

Trunk rotation affects temporal order judgments: evidence from spatial neglect

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1 Introduction

1.1 General introduction to visual attention

Perceptual systems provide a huge amount of information. There is always so much complicated visual information around us. Even in a single glance, thousands of stimuli reach our eyes and are transferred to the visual cortex. Our human visual system is capable of processing lines, angles, curves and movements in parallel. But actually, not all the stimuli presented to us need to be perceived. Instead, perceptual resources could be focused on particular stimuli and ignore those irrelevant stimuli. Attention filters unwanted information and enhances those objects that either draw attention or voluntarily focused on.

Attention is a very broad process with numerous different aspects to it. For instance, when walking in a shopping mall, one can voluntarily choose to pay attention to the shoes and clothes exhibiting in the window or it can be involuntarily drawn to a baby's crying. The voluntary and involuntary nature of attention is referred to as endogenous and exogenous attention. Endogenous attention allows us to attend to an object of interest for an extended period of time, while exogenous attention is more transient.

Why we can't pay attention to every detail? Our brain is not highly sophisticated information-processing machines, if so, there would be no need for the selection of information. We would just feed them with whatever information that meets our senses. However, our brain is evolved to make actions, not for information storage. The sensory resources are unlimited while the action resources are restricted. This is the reason why there is a biological need for a mechanism that is able to filter those relevant information from all the incoming stimuli. This mechanism is what we called 'attention'.

The spirit of attention is perhaps best captured by William James:

"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with other."

Attention is a selective process. The notion that stimuli compete for limited resources (Broadbent, 1958; Treisman, 1960; Neisser, 1967; Kinchla, 1980, 1992) is supported by electrophysiological, neuroimaging and behavioural studies (for reviews see Desimone & Duncan, 1995; Reynolds & Chelazzi, 2004; Beck & Kastner, 2009). According to the competition hypothesis, stimuli in the visual field activate populations of neurons that engage in competitive interactions. Literally, the competition is biased in favour of the neurons with receptive fields at the attended location either become more active or remain active while the others are suppressed (for a review, see Desimone & Duncan, 1995). In humans, evidence for neural competition has been also found using an fMRI paradigm in which multiple stimuli are presented in close proximity at distinct peripheral locations of the visual field either sequentially or simultaneously, while observers maintain fixation. Studies report that show that sequential presentations evoke stronger than simultaneous presentations and that response differences increase in magnitude from striate to ventral and dorsal extrastriate areas (Moran & Desimone, 1985; Snowden et al., 1991; Miller et al., 1993; Luck, et al., 1997; Recanzone et al., 1997; Kastner et al., 1998, 2001; Reynolds et al., 1999; Pinsk et al., 2004; Beck & Kastner, 2005, 2007). Moreover, fMRI experiments reporting a retinotopically-specific signal enhancement at the focus of attention together with a signal reduction at the same location when attention is allocated elsewhere (Tootell et al., 1998; Somers et al., 1999; Slotnick et al., 2003; Beck & Kastner, 2009). Additionally, there was widespread baseline-activity reduction throughout the remaining visual field when directing attention to a specific location (Smith et al., 2000). All of these results are consistent with the idea that selective attention results in greater resource allocation to the attended location, at the cost of available resources at the unattended location.

In summary, attention allows us to overcome the limited capacity of the visual system and optimize performance in visual tasks. To achieve this, attention enhances the representations of the relevant while diminishes the representations of the less relevant, locations or features of our visual environment. Selective attention is the key factor for the evolutionary success which enables us to gather relevant information and guides our behaviour. (Carrasco, 2011).

1.2 Introduction to spatial neglect

Spatial neglect is a neuropsychological condition that frequently results from stroke (Stone et al., 1991, 1993). It can be defined as the inability to respond to or to orient towards stimuli located in the hemispace contralateral to the lesion of one of the cerebral hemispheres, where these symptoms are not due to the primary sensory or motor deficits (Heilman, Watson & Valenstein, 2001). Patients with spatial neglect usually fail to eat food on the contralesional side of the plate, do not shave the contralesional side of the face, do not respond to people on the neglected side or colliding into object located on the contralesional side (e.g. Bisiach, 1996; Becchio & Bertone, 2005). In contrast to stroke survivors without neglect, patients with spatial neglect experience prolonged inpatient periods, impaired functional recovery and a poor rehabilitation outcome if left untreated (Kalra et al., 1997; Pederson et al., 1997; Di Monaco et al., 2011; for review Karnath and Zihl, 2003). Up to 85% of patients suffering from right hemisphere stroke demonstrate neglect, if only for a short period of time (Stone et al., 1993), thus spatial neglect poses a great challenge to our health system. However, there is still no established treatment for neglect and conventional methods have been singularly unsuccessful. Therefore, it is important to understand the underlying deficits involved in spatial neglect in order to develop effective rehabilitative techniques. Moreover, spatial neglect is also of scientific interest, due to the insight gained regarding elusive functions of the brain, such as how the brain codes spatial information, allocates attention and processes visual information (Buxbaum, 2006) and how these factors interact.

1.2.1 Spatial deficits in spatial neglect

Most research into spatial neglect focused on its spatial deficits, namely lateralized spatial presentation (Robertson & Marshall, 1993; Rafal, 1994; Halligan & Marshall, 1994; Mesulam, 1999; Bisiach & Vallar, 2000; Pouget & Driver, 2000; Heilman & Watson, 2001; Bartolomeo & Chokron, 2002; Thier & Karnath, 2013). And the hot-spot issue that researchers posed most interests on is the nature of the spatial representational mechanisms underlying spatial neglect. One fundamental and important question is how the spatial information in

the 3D world is coded by the brain. A further question is what exactly the patient neglect of.

Spatial information is coded by the brain with a set of coordinates. These coordinates define 'Left' and 'Right' depending on the frame of reference that is operating (Halligan et al., 2003). Two main spatial reference frames are emphasized: egocentric and allocentric reference frames. Egocentric reference frames determine the position of a feature relative to the viewer's perspective and it may be based upon eye, head and/or body position (Behrmann et al., 2002). However, allocentric reference frames determine the position of a feature on an object relative to the object itself, regardless of the object's orientation or its position in relation to the viewer (Behrmann & Moscovitch, 1994). Individuals who suffer spatial neglect provide a unique insight into this issue. These neglect patients may show egocentric neglect (where information on the contralesional side of the viewer's perspective is ignored) or allocentric neglect (where the contralesional side of stimuli are ignored, irrespective of the individuals' viewpoint). Thus using presenting carefully designed stimuli or tests one should be able to infer the spatial coordinates that are disturbed. However, in normal viewing conditions, egocentric and allocentric coordinates are often confounded, since stimuli being presented centrally and horizontally to the patients. Therefore, the midline of the egocentric reference frame is aligned with the midline of the allocentric reference frame. Researchers have tried many ways to isolate these two reference frames and the basic idea is to manipulate the egocentric and allocentric midlines in order to present them out of alignment with each other.

The most commonly used test for allocentric neglect was developed by Ota et al. (2001). The patients were presented with a sheet of paper containing both normal circles and 'pseudo-circles' which randomly and evenly distributed across both visual field (egocentric left and egocentric right). The pseudo-circles had a portion of the loop missing and the gap was either on the left or right side of the circle (allocentric left gap or allocentric right gap). Patients were asked to circle the complete circles and cross out incomplete circles. Ota et al.(2001) found that one patient failed to identify the circles on the left side of the testing sheet (egocentric left side) but accurately found the circles with gaps (both with left-sided gaps and right-sided gaps) on the right side of the sheet. However, the other patient marked every circle on the testing sheet but mistook the left-gapped circles as complete

ones. This phenomenon showed that these patients did not neglect their egocentric left side but neglected the allocentric left side of the circles. Ota et al. (2001) claimed that the independence of the two reference frames is clearly determined in this study and there was no interaction of relationship between egocentric and allocentric neglect. However, the deficit of the design from Ota et al. (2001) is that the stimuli (left or right gapped circles) was contaminated with egocentric coordinates because the circles' allocentric left side is also egocentrically left to its other side. Pouget et al. (1999) noted that clinical measures of allocentric neglect could be parsimoniously explained by models that do not encode the objects' frame of reference: according to this 'relative egocentric neglect' theory one sees poor allocentric performance simply because the objects' impaired side is egocentrically contralesional to its other side. Therefore, common tests cannot discriminate between this simple one-dimensional egocentric model from two-dimensional models that attempt to encode both egocentric as well as allocentric information.

Moreover, Pouget et al. (1999) suggested that the only way to distinguish between the egocentric and allocentric alternatives is to rotate the object so that the left-right axis of the object is no longer lined up with left-right axis of the subject. Driver et al. (1994) employed triangle stimuli that remained physically identical across trials but could differ in the perceived direction in which they were pointing. This manipulation allows the gap, which was the patients' task to detect, to locate either on the left or right of one of the triangles according to the perceived viewpoint. Their results showed that neglect patients missed gaps more frequently when the gaps appear on the left side of the object's axis relative to gaps on the right side of the object's axis. Note that the egocentric location of the gap is identical for the two configurations, with left or right allocentric positions defined by the configural axis.

There have been numerous studies discussing upon the topic of the relationships between egocentric and allocentric neglect. Some researchers believed that these two subtypes of spatial neglect are independent and dissociable. For instance, in a study of 50 individuals with right hemisphere injury it was found that eleven exhibited only egocentric neglect, four suffered from allocentric neglect and only one had both deficits (Hillis et al., 2005). Additionally, results from a meta-analysis study pointed out that, while egocentric symptoms were associated with damage

within the perisylvian network and damage within sub-cortical structures, more posterior lesions were associated with allocentric symptoms (Chechlacz et al., 2012a,b). On the other hand, in a study of 110 acute right hemisphere patients Yue et al.(2012) only observed allocentric neglect in conjunction with egocentric neglect. Moreover, Rorden et al.(2012) examined 36 patients with continuous measures for these deficits and found a strong association between the severity of egocentric and allocentric neglect. In a recent fMRI study (Chen et al., 2012), BOLD responses were measured while healthy subjects performed egocentric or allocentric visuospatial judgements on a three-dimensional object (a pork on a plate). The results showed that the egocentric judgments and allocentric judgments conjointly activated both the ventral and the dorsal stream. By comparing with allocentric judgements, they also found that egocentric judgments more strongly activated certain areas while no significant activation was found in the reverse contrast. This indicated that obviously no isolated networks exists for allocentric judgments. Previously, Karnath and Niemeier (2002) examined exploratory eye movements when patients were directed via the experimenter's instructions to either attend to the whole space or only a restricted part of it. They observed that the same physical stimulus was attended to or, in another situation, neglected, just depending on the individuals' goal. Likewise Baylis et al. (2004) asked patients with spatial neglect to either search for a letter across the entire extense of a computer screen or within a particular object presented on that display. Patients exhibited egocentric deficits when searching globally yet allocentric deficits for identical stimuli when searching within an certain object. Karnath et al. (2011) recorded neglect patients' eye and head movements while they explored objects at five egocentric positions along the horizontal dimension of space. They found that allocentric neglect varied with egocentric position. The allocentric neglect was less severe on the ipsilesional egocentric positions comparing with the more contralesional egocentric positions. All these studies pointed out the conclusion that allocentric neglect co-exists with egocentric neglect and allocentric information should be influence by egocentric manipulations.

1.2.2 Non-spatial deficits in spatial neglect

As mentioned above, much of the research into spatial neglect focused on its spatial deficit. It is understandable since spatial neglect is defined regarding to its spatial deficits and the lateralized spatial presentation is its most distinct manifestation. However, to fully understand spatial neglect and to develop effective rehabilitative techniques, only concerning the spatial gradient of neglect may not be enough.

Our visual system has limitations and one approach to probe the limits is to measure the time course of attentional processing (Duncan et al., 1994). When we identify a visual object, our ability to detect a second object is impaired if it is presented within 400ms after the first. This phenomenon has been termed 'attentional blink (AB)'. AB is usually observed in rapid serial visual presentation (RSVP), in which two targets are embedded in a stream of objects that are rapidly and sequentially presented.

Husain et al. (1997) has firstly reported a temporal deficit in allocating attention in visual neglect using the attentional blink paradigm. In that study, a stream of different black letters was presented in the center of a screen with one white target letter. In some of the trials, a second target letter 'X' followed the white letter at some point in time. Patients were asked to report what the white letter was and whether there was also an 'X' presented. Healthy observers required about 400ms between the two targets to report both targets accurately. Neglect patients showed a more severe and protracted AB; their ability to detect the second target letter 'X' was delayed with more than 1200ms. The finding demonstrated that abnormal temporal dynamics of attentional deployment was present in neglect patients even when stimuli were presented at the same spatial location. Further evidence for temporal deficit of attention in patients with neglect came from studies which reported impairments on both sides of space. Duncan et al.(1999) measured the capacity of visual attention and found that neglect patients showed reduced capacity for encoding stimuli presented transiently in both sides of visual field. Moreover, auditory studies also found evidence for a temporal deficit in selective attention. Pavani et al.(2003) reported that neglect patients showed a bilateral deficit when auditory stimuli presented to both ears but with an interaural time difference to act as a localization cue.

Although these studies provided evidence of temporal deficits in spatial neglect, a critical question is that what is the relationship between the temporal deficits and the lateralized spatial bias in spatial neglect (Husain, 2001; Husain & Rorden, 2003; Hillstrom et al., 2004). Di Pellegrino et al.(1997,1998) have compared spatial and temporal shifts of attention in a patient with left-sided extinction. The patient was instructed to identify two letters that appeared at a single location (either left or right hemifield) or to report two letters that appeared in both hemifields with either left or right letter showing first. They found that when the two letter showing in both hemifields, patient reporting the right letter was always accurate but the accuracy of reporting of the left letter depended on the stimulus onset asynchrony (SOA). When the two letters were successively presented at the same location in the right hemifield, the patient could report both letters accurately if the SOA was more than 400 msec which is consistent with a normal attentional blink limit. But when the two letters were sequentially presented at the left hemifield, a prolonged SOA was needed for accurate response which is consistent with Husain et al.(1997) findings of a prolonged attentional blink in spatial neglect. In a pioneering study, Di Pellegrino et al.(1998) investigated left-sided extinction patient using a variant of the attentional blink design. They found a prolonged attentional blink for stimuli presented in the contralesional space. Similarly, Hillstrom et al. (2004) reported a study of one patient with left neglect indicating that there might be a lateralized spatial gradient in the temporal dynamics of attention. The authors also used a RSVP stream of different letters but – other than Husain et al.'s (1997) original design – the second target letter appeared not only at fixation but in addition left or right of fixation. The right brain damaged neglect patient showed a prolonged AB when the second target appeared on the contralesional left side of fixation. These results suggested a spatial, horizontal gradient in the allocation of visual attention. Moreover, Snyder and Chatterjee (2004) discussed whether the vertical spatial gradient may modulate temporal processing. The experiment was tested on a patient showing extinction and found that the patient was poorer at judging the order of events for vertically aligned stimuli in the contralesional space than in ipsilesional space. Interestingly, his performance improved with stimuli of larger vertical separations. Additionally, Bartolomeo et al.(2005) also suggested that spatio-temporal dynamic may also affect imagination. In this study, patients were asked to imagine a map

of France and then to report whether auditorily presented towns or regions were situated to the left or right of Paris. Their results showed that neglect patients were slower for left than for right imagined location. This demonstrated that under certain circumstances prolonged temporal dynamics of attention may affect also mental imagery abilities.

However, some studies claimed that this temporal deficits might be anatomically specific rather than neglect-specific. Shapiro et al.,(2002) reported that non-neglect patients with lesions of the inferior parietal lobe and superior temporal gyrus could also show temporal impairment. But when combined with a lateralized bias it could also exacerbate spatial neglect. Russell et al.(2004) revealed that non-neglect patients with damage to right parietal cortex missed peripheral stimulus when they were required to complete a high demand task at fixation. The performance was particularly poorer on the contralesional side. Moreover, Russell et al.(2013) found that not only non-neglect patients with right hemisphere lesions but also even healthy aging individuals exhibited a spatiotemporal attentional blink in detecting peripheral targets.

In conclusion, recent investigations that temporal abnormalities and lateralized spatial bias are combined and interacted with each other in spatial neglect. Thus, we should reconsider the phenomena spatial neglect. It is not simply that the neglect patient just fails to represent half the space, but rather that the patient does not conceive it. The temporal impairment in spatial neglect explained somehow why the patient with spatial neglect behaves as if the half of space does no exist (in the present), has never existed (in the past) and will never exist (in the future) (Becchio & Bertone, 2006).

1.3 Interactions between time and space

In our daily lives, time and space are hardly separated. When we travel, we have to plan the destination as well as the time we need spend on the way the same time; when we play piano, we need to organize the location of our fingers according to the rhythms; when we cook, we need to organize when and where to put the ingredience, etc. Moreover, there has been increasing evidence to proof that time and space are linked not only physically but also mentally.

Piaget provided the first evidence for the interaction between time and space. He found out that children under certain age intuitively have not the capability to differentiate between the concepts of time and space. That is, “longer (time) is equivalent to further” (Piaget, 1969; see also Levin, 1979). Moreover, in adults, the subjective passage of time is also influenced by the differentially size-scaled model environments. For example, compressed environments might lead to a likewise compression of subjective time relative to clock time (De Long, 1981; Mitchell & Davis, 1987). Following investigations have corroborated the idea of time-space associations (see Oliveri et al., 2009 for a review). For instance, adults might overestimate the duration of stimuli presented on the right side of visual space, and underestimate them when presented in the left hemi-space (Vicario et al., 2008; Oliveri et al., 2009). Moreover, the speed of visual stimuli can also influence the subjective time, i.e. when viewing speed-altered movie scenes (Levin, 1977; Levin, 1979; Grivel et al., 2011).

According to this time-and-space interaction hypothesis, techniques which modulate space perception have been tested to alter subjective time sensation. For instance, adapting to left- or rightward deviating prism lenses shifts visuospatial attention to the side of the induced aftereffect (Rossetti et al., 1998). Interestingly, subjects underestimate temporal durations after being exposed to prisms inducing leftward attentional shifts, and likewise overestimate them for opposing aftereffects (Frassinetti et al., 2009; Magnani et al., 2011). Similarly, participants underestimate the duration of stimuli after the exposure to leftward optokinetic stimulation (OKS), and overestimate them after rightward OKS (Vicario et al., 2007).

The evidence for the time and space interaction can also be found in the anatomical structures. The brain areas that might involve in time processing include the dorsolateral prefrontal cortex (DLPFC, Rao et al., 2001; Macar et al., 2002; Koch et al., 2003; Jones et al., 2004; Tregellas et al., 2006), the inferior frontal gyrus (Smith et al., 2003), the supplementary motor areas (SMA, Macar et al., 2002; Smith et al., 2003; Tregellas et al., 2006), the insula (Tregellas et al., 2006), the cerebellum (Rao et al., 2001; Smith et al., 2003; Smith et al., 2011), and the basal ganglia (Rao et al., 2001; Tregellas et al., 2006; Smith et al., 2011). In details, the frontal areas (DLPFC) are related to working memory processes and are thought to mediate the cognitive control of time perception, while the

basal ganglia and the cerebellum have been proposed as general time generators (Lewis & Miall, 2003; Koch et al., 2009; Smith et al., 2011). Worth to point out that an increasing number of studies reported the posterior parietal cortex (PPC) as playing an essential role in time processing and time-space interactions (Battelli et al., 2007; Bueti et al., 2008; Oliveri et al., 2009). The PPC is reported as the neural anatomical substrate for visuospatial attention (Corbetta et al., 1993; Coull & Nobre, 1998; Bjoertomt et al., 2002) and perception of the body in space (Brotchie et al., 1995; Bremmer et al., 1998; Mulette-Gillman et al., 2005). Moreover neuropsychological reports of neglect patients with time deficits provided further evidence for the PPC's involvement in time processing (Roberts, et al., 2012). Functional imaging data have revealed the activation of the temporo-parietal junction during temporal order judgments (Davis et al., 2009). Last but not least, in animal research, neuronal activation in the IPS of the monkey's brain is associated with the integration of visual stimuli over time (Nieder et al., 2006). All of these observations pointed out that PPC represents both the neuronal structures for time and space processing which provides a strong evidence for the time and space interactions in the brain.

1.4 Temporal order judgement

Temporal Order Judgment (TOJ) refers to participants deciding which of two (or more) unimodal cues (e.g. audio or video) was presented first (or sometimes second) in a cross-modal stimulus. TOJ tasks have been historically used to study topics in sensory systems including selective attention (Sternberg & Knoll, 1973), lateralization of function in the cerebral hemispheres (Kappauf & Yeatman, 1970), identification of speech sounds (Liberman et al., 1961) and auditory stream segregation and perception of melodic lines (Bregman & Campbell, 1971). TOJ tasks are almost based on the same logic: systematic difference exists between the objective and subjective simultaneity of a pair of stimuli. This difference can be represented by the physical time difference or response accuracy difference needed for the pair of stimuli to appear simultaneous, or for the two possible orders to be reported with equal frequency (Sternberg & Knoll, 1973).

According to Edward Titchener's law of prior-entry "The object of attention comes to consciousness more quickly than the objects which we are not attending to"

(Titchener, 1908), temporal order judgment task is a popular paradigm in selective attention studies. Studies that controlled for response bias have confirmed the existence of prior-entry in vision (Schneider & Bavelier, 2003; Weiss & Scharlau, 2011) as well as in the somatosensory domain (Yates & Nicholls, 2009). TMS studies suggest the parietal cortex is involved in TOJ tasks (Woo et al., 2009). The authors applied a single pulse TMS at either the left or right posterior parietal cortex while subjects made order judgments of two stimuli, one in each visual field. They found that the processing of the contralateral stimulus was delayed for 20-30 ms, only when TMS was applied on the right, but not on the left side. In a fMRI study, Davis et al. Coincidentally, the disruptive effect was evident only when the TMS pulse was given 50-100 ms after the onset of the first stimulus. Patient studies also point to a role for the parietal cortex in TOJ. Rorden et al. found that patients reported the ipsilesional stimulus preceding the contralesional stimulus unless the latter was presented at least 200 ms earlier (Rorden et al., 1997). Sinnott et al. presented one shape in each hemifield of right parietal patients and found that the contralesional stimulus had to be presented at least 200 ms before the ipsilesional stimulus in order for patients to identify them correctly with equal frequency (Sinnott et al., 2007). Baylis et al. asked patients with either left or right parietal damage to report which of two stimuli was the second to appear, and found that a temporal lead of at least 200 ms was necessary for the contralesional stimulus to be reported as frequently as the ipsilesional stimulus, regardless of the lesion side. As suggested by Driver et al., patients might simply have preferred to report the stimulus on their "good" side as first when they were uncertain of the temporal order of stimuli: it is well established that parietal patients show strong biases to respond to stimuli on the ipsilesional side (Driver, 1998). An orthogonal design reduces this confound by asking subjects not to report the side (left vs. right) of the first stimulus, but to report a feature (color, orientation) of the stimulus they perceived first. As expected, TOJ deficits were still observed in patients (Baylis et al., 2002; Sinnott et al., 2007).

1.5 Effects of head-on-trunk position

Head-on-trunk position has been proved to affect the visuospatial attention. Most evidence is coming from studies regarding spatial neglect patients after stroke.

First, neuropsychological research has demonstrated that neglect patients experience a subjective shift of their trunk midline towards the ipsilesional side (Ferber & Karnath, 1999; Karnath 1994). This subjective shift of the trunk midline in neglect patients seems to be associated with the occurrence of a rightward spatial bias, as the pattern of exploratory eye movements is shifted in respect to the objective trunk midline, while being symmetrical in respect to the objective trunk midline (Karnath et al., 1991; Hornak, 1992). Moreover, studies also demonstrated that manipulations of the physical or perceived trunk midline (via neck muscle or caloric-vestibular stimulation) can alleviate visual neglect symptoms (Johannsen et al., 2003; Karnath et al., 1993,1991; Rode & Perenin, 1994; Schindler & Kerkhoff, 1997; Schindler et al., 2002). These studies either physically or illusionarily rotated the trunk towards the contralesional side shortened saccade latencies towards the neglected hemifield (Karnath et al., 1991), re-centered exploratory eye movements and improved visual detection performance in the absence of an overt motor response (Karnath et al., 1993).

Trunk rotation has been also reported consistently to improve spatial performance in neglect patients (Karnath et al., 1991,1993; Chokron & Imbert, 1995; see Chokron et al., 2007 for review; Li et al., 2014). The possible underlying mechanism has been attributed to alterations of afferent retinal, eye- and neck-proprioceptive information. The visual signals are integrated into a global, body- or egocentric reference frame which allows an adequate orientation in space. During the rotation, the afferent information is changed, thereby leading to a shift of the internal body-centered coordinates. The anatomical substrate for the integration and transformation process seems to be the posterior parietal cortex (Brotchie et al., 1995; Duhamel et al., 1997; Bremmer et al., 1998, 1999; Mulette-Gillman et al., 2005). As mentioned in 1.3, the posterior parietal cortex has also been suggested to establish a principal anatomical site of time processing and time-space interactions. Thus, an interesting question is raised that whether head-on-trunk position will also influence time perception?

2 Aims of this study

One of the hot-spot issues regarding spatial neglect is whether or not spatial and temporal components of visual attention interact in attentional performance. The aim of my present study was to investigate the relationship between the spatial and temporal deficits in patients with spatial neglect. We used typical temporal order judgement paradigm as a basis and explored whether trunk position influenced the patients' temporal deficit. Here we had individuals point their head and eyes toward the center of a computer screen, which was positioned either left or right of the subject's saggital trunk midline. This design kept the retinotopic and the head-centered coordinates of the stimuli constant: we only manipulated its position relative to the subject's trunk. The expectation of the study is that the temporal dynamics of neglect are biased by egocentric (trunk related) spatial position.

Spatial neglect is the most frequent cognitive disorder following right hemisphere brain damage. Patients with spatial neglect experience prolonged inpatient periods, impaired functional recovery and a poor rehabilitation outcome if left untreated (Kalra et al., 1997; Pederson et al., 1997; Di Monaco et al., 2011; for review Karnath and Zihl, 2003). The present study might provide evidence and support for better intervention tools to reach a better rehabilitation outcome.

3 Materials and methods

3.1 Participants

Fifteen consecutively admitted patients with first ever right hemisphere stroke participated. Patients with a left-sided stroke, patients with diffuse or bilateral brain lesions, as well as patients who were unable to follow the instructions to finish the experiment were excluded. All of the patients conducted the initial clinical testing on average 5.1 days post-stroke (SD 4.5) and the second clinical testing in the chronic phase on average 1042.1 days (SD 415.1) post-stroke. Five of them showed spatial neglect (NEG) in both acute and chronic phase, five of them showed spatial neglect in the acute phase but no longer in the chronic phase (neglect recovered, NR) and the other five did not show spatial neglect neither in the acute nor the chronic phase (right brain damaged controls, RBD). Three of the five neglect patients showed extinction in varying degrees (details see in Table 1). Additionally, fifteen age-matched healthy participants (non-brain damaged controls, NBD) without neurological or psychiatric disorders were tested. All thirty subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standard of the 1964 Declaration of Helsinki. Demographic and clinical data of all subjects are presented in Table 1.

Table 1. Demographic and clinical data of all 30 participants.

	NEG	NR	RBD	NBD
Number	5	5	5	15
Sex(m/f)	3/2	3/2	3/2	5/10
Age(years)	73.4(1.52)	68.6(7.3)	69(7.55)	70(4.42)
Etiology	5 Infarct	3 Infarct 2 Hemorrhage	4 Infarct 1 Hemorrhage	
Time since lesion (days)	1140.6(461.4)	1169.6(527.4)	816(124.8)	
Visual field defects (% present)	0%	0%	0%	
Visual extinction (% fail to report contralesional stimuli in bilateral displays)	NEG01 75% NEG02 100% NEG03 20% NEG04,05 0%	0%	0%	
Spatial neglect scores				
Letter cancellation (CoC)	Acute: 0.51(0.24)	Acute: 0.42(0.25)	Acute: 0.004(0.01)	
	Chronic: 0.07(0.04)	Chronic: 0 (0.02)	Chronic: 0 (0.01)	
Bells test (CoC)	Acute: 0.58(0.29)	Acute: 0.26(0.14)	Acute: -0.01(0.02)	
	Chronic: 0.17(0.16)	Chronic:0.04(0.04)	Chronic: 0 (0)	
Copying (% omitted)	Acute: 62.5(17.7)	Acute: 47.5(24.0)	Acute: 0 (0)	
	Chronic: 12.5(10.2)	Chronic: 0 (0)	Chronic: 0 (0)	

Data are presented as mean (SD). CoC, Center of Cancellation (Rorden and Karnath, 2010); NEG, right brain damage with both acute and chronic spatial neglect; NR, right brain damage with acute spatial neglect but no chronic neglect; RBD, right brain damage without spatial neglect; NBD, non-brain damage; m, male; f, female.

3.2 Clinical assessments

All fifteen brain damaged patients were assessed in the acute and in the chronic phase of the stroke with the following clinical neglect tests: Letter Cancellation Task (Weintraub and Mesulam, 1985), Bells Test (Gauthier et al, 1989), and a Copying Task (Johannsen and Karnath, 2004). All three tests were presented on a horizontally oriented 21*29.7cm sheet of paper. For the Letter Cancellation Task and the Bells Test, we calculated the Center of Cancellation (CoC) using the procedure and software by Rorden and Karnath (2010). This measure is sensitive to both the number of omissions and the location of these omissions. CoC scores > 0.09 in the Letter Cancellation Task and the Bells Test were taken to indicate neglect behavior (cf. Rorden and Karnath, 2010). In the Copying Task, omission of at least one of the contralateral features of each figure was scored as 1, and omission of each whole figure was scored as 2. One additional point was given when contralesional figures were drawn on the ipsilesional side of the test sheet. The maximum score was 8. A score higher than 1 (i.e., >12.5% omissions) indicated spatial neglect (Johannsen & Karnath, 2004). For a firm diagnosis of spatial neglect in the acute phase of the stroke, i.e. when the pathological behavior is most extreme, the patients had to fulfil the above criteria in at least two of the three tests. At the time of the second (chronic) assessment, patients were classified as showing chronic neglect when they fulfilled the above criteria in at least one of the three tests.

Visual field defects were examined by the common neurological confrontation technique. Visual extinction was examined by the common neurological confrontation technique as well as a computerized task. The task included four geometrical figures (square, circle, triangle, diamond), each 0.7° in size, presented for 180ms in random order 4° left and/or right of a central fixation point presented on a PC monitor; stimuli were generated and presented by software E-Prime 1.0 and displayed on a ThinkPad laptop (type 8932) with a screen size of 1280*800 pixel. There were 10 trials with bilateral and 20 trials with unilateral left or right presentations. Patients were classified as showing visual extinction when they failed to report at least 50% of the contralesional stimuli during bilateral stimulation in the presence of correct detection of at least 90% of the contralesional stimuli during unilateral stimulation.

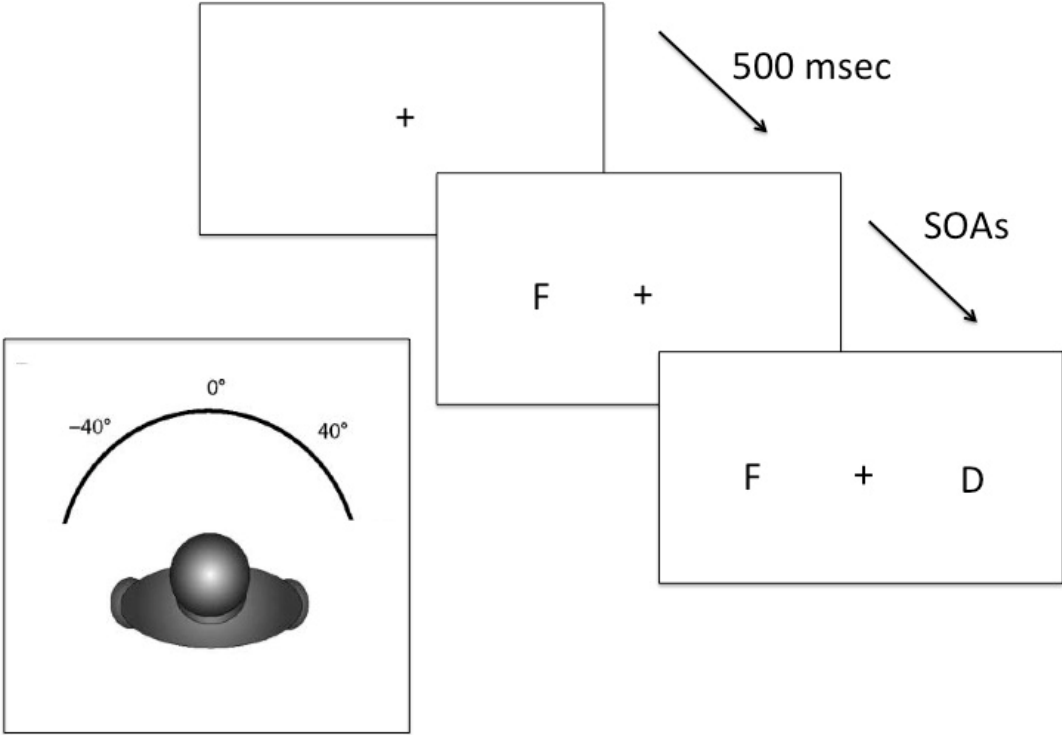
3.3 Stimuli and procedure

The temporal order judgement (TOJ) task has used the experimental design by Rorden et al. (1997) and Pellegrino et al. (1997) as reference. Stimuli were generated by using Matlab R2013a software and were displayed on a Macbook Pro laptop with a screen size of 1280*800 pixels. The viewing distance was 60 cm and fixation was positioned at the center of the monitor and at eye height. All displays appeared in black against a uniform gray background. Stimuli were the upper case letter from alphabet 'A' to 'X' without 'W' or 'M' and located ca 6.8° to the left and right of a central cross. The size of the letter was 1.55° in height and the size of the central cross is 0.2° in height.

After pressing the spacebar, the display was initiated. The fixation cross then appeared for 500 msec. Two different letters were then presented, one to the left and one to the right of fixation, at the same eccentricity. The stimulus-onset-asynchrony (SOA) between the two different letters could be 83, 167, 250, 333, 417, 500 or 583 msec and was varied across trials (Figure 2). The participants were asked to report which letter appeared first on each trial. Both letters remained visible until the response was made verbally from the participant and typed in by an experimenter. Afterwards, we shall adopt the convention of describing left-first SOAs as negative and right-first SOAs as positive.

Figure 2

Schematic of the settings in the experiment. A temporal order judgement paradigm was presented with two letters located ca 6.8° to the left and right of a central cross. The horizontal position of the center of the presentation monitor was positioned in pseudo-random order either -40° left or +40° right of the subject's midsagittal trunk position at eye level. Subjects were requested to orient head midline and gaze towards the fixation cross at the respective egocentric position while keeping trunk position stable.



In all fifteen brain damaged patients, the experiment was conducted in the chronic phase of their stroke. There were 9 blocks of stimulus presentation in the whole experiment for each participant with 240 trials in each block, containing 16 trials at each of 15 SOAs (0 and ± 83 , 167, 250, 333, 417, 500, 583) in a random order. The first block served as a training block and was conducted with the center of the presentation monitor aligned with the subject's straight ahead head and trunk midline at eye level; data were not considered for later analysis. In the following eight experimental blocks, the horizontal position of the center of the presentation monitor was positioned in pseudo-random order (counter balanced between participants) either -40° left or $+40^\circ$ right of the subject's mid-sagittal trunk position at eye level. The subjects were requested to orient head midline and gaze towards the fixation cross at the respective egocentric position while keeping trunk position stable. The retinotopic and the head-centered coordinates of the presentations thus was kept constant throughout the whole experiment; only its position relative to the subject's trunk was manipulated. In total, 4 blocks were performed at each egocentric position. Maintaining of gaze and head position was controlled by one experimenter situated opposite of the participating subject.

4 Results

4.1 Lesion analysis

All patients included in the study had unilateral stroke lesions demonstrated by MR or CT scans. For patients with MR scans, we used diffusion-weighted imaging (DWI) when imaging was conducted within the first 48 hours post-stroke and T2-weighted fluid attenuated inversion recovery (FLAIR) sequences when the images were acquired at least 48 hours after stroke onset. The mean time between stroke-onset and imaging was 2.5 days (SD 2.9). Although experiments were carried out with patients in the chronic phase of stroke, brain scans obtained in the acute phase were chosen for the imaging analysis.

Lesion boundaries were manually delineated on axial slices of the individual digital CT (n=9) or digital MRI (n=6) scans using MRICron software (www.mccauslandcenter.sc.edu/mricro/mricron). Both the lesion map and the patient CT or MR image were subsequently transferred into stereotaxic space using the Clinical toolbox (Rorden et al., 2012) with SPM8, running under Matlab R2013b. The simple lesion overlap results were shown in Figure 1A for the group comparison and Figure 1B for each individual in NEG group.

Figure 1A

Simple lesion overlaps of the 5 chronic neglect patients (NEG), 5 recovered neglect patients (NR), and 5 right brain damaged patients without neglect in both acute and chronic phases (RBD).

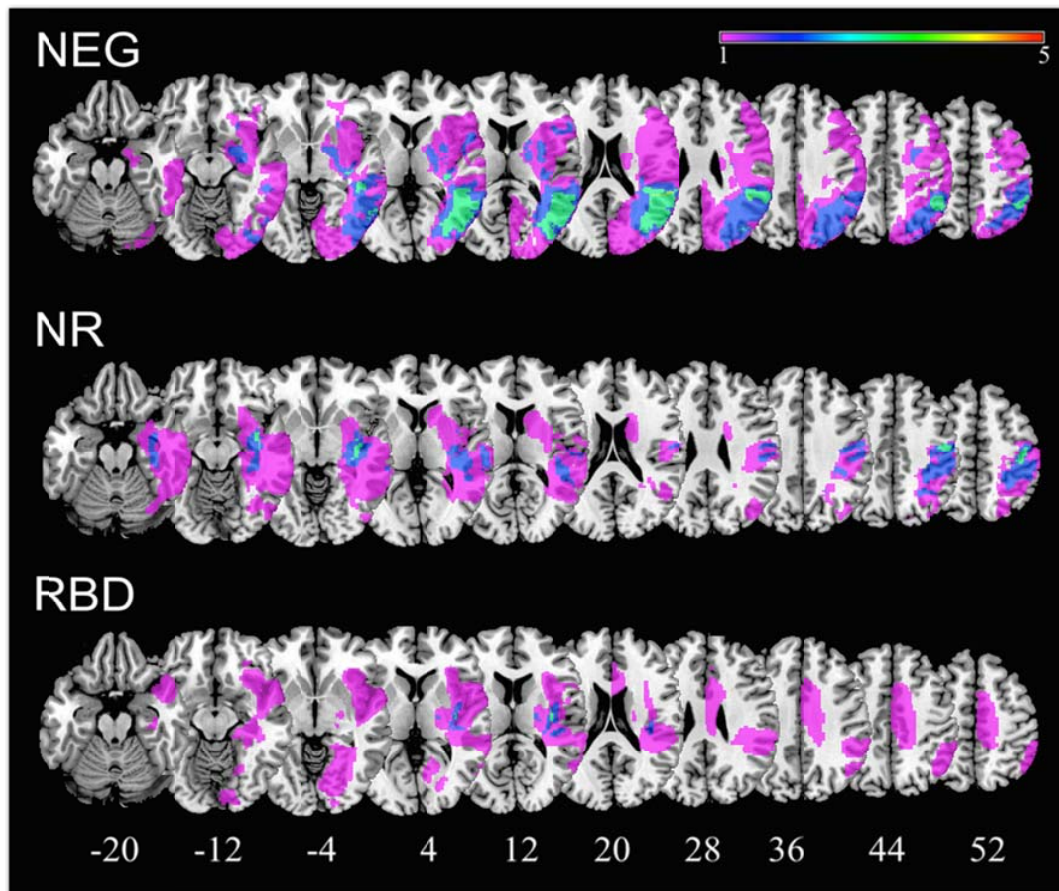
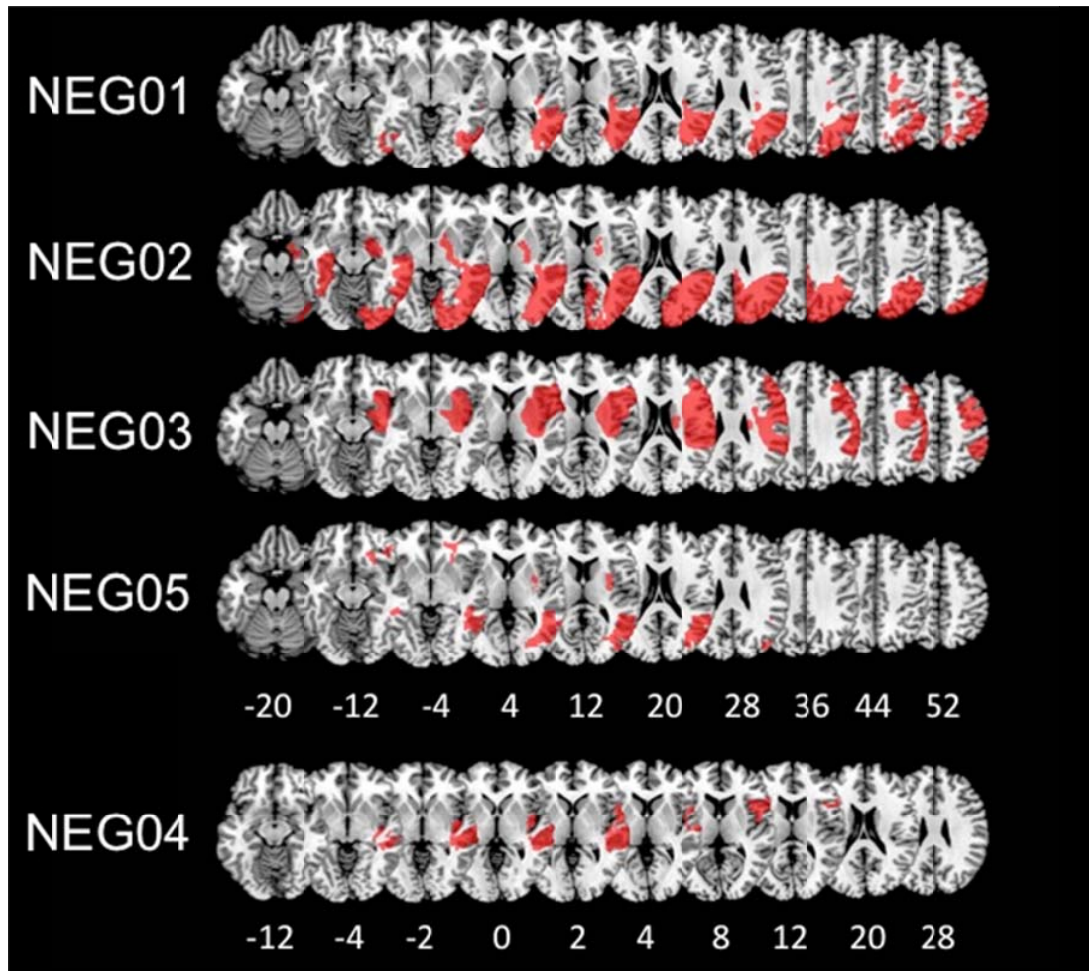


Figure 1B

Simple lesion overlaps of each chronic neglect patient.



4.2 Group analysis

For statistical analysis we calculated the right-then-left judgements overall (RTL_all) and at the zero SOA (RTL_0) for each participant. Two-way repeated measures ANOVA using the within-subject factor 'egocentric position' (left, right) and the between-subject factor 'group' (NEG, NR, RBD, NBD) was performed for both variables RTL_all and RTL_0.

For the variable RTL_all, the interaction between the two factors was significant ($F(3,26)=6.138$, $P=0.003$). We then conducted one-way ANOVAs for factor 'group' separately for the two egocentric positions. For egocentric position left, there was a significant main effect of group ($F(3,26)=15.326$, $P<0.0001$). For post-hoc comparisons, Tukey tests were used with a Bonferroni correction for multiple testing. There were no significant differences for NBD versus RBD ($P=0.792$), NBD versus NR ($P=0.686$) and RBD versus NR ($P=0.364$), but significant differences between the NEG group and the other three groups (vs NBD and NR $P<0.0001$; vs RBD $P=0.011$). For egocentric position right, there was again a significant main effect of factor group ($F(3,26)=11.668$, $P<0.0001$). Tukey post-hoc tests showed that again there were no significant differences again for NBD versus RBD ($P=0.960$), NBD versus NR ($P=0.936$) and RBD versus NR ($P=0.815$). In contrast, we found significant differences between the NEG group and NBD ($P=0.007$) as well as NR ($P=0.011$); the difference between NEG and RBD was not significant ($P=0.083$). Post hoc paired t-tests for the two egocentric positions (-40° , $+40^\circ$) revealed a significantly more right-then left responses at egocentric position -40° compared to egocentric position $+40^\circ$ ($t(4) = 3.698$, $P=0.021$) in the NEG group. In contrast, this difference between egocentric positions was not significant in the NR group ($t(4) = -0.702$, $P=0.521$), the RBD group ($t(4) = 1.134$, $P=0.320$), and NBD group ($t(14) = -0.450$, $P=0.660$).

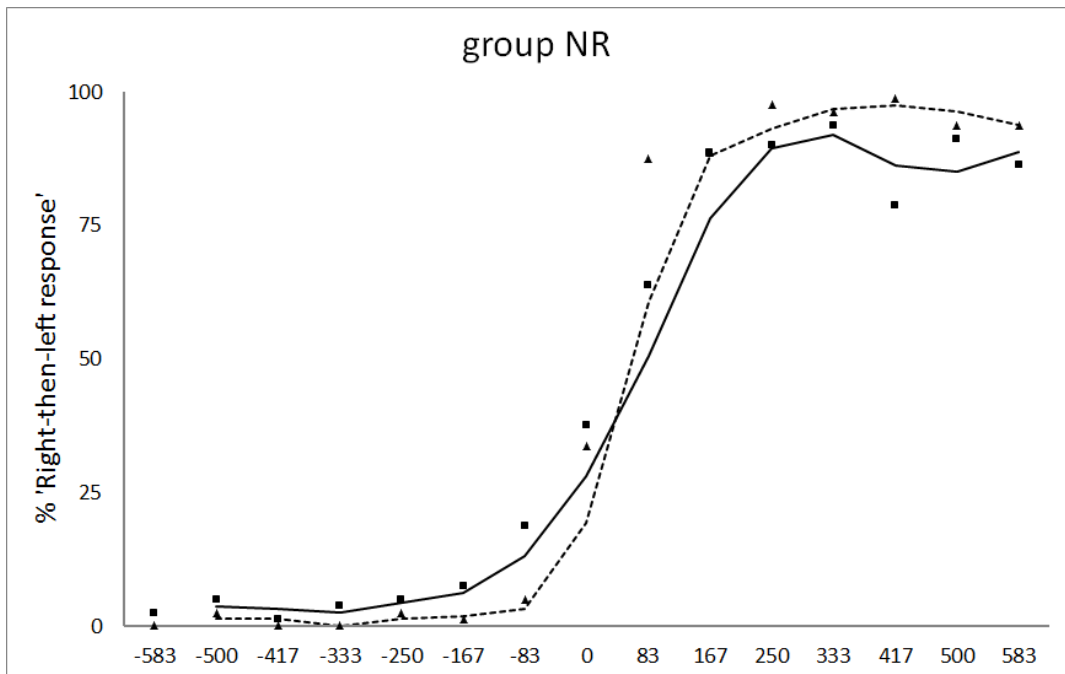
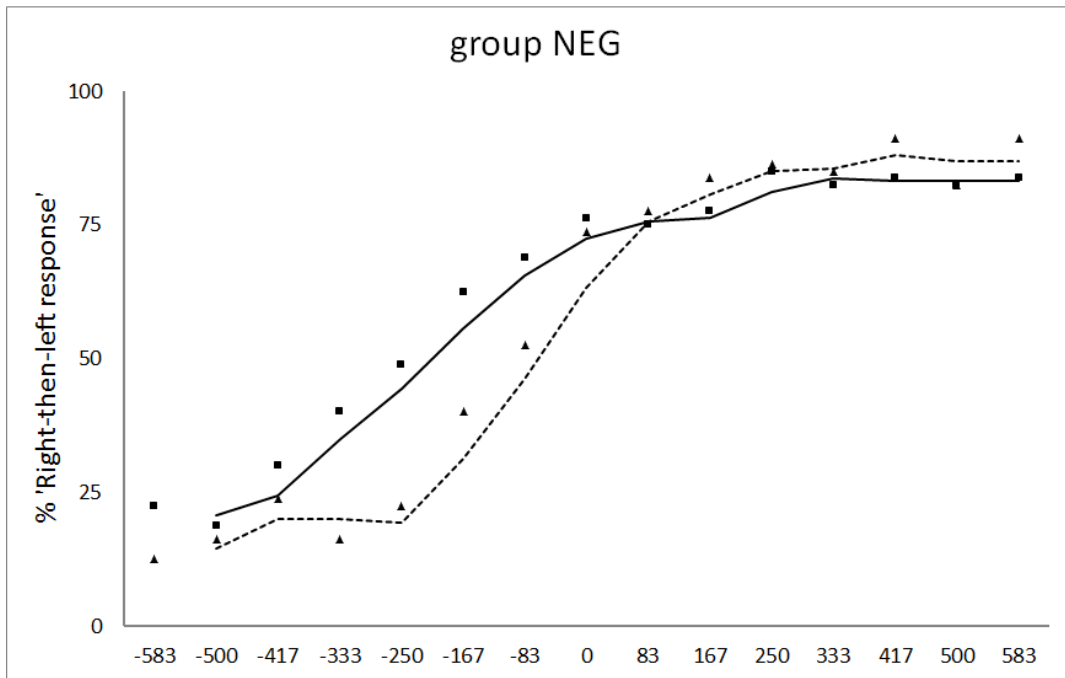
For the variable RTL_0, the interaction between the two factors was not significant ($F(3,26)=2.195$, $P=0.202$). The effect of 'egocentric position' was either not significant ($F(1,26)=1.586$, $P=0.058$). However the effect of the between subject factor 'group' was significant ($F(3,26)=10.535$, $P<0.0001$). We then conducted one-way ANOVAs for factor 'group' separately for the two egocentric

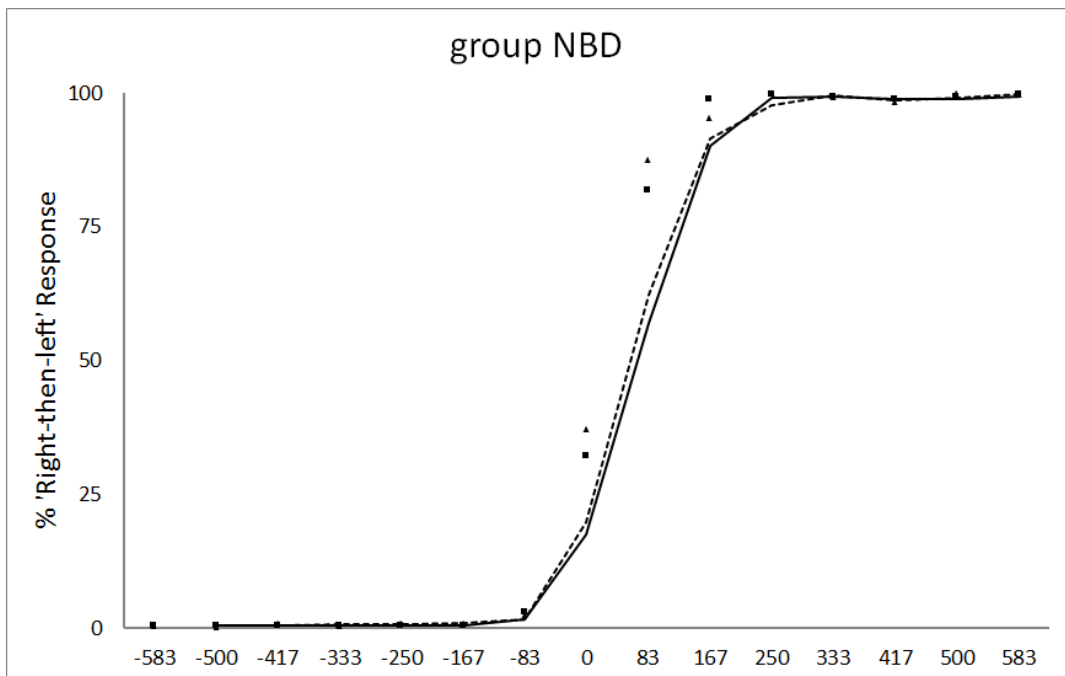
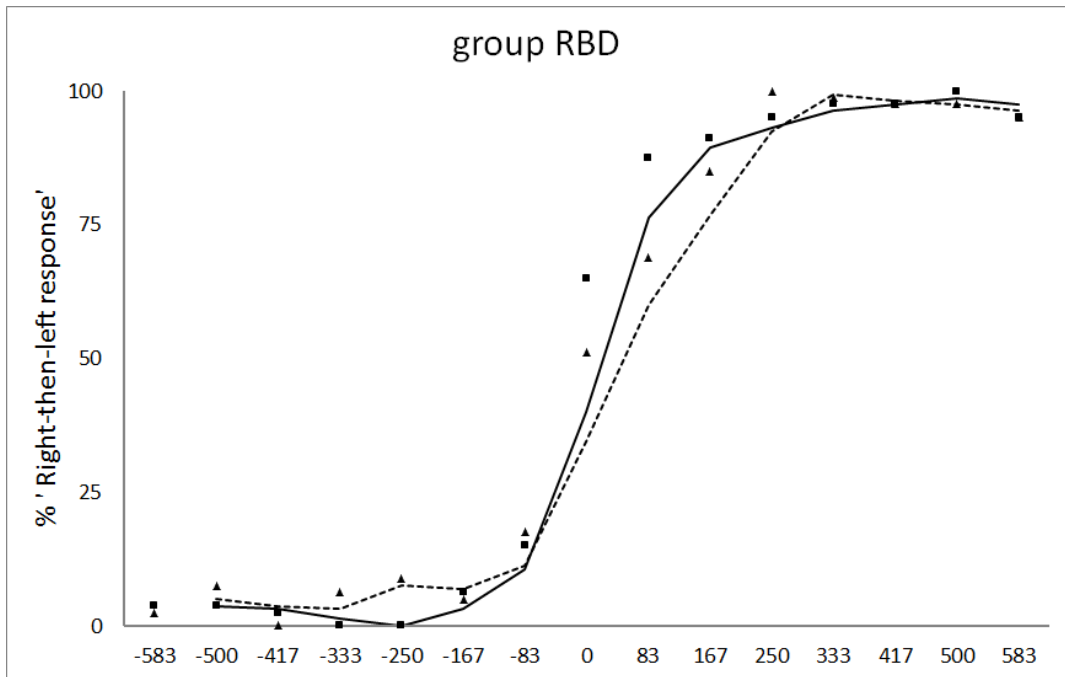
positions. For egocentric position left, there was a significant main effect of group ($F(3,26)=13.742$, $P<0.0001$). For post-hoc comparisons, Tukey tests were used with a Bonferroni correction for multiple testing. There were no significant differences for NBD versus NR ($P=0.902$) and RBD versus NEG ($P=0.655$), but significant differences for NEG versus NBD ($P<0.0001$) and NR ($P=0.002$), NBD vs RBD ($P=0.002$) and RBD versus NR ($P=0.040$). For egocentric position right, there was again a significant main effect of factor group ($F(3,26)=5.749$, $P=0.004$). Tukey post-hoc tests showed significant differences for NEG versus NBD ($P=0.004$) as well as NR ($P=0.011$) but no other significant differences among the other group comparisons.

Figure 3 illustrate the percentage of 'right-then-left' responses of the four groups and each patient inside group NEG. The curves drawn follow a smoothing function introduced by Rorden et al. (1997) which derives a point for each SOA which is the average for that SOA plus those immediately on either side of it; each SOA is weighted by its total number of observations when deriving these smoothed averages.

Figure 3

Performance of the four groups. Data obtained at the egocentric left position are characterized by continuous lines and square dots; data at the egocentric right position by dotted lines and triangle dots. NEG, chronic neglect patients; NR, recovered neglect patients; RBD, right brain damaged patients without neglect in both acute and chronic phases; NBD, healthy controls.





4.3 Single-case analysis

Additionally, the differences of right-then-left response between egocentric right and left display positions are also tested by using the RSDT proposed by Crawford and Garthwaite (2005) for the group NEG. This single-case statistics compares the patients' performance in both tasks with the performance of the healthy controls and tests for the difference between tasks. As a certain degree of discrepancy can be expected between both tasks in the control group, patients with a significant deficit in on task do not necessarily show a significant dissociation between tasks.

In each chronic neglect patient, this test statistically compares the discrepancy between the performance in the respective egocentric positions with the performance in the tasks in healthy controls. The right-then-left responses are significant different between egocentric right and left display locations in all of the five chronic neglect patients (one-tailed possibility; $df=14$):

NEG01($p<0.000001$, $t=8.994$);

NEG02($p=0.00008$, $t=5.124$);

NEG03($p=0.00536$, $t=2.942$);

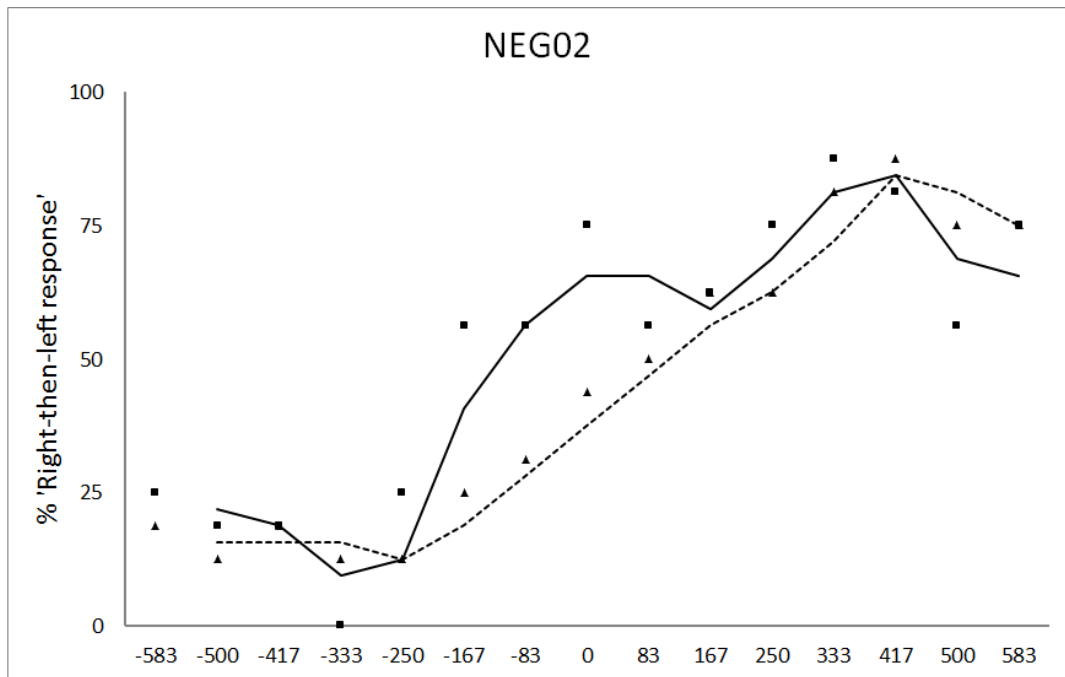
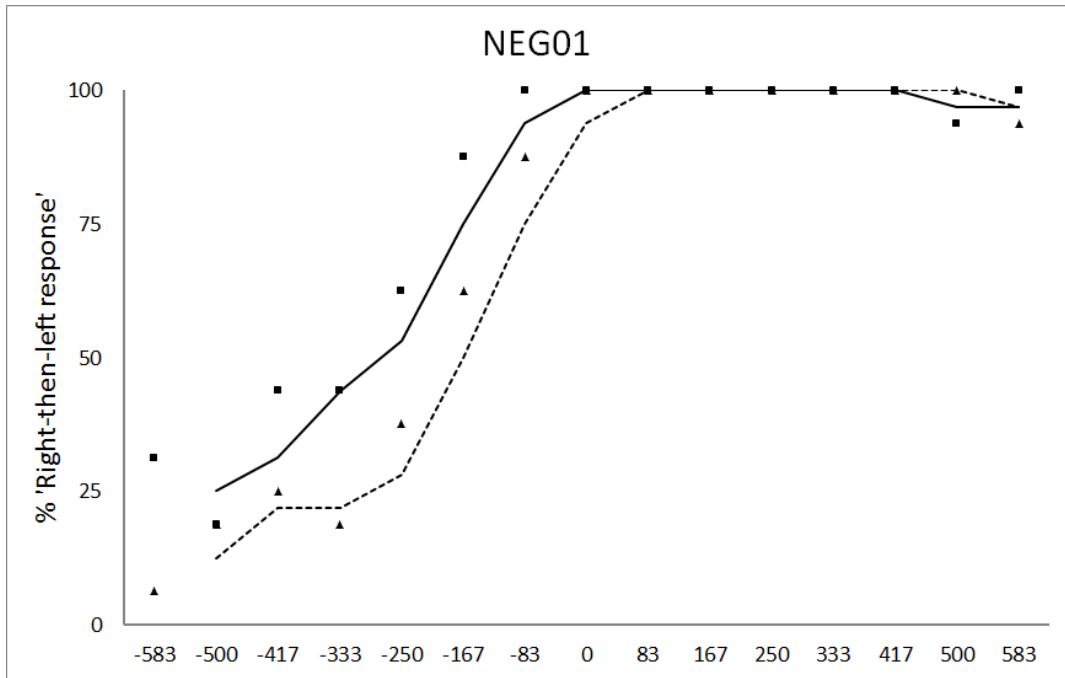
NEG04($p<0.000001$, $t=7.835$);

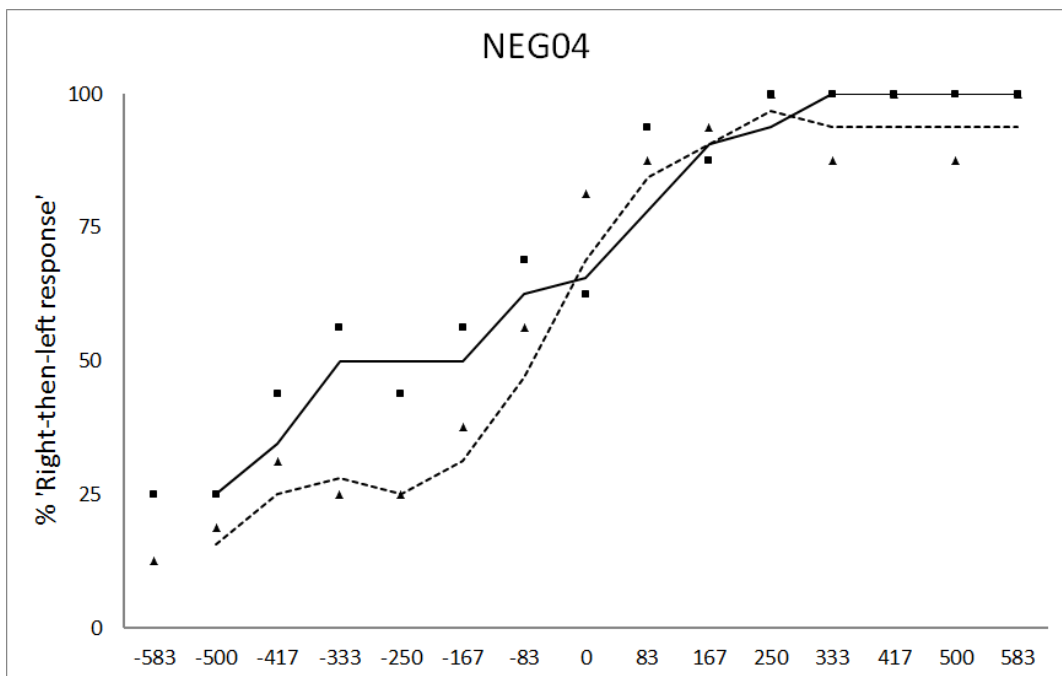
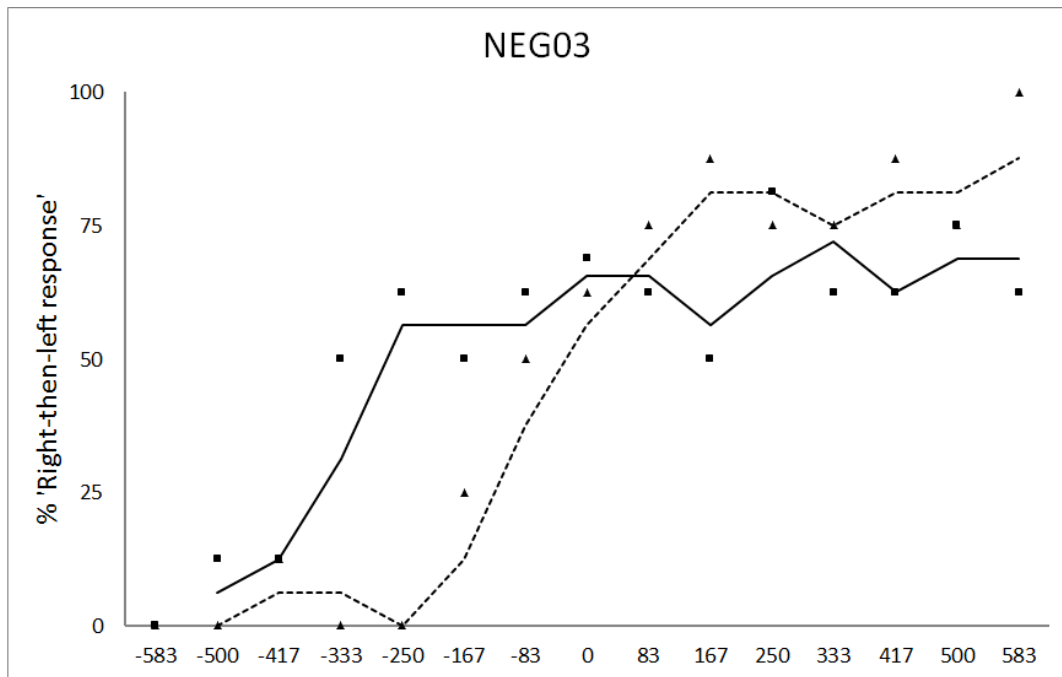
NEG05 ($p=0.02371$, $t=2.173$).

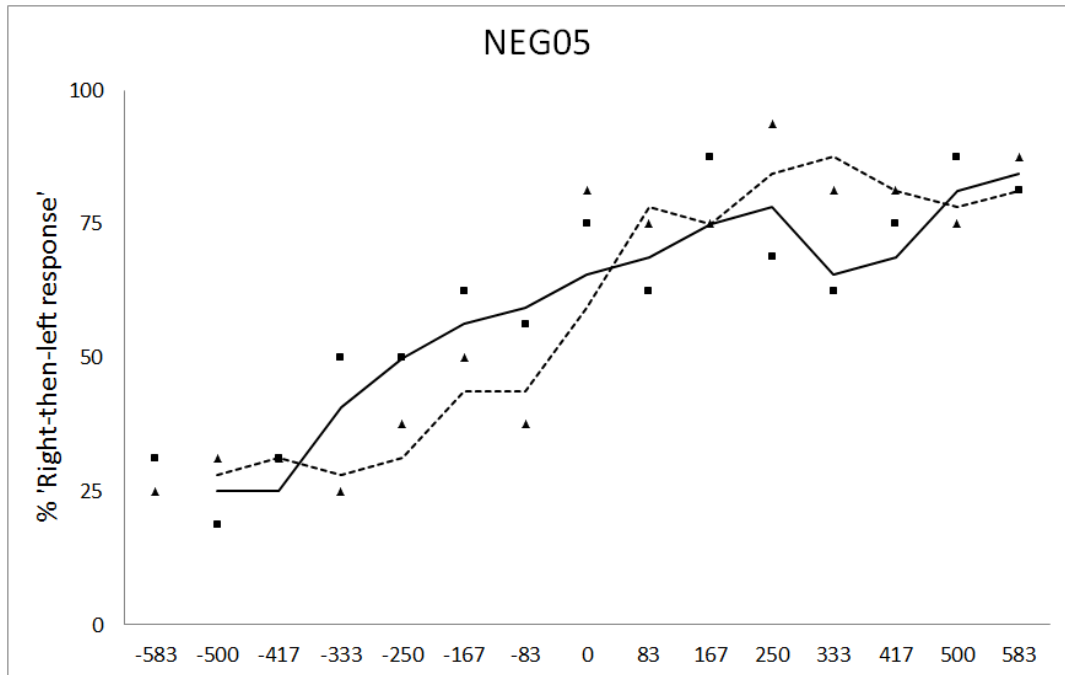
Figure 4

Individual performance of the five chronic neglect patients.

NEG01 and NEG02 showed also visual extinction while NEG03, NEG04 and NEG05 had no visual extinction.







5 Discussion

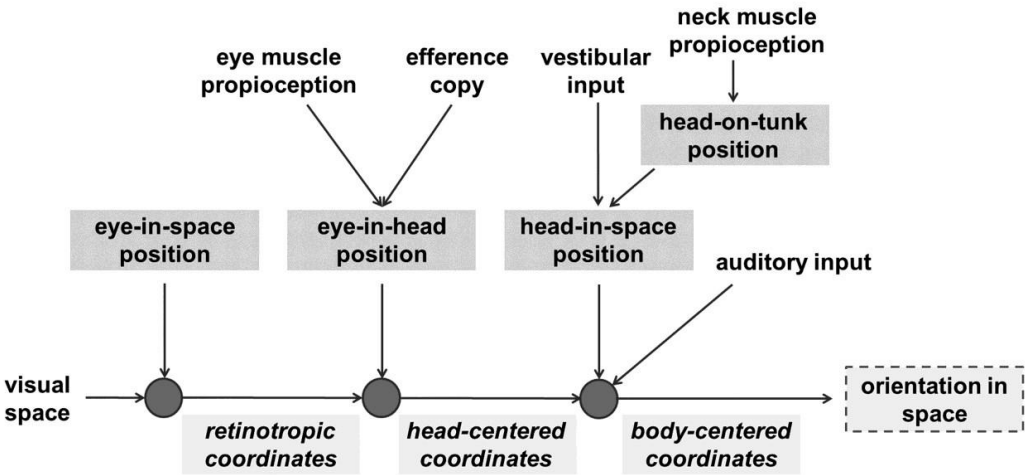
Here are the main findings of the present study: (i) using visual temporal order judgments (TOJ) paradigms, we observed that patients with neglect (no matter with or without visual extinction) made more right-then-left judgements than those without neglect and visual extinction. In consistence with findings of Rorden et al.(1997), these results again implied a disruption to the time-course of visual awareness for competing contralesional and ipsilesional items. (ii) in a group of chronic neglect patients, we observed that this temporal deficit indeed varied with egocentric position. Specifically, the magnitude of the 'right-then-left' response was exaggerated when the stimuli were presented at a more contralesional versus ipsilesional trunk position. Our results thus appear to challenge the notion that spatial and temporal attention are independent mechanisms, as previously espoused by others (e.g. Husain & Rorden, 2003; Batelli et al., 2007). Rather, they demonstrate a tight coupling between the spatial and temporal deficits seen in neglect.

In the past decade, one hot-spot scientific question is the relationship between spatial and temporal attention. Several researches tried to illustrate the complex relationship between these two forms of attention. Many observations point to the existence of common neural structures engaged in both temporal and spatial attention. Moreover, in the unilateral neglect syndrome, which is classically described as a deficit in the allocation of spatial attention, it has reliably been shown that many of these patients can be impaired in the allocation of temporal attention in tasks such as the attentional blink (Husain et al., 1997; Russell et al., 2013). Additionally, functional brain imaging such as PET and fMRI revealed the links prevailing between cortico-subcortical networks associated with each of these two forms of attention. The ventral and dorsal cortical networks subtending spatial attention (Corbetta and Shulman, 2002) show some overlap with the regions correlated with temporal attention (Coull and Nobre, 1998; Coull, 2004), including in particular supplementary motor areas (SMA), supplementary eye-fields (SEF) and lateral intraparietal areas (LIP). In consistence with these previous studies, our results also demonstrated that the spatial and temporal attention are both defected in spatial neglect.

Moreover, we also found the temporal attention deficit is affected by trunk rotation. There were more 'right-then-left' responses the presentation was at a more contralesional versus ipsilesional trunk position. For a successful orientation in space, it is required information from the retina (stimulus-on-retina position), the eyes (eyes-in-head position), and the neck (head-on-trunk position), as well as signals from the vestibular system are integrated and transformed to build up a global, ego-centered reference frame which represents the body position in space (see Figure 4). The transformation hypothesis of neglect suggests that this integration process is disturbed in the patients, entailing an ipsilesional (rightward) deviation of the body-centered coordinates (Karnath, 1994; Karnath, 1997). Head or trunk rotation to the left causes a lengthening of the neck muscles and changes of the gaze direction. The retinal, eye- and neckproprioceptive information is hereby altered, leading to a compensatory leftward shift of the subjective sagittal head or trunk axis, which add up to the global, body-centered reference. This in turn ameliorates the typical inattention to the left side in neglect. Head or trunk rotation to the right, in contrast, leads to a rightward shift of the subjective sagittal and therefore to some further impairments.

Figure 4

Transformation hypothesis of visuospatial neglect (adapted and modified by Kardinal, 2014; according to Karnath, 1994).



In addition to the core disorder of neglect (Karnath & Rorden, 2012; Karnath, 2015), further symptoms of the neglect syndrome are often expressed differently across individuals. One intriguing possibility is that these symptoms are in fact dissociable, and the overall syndrome simply reflects the fact that large lesions often damage multiple distinct functional modules. This has led to a quest to associate individual symptoms with specific anatomy (Husain & Rorden, 2003; Verdon et al., 2010; Karnath & Rorden, 2012; Chechlacz et al., 2012). Although the present work does not provide anatomical data sufficient to draw own conclusions on this debate, it still suggests that there is a strong functional interaction between deficits. While this does not necessarily mean that there are not distinct modules, our behavioral findings suggest interactions between these systems that make disentangling these supposed modules difficult. It appears that the core spatial egocentric bias underlies or modulates the other symptoms of the neglect syndrome. Further evidence for this notion is provided in the next paragraph.

The present work nicely parallels our recent findings regarding the interaction between egocentric and allocentric neglect (Karnath et al., 2011; Li et al., 2014). Patients with neglect often fail to respond to the contralesional side of objects (allocentric contralesional side), regardless of the object's position with respect to the participant, i.e. its egocentric position. Previous studies have suggested that these components can dissociate (e.g., Hillis et al., 2005), even though these symptoms tend to associate (Rorden et al., 2012; Yue et al., 2012). Interestingly, we have observed that object-based neglect varies with egocentric position (Karnath et al., 2011; Li et al., 2014). The neglect of an object's left side was more severe at contralesional egocentric, trunk-centered positions and ameliorated continuously towards more ipsilesional egocentric positions. Again, this work suggests that the symptoms associated with neglect tend to interact with each other.

Our work also is consistent with work in healthy subjects, suggesting that perception reflects a synergistic influence of temporal and spatial expectations (Rohenkohl et al., 2014). While it is logically possible that the different symptoms of spatial neglect do reflect injury to distinct modules, if this is the case, these modules appear to be tightly interconnected with perception. Alternatively, we speculate that neglect may indeed be a unitary deficit. According to this view, the

pathological temporal deficit is simply a consequence of the compromised perceptual processing that is the hallmark for the core deficit in neglect. In other words, visual perception in these participants is compromised throughout space, though in particular in the contralesional field (Driver & Pouget, 2000). Since the representation is weakened at all locations, there is limited capacity at all locations leading to a pathological attentional blink on the contra- as well as on the ipsilesional side. However, due to the spatial gradient, this deficit is more exaggerated in contralesional space. Likewise, we speculate that variation in allocentric versus egocentric biases observed between patients may simply reflect different strategic choices made by the patient. In other words, individuals may choose to attend to the forest (egocentric frame of reference), or sequentially to each tree (allocentric frame of reference) (see Karnath & Niemeier, 2002; Baylis et al. 2004).

In conclusion, our work clearly demonstrates that the temporal dynamics of neglect are clearly biased by egocentric (trunk-related) spatial position. This indicates that these are not independent functional components, as some have suggested. This work supports our previous assertion (Karnath & Rorden, 2012; Karnath, 2015) that neglect includes a core deficit that reflects a trunk-based frame of reference. While early visual processing maintains retinotopic coordinates, there is clear evidence that cells in association cortex are modulated by nonretinal egocentric position (e.g., Andersen et al., 1993, 1997; Battaglini et al., 1997; Galletti et al., 1993). Unlike retinotopic coordinates (which shift with each saccade), this coordinate system provides a relatively stable basis for acting in space. We feel that one of the crucial insights that neglect provides regarding the human perceptual system is the importance of this frame of reference (for review see Karnath, 2015).

6 Future directions

Researchers once pointed out that ‘greater insight into the heterogeneous nature of neglect, and its fine-grained anatomical basis, might be the key to unlocking the syndrome, tailoring treatment to deficits in individual patients, and revealing the functions of the brain regions that are commonly damaged in neglect’ (Husain & Rorden, 2003).

The conclusion of the present study is that the temporal dynamics of neglect are clearly biased by egocentric (trunk related) spatial position. This indicates that these are not independent functional components, as some have suggested. This work supports our previous assertion (Karnath & Rorden, 2012; Karnath, 2015) that neglect includes a core deficit that reflects a trunkbased frame of reference. While early visual processing maintains retinotopic coordinates, there is clear evidence that cells in association cortex are modulated by nonretinal egocentric position (e.g., Andersen et al., 1993, 1997; Battaglini et al., 1997; Galletti et al., 1993). Unlike retinotopic coordinates (which shift with each saccade), this coordinate system provides a relatively stable basis for acting in space. We feel that one of the crucial insights that neglect provides regarding the human perceptual system is the importance of this frame of reference (for review see Karnath, 2015). Perhaps future brain functional studies or brain stimulation studies can adapt our paradigm to reveal the possible anatomical basis and mechanism underneath. Furthermore, the conventional methods that targeted at spatial impairment alone have been singularly unsuccessful, our findings may broaden the mind of therapeutic strategies to treat neglect syndrome.

7 Abstract

Spatial neglect is a common consequence of brain injury where individuals fail to respond to stimuli presented on their contralesional side. It has been argued that beyond the spatial bias, these individuals also tend to exhibit temporal perceptual deficits. Here we demonstrate that the deficits affecting the temporal dynamics of attentional deployment are in fact modulated by spatial position. Specifically, we observed the severe bias to the right affecting the time-course of visual awareness in chronic neglect is enhanced when stimuli are presented on the contralesional side of the trunk, while keeping retinal and head-centered coordinates constant. We did not find this pattern in right brain damaged patients without neglect or in patients who had recovered from neglect. Our work suggests that the temporal attentional deficits observed in neglect are heavily modulated by egocentric spatial position. This provides strong evidence against models that suggest independent modules for spatial and temporal attentional functions, while also providing strong evidence that trunk position plays a dominant – if not the principal – role in spatial neglect.

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