MFG	medial frontral gyrus
MNI	Montreal National Institute
MTG	middle temporal gyrus
MVPA	Multi-Voxel Pattern Analyses
MWT-B	Mehrfachwahl-Wortschatztest Version B
NFB	neurofeedback
NICE	National Institute for Clinical Excellence
NRG-1	Neuregulin-1
O_2HB	oxygenated haemoglobin
OFC	orbitofrontal cortex
PANAS	Positive and Negative Affect Schedule
PANSS(-pos/-neg/-g)	Positive and Negative Symptom Scale (-positve/-negative/-general)
PET	positron-emission tomography
PT(s)	peak time(s)
QoL	quality of life
ROI(s)	region(s) of interest
RT(s)	reaction time(s)
SD	standard deviation
SGAs()	second-generation antipsychotic(s)
SMT	structure mapping theory
SNPs	single nucleotide polymorphisms
SOA(s)	stimulus onset asynchrony

SPECT	single-photon emission computed tomography
SPM	Statistical Parametric Mapping
SPQ	Schizotypic Personality Questionnaire
STAI	State-Trait Anxiety Inventory
STG	superior temporal gyrus
SZ	schizophrenia
TACS	transcraniel altered current stimulation
TDCS	transcraniel direct current stimulation
TMS	transcraniel magnetic stimulation
ToM	theory of mind
TPJ	temporo-parietal junction
V1	primary visual cortex
VF	visual field
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
WLG (model)	Wernicke-Lichtheim-Geschwind (model)
WM	white matter

8. List of Tables

List of Figures

9. Organisational Remarks

The present thesis comprises two published and two submitted publications. According the guidelines of the publisher (both published articles have been published by Elsevier, see http://www.elsevier.com), these original texts can be used for scholarly, non-commercial purposes and therefore can be included in a dissertation or thesis (please see http://www.elsevier.com/journal-authors/author-rights-and-responsibilities). Details on the author's rights of publication can be checked with the author (S.Schneider@med.uni-tuebingen.de).

9.1 Contributions of the author

For all included studies, the author was the person in charge, i.e., essentially involved with regard to the development of the research questions, the programming of the paradigms, the collection, analyses and interpretation of the data as well as the final publication. The coauthors supported and contributed at single processing stages, such as study preparation or data analyses.

9.2 Styles and formatting

Throughout the manuscript, the APA style in its 6th edition has been followed. The formatting of the published studies included in this dissertation may not be changed. Therefore, **each study is handled as a unique entity with regard to the use of abbreviations as well as details in the text layout**. Solely the numbering of (sub)headings, footnotes tables and figures (and the way in which they are referenced within the text) are altered in such a way that all chapters form a coherent sequence. Moreover, British English spelling was adopted to achieve a uniform style of writing.

9.3 Eidesstattliche Erklärung

Ich erkläre hiermit, dass ich die zur Promotion eingereichte Arbeit mit dem Titel: *Verbal and Nonverbal Communication in Schizophrenia – New insights from uni- and multimodal brain imaging* selbständig verfasst, nur die angegebenen Quellen und Hilfsmittel benutzt und wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe. Ich erkläre, dass die Richtlinien zur Sicherung guter wissenschaftlicher Praxis der Universität Tübingen (Beschluss des Senats vom 25.5.2000) beachtet wurden. Ich versichere an Eides statt, dass diese Angaben wahr sind und dass ich nichts verschwiegen habe. Mir ist bekannt, dass die falsche Abgabe einer Versicherung an Eides statt mit Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft wird.

Ort, Datum Unterschrift