

Effect of visual attention on functional connectivity

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Abstract

In our environment, there are so many things to see, e.g., computer screen, buildings, trees and cars in the street. In this busy scenery, we do not process all the information equally, but rather filter out some information and focus more on certain characteristics in the whole scene. In this process, attention plays an important role, and underlying neural correlate is the matter of interest.

We focus on investigating how attention changes the connectivity of the fMRI signal in the human brain. Prior studies examined this question, yet most studies used short trial interval (<20s) in examining the connectivity during attention. The short trial interval excludes the slow fMRI fluctuations (<0.1Hz) that showed segmented connectivity structure in the resting-state studies supported by the neurophysiological observations.

In the thesis, we introduce an ultra-long trial (2-3mins) to examine connectivity during task conditions, in attention demanding task. In the first study, we asked whether trial length affects the functional connectivity (FC) strength in general during attention task compared to visually matched condition as control. We observed that the long trial interval (2mins) condition showed nearly twice the FC strength compared to short traditional trials (20s). Moreover, attention reorganized the FC as enhanced positive FC between dorsal attention network (DAN) and visual network (VIS) and decreased negative FC between default mode network (DMN) and DAN/VIS, but reduced positive FC within VIS. Notably, the reorganization is frequency dependent: FC changed relied more on slow frequency (0.004-0.05Hz) for the connection between DAN and VIS and high frequency (0.05-0.2Hz) for decorrelation within VIS.

In the second study, we addressed the question whether FC strength relies on visual hierarchical distance in visual processing and attention task. We observed a gradient of connectivity, such that DAN connected strongly with high visual region (e.g., V5/MT) that degrades towards lower visual region (e.g., V1). A reversed effect was observed between DMN and VIS, revealing that DMN connected strongly negatively with high visual region that degrades its negative connectivity strength towards lower visual region. More interestingly, we implemented general linear model to the FC strength that showed attention modulates multiplicatively and additively the connectivity strength along this visual hierarchy.

In the third study, we observed how attention changes the connectivity in different features, e.g., color and motion attention. Here, we used seed-to-whole brain connectivity with regressing out the mean signal from the whole brain. First, we observed that V4 and V5/MT selectively connected to the task positive network, including DAN and visual regions, and negatively connected to the DMN.

Then, feature-specific analysis showed that color compared to motion attention, selectively connects the V4 to DAN more than V5/MT to DAN, with selective negative connections between V4 and DMN than V5/MT and DMN. This suggest that feature-based attention led the brain communicate specifically cooperative (positive) way, but also competitive (negative) way.

Taken together, attention not only reorganizes the connectivity in frequency dependent way, modulates differentially along the visual hierarchy as well as feature-specific manner. More interestingly, our results showed advantages of using long trial block experiment to detect important network connectivity change during attention. Not only applying frequency dependent analysis, but implementation of the GLM in comparing conditions, as well as, regressing out the mean signal from the whole brain for seed-to-whole brain connectivity analysis. All these methods that is used in the thesis can be extended to examine brain connectivity structure noninvasively, that may show important findings in other cognitive tasks, such as decision making or memory tasks.

Synopsis

1. What is attention

Human has amazing ability when perceiving the external stimuli. That is the selection of only subset of the stimuli among the available stimuli. Attention play important role in this process. We review the basic definition of the attention and discuss different types of attention in human cognition.

1.1 Example of attention in daily life

If I ask you to look at the 3 pictures in figure 1 and find where the change occurred between original and change 1, it may not take so long time to find the difference. In contrast, the change between original and change 2, it may take longer time to find the difference. Because change did not happen at the attended spot, but somewhere else. To see the answer, look at the figure 2. Why does this happen? In both pictures, you will probably pay attention to the area around the tip of the finger. Since the difference was not found at the tip of the finger in the change 2, it becomes very difficult to detect the change. Human visual perception is high when visual search is done on an attended spot. This phenomenon illustrates how attention play role in visual perception and reflects how human do not perceive external information equally across the visual scenery.



Figure 1.1. Find the changed spot from the original picture a. A) original picture, B) picture has been modified from the original picture, change 1, C) another spot has been altered from the original picture, change 2. It is relatively easier to detect the change in b) change 1 compared to c) change 2. This figure illustrates how attention helps to detect the change. The changed spot is marked at Figure 1.2.



Figure 1.2. Marked where the change occurred from the original. Change 1 was easier to detect the changed spot, because the change occurred at the tip of the finger where people typically pay attention to. Change 2 was difficult to detect the difference, because the change was detected in an unattended spot.

1.2 Types of attention

Although attention is such an important process that plays role in human cognition, there is still no standard accepted definition yet. There are many types of attention, such as 1) arousal attention, 2) sustained attention, 3) selective attention and 4) divided attention.

Arousal and alertness represent the most basic levels of attention; with low arousal attention, you may be sleepy and tired, not able to listen or read something. *Sustained attention* is also known as vigilance; that reflects the ability to maintain continuous alertness over time. This is most critical type of attention such that most people want to improve it in their daily life. Having high level of sustained attention means that one can concentrate in a given task for a long time, without getting distracted by other people or tasks.



Figure 2. Types of attention. a) Arousal attention, b) Sustained attention, c) Selective attention, d) Divided attention ^{1,2,3,4)}

A third category of attention is *selective attention*, which involves the selection of certain information in a given task. Selective attention is often regarded as filtering relevant information. Many different

models of selective attention has been discussed and most models distinguish “bottom-up attention” and “top down attention” (Maurizio Corbetta & Shulman, 2002). In bottom up attention, attention is driven automatically, typically by salient stimuli. Attention is also driven in top-down manner that observers’ willingness directs the attention themselves (M Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). In this type of selective attention, both spatial location (Eriksen & Hoffman, 1972; Posner, Snyder, & Davidson, 1980) and nonspatial stimulus features (e.g., color) (M Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1990) are elementary dimensions. The last category of attention is known as *divided attention* (Kahneman, 1973), which is basically splitting the attention across multiple tasks. The brain is known to have limited resources to process multiple tasks, so dividing attention to multiple tasks, such as reading this thesis and watching a youtube video simultaneously would be challenging.

2. Brain regions involved in visual perception

Attention can be in the context of several types of sensory stimulus, but the studies in this thesis focus on attention to vision, since the visual system is more precise in the sense of perception compared to the other sensory processing systems. In this chapter, we discuss the basic process of visual perception in human.

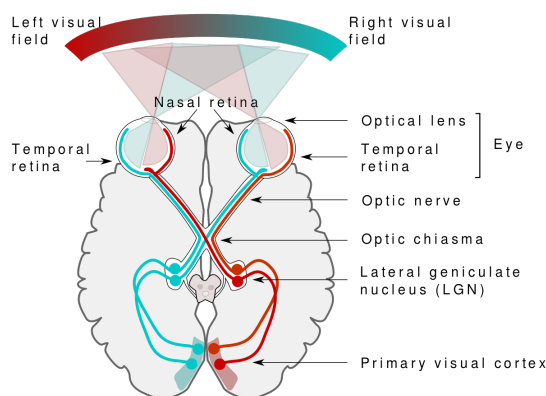


Figure 3. Visual processing pathway. From retina in the eye to optic nerve, to Pulvinar, to Lateral Geniculate Nucleus (LGN), then to Occipital lobe⁵⁾

2.1 Visual Processing in subcortical structures

Before examining the neural mechanisms of the visual attention, we need to understand how the visual stimulus is processed in the brain. As illustrated in Fig. 3, when external visual stimuli are presented; it excites the neuron in the retina of the eye, which transmits the information to superior colliculus (SC), part of the tectum. This pathway is very fast-responsive and especially sensitive to motion. From the SC, the pathway extends “upstream” to the pulvinar nucleus in the thalamus that

govern eye and head movement; as well as it extends “downstream” to brain stem areas that control eye muscles.

This downstream connection eventually projects to the complex structure in the thalamus, the lateral geniculate nucleus (LGN). From there, the information continues to the occipital lobe, also known as visual cortex.

2.2 Visual Processing in the visual cortex and beyond

Visual stimuli excite multiple regions in subcortical structure and then transfer information to cortical structure, the visual cortex. How large is visual cortex in the human? Due to the complex and high precision of visual perception, there are multiple levels that are involved in the processing of the visual stimuli. The cortical area that initially responds to the visual stimuli is the primary visual cortex, called V1. It receives information from the LGN and projects to the next layer of the visual cortex, V2, then to V3, V4 and V5/MT as well.

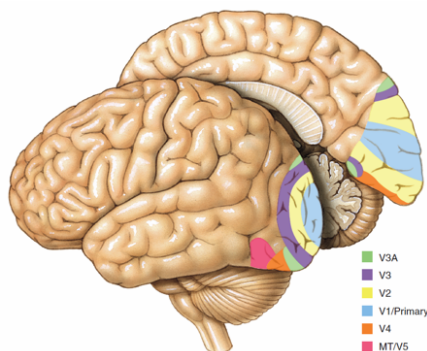


Figure 4. Visual regions involved in visual processing. The primary visual area (V1) and higher visual areas (V2, V3, V3A, V4 and V5/MT) responds to visual stimulation ⁶⁾

3. Neural correlates of visual attention

This section will review from the basic regions involved in arousal attention. Then, we overview the regions that enhance brain signals in visual attention from the subcortical, parietal, frontal and visual regions. The default mode network that decreases brain signals by attention is reviewed in this section.

3.1 The role of subcortical regions in attention

The most basic type of attention, arousal attention, is governed by brain stem, so called reticular activating system (RAS) (Bremer 1935). In the reticular part of the brain stem, cholinergic and noradrenergic neurotransmitters are released, and when it is damaged, people will go into coma

(Lindsley, Bowden, & Magoun, 1949). Not surprisingly, this system is also responsible for sleep-wake cycles (Akimoto et al. 1956).

This system in brainstem projects to the thalamus, especially to the medial dorsal intralaminar nuclei and reticular nuclei. Similarly, previous studies showed that damage to these thalamic nuclei will also result in coma (Schiff, 2008). Many regions in subcortical structure, such as superior colliculus (SC) or pulvinar are involved in shifting attention and executing eye movements between attended object (Kustov & Lee Robinson, 1996; Petersen, Robinson, & Morris, 1987). The SC appears to be a key part of the circuitry that is involved in the processing of distractibility (Winterkorn et al. 1981).

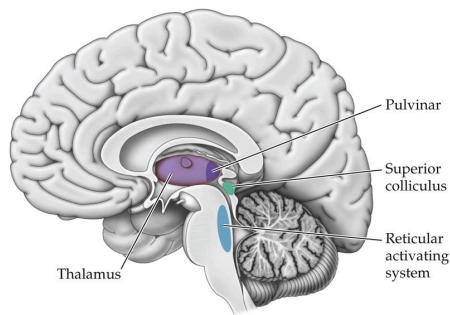


Figure 5. Subcortical structures involved in attention. Reticular Activating System (RAS) is involved in arousal attention. RAS acts to release neurotransmitters to the subcortical area, superior colliculus, pulvinar, thalamus.

3.2 The role of frontoparietal regions in attention

Attention not only affects the subcortical regions, but also affects the frontoparietal regions. In bottom-up attention, ventral stream of the cortex is involved in directing the attention. Bottom-up attention typically activates temporal parietal junction (TPJ) and inferior frontal cortex (IFC) and the responses are right-hemisphere dominant (M Corbetta et al., 2000).

In ‘top-down attention’, is driven by observers’ internal attention willingness, that activates dorsal part of the cortex, so called dorsal attention network (DAN) (M Corbetta et al., 2000; Hopfinger, Buonocore, & Mangun, 2000). The dorsal attention network (DAN) network includes FEF and PPC (IPS for human, LIP for primates) (Colby, Duhamel, & Goldberg, 1996)(REF). This type of attention is driven voluntary, by top down control, therefore, compared to bottom up attention, the response is not automatic and is slower (Maurizio Corbetta & Shulman, 2002).

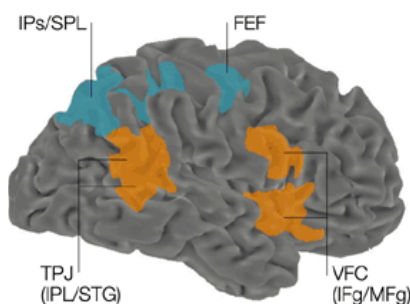


Figure 6. Dorsal Attention Network (DAN) and Ventral Attention Network (VAN). DAN play role in top-down attention, and includes regions such as Frontal Eye Field (FEF) and Intraparietal Sulcus (IPS). VAN play role in bottom-up attention and includes Prefrontal cortex (PFC), Temporal Parietal Junction (TPJ) and Inferior Frontal Gyrus (IFG).

In IPS, there is a coarse representation of spatial topography (Swisher, Halko, Merabet, McMains, & Somers, 2007). LIP has been shown to represent both voluntary and stimulus-driven contributions to attentional priority. A rapid ‘on-response’ is observed when a stimulus is flashed within the RF of an LIP neuron; this response reflects the stimulus-driven capture of attention by a salient onset stimulus and not just the luminance change within the neuron’s RF (Bisley, Krishna, & Goldberg, 2004). Moreover, the activity of LIP neurons represents the location of a cued target, reflecting the voluntary allocation of attention to a region of space away from fixation (Bisley & Goldberg, 2003).

The FEF has been long known to play a role in generating saccades (Sato, Murthy, Thompson, & Schall, 2001) or planning eye movements (Bruce & Goldberg, 1985), and most neurons show little stimulus driven selectivity (K. G. Thompson & Bichot, 2004). Human studies show that activity in FEF reflects both voluntary and stimulus-driven deployments of attention during spatial cueing and visual search tasks, even when no eye movements are made (Grosbras & Paus, 2002).

3.3 Attentional modulation in visual regions

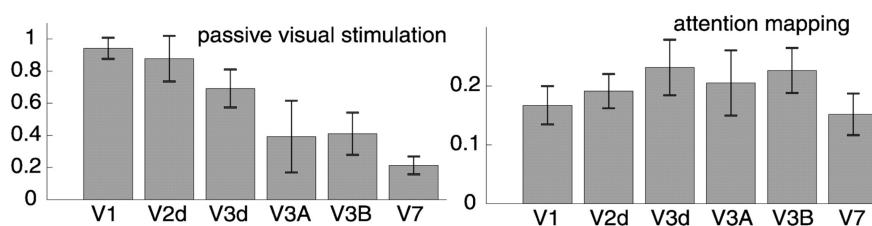


Figure 7. Gradient modulation along the visual regions. Visual regions respond inverse hierarchically to visual stimulation, but this tendency is reversed by attention, showing hierarchically response in the BOLD signal (Silver, Ress, Heeger, Michael, & Topographic, 2005)

Various regions in subcortical regions and frontoparietal regions are involved in attention processing. But, then is visual cortex itself involved in attention? As previously discussed, visual cortex, by name, responds to external stimulus. Primary visual area V1 responds to the stimulus strongest and the response degrades towards higher visual areas; V2 towards V4 (Silver 2005), reflecting inverse hierarchical relationship in visual hierarchy. Not only visual region involved in visual perception, but also responds to attention task. Interestingly, attentional modulation strength in visual cortex is opposite to the visual stimulus modulation effect with late visual areas exhibiting the largest values and early visual areas having the smallest values (Silver et al., 2005). Yet it is unclear how this

relationship is reversed. It is assumed that frontoparietal regions may inverse this relationship by projecting signals to the sensory area (Moore & Armstrong, 2003).

3.4 The Default Mode Network

Attention increases the neural activity in some networks, but it is also possible that some regions decrease signal by attention. If there is region that activates more during rest or baseline state, those regions could decrease its activity during attention. By examining the baseline activity, a PET study revealed the regions in MFC, PCC, and bilateral LP was enhanced signal during rest compared to more active state, e.g., attention task (Raichle et al., 2001). Since these regions show more activity during rest, it was called resting-state network or default mode network (DMN). In the meantime, several studies suggest that the DMN is not just “silenced” during task execution, but that it is involved in tasks of introspective nature, and correspondingly less involved in tasks involving processing of external stimuli. The DMN network is hence involved in processes such as mind-wandering (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009), or even in cognitive tasks (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010). In some tasks, its activity is also correlated with behavior (Sala-Llonch et al., 2012).

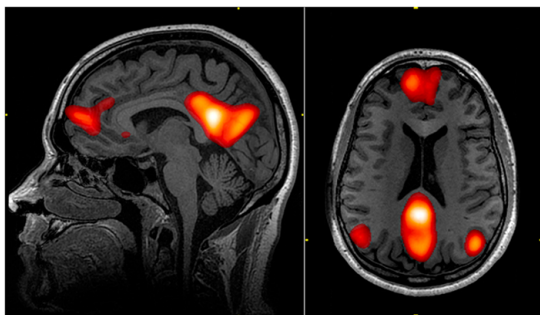


Figure 8. Default Mode Network (DMN) consists of the lateral parietal lobe (LP), middle frontal cortex (MFC) and posterior cingulate cortex (PCC). The DMN decreases its activity during attention task (Graner, Oakes, French, & Riedy, 2013).

Many connectivity studies were conducted on this network; it showed positive correlation with other nodes in the DMN, and negative correlation with task positive networks, such as DAN (Fox et al., 2005).

4. Functional connectivity

We have discussed how attention changes the brain activity in signal region. In this section, we will overview how attention changes the functional connectivity across brain regions. In prior to observing the change in human brain, we first review the animal physiology that observed the neuronal synchronization across brain regions. Then, we review the mechanism of the fMRI signal and how it is used to study the connectivity across brain regions during resting-state as well as task, such as attention task.

4.1 Neuronal synchronization

Attention not only changes the brain activity in single region, but also changes the connectivity across regions in the human brain (Gregoriou, Gotts, Zhou, & Desimone, 2009; Saalmann, Pigarev, & Vidyasagar, 2007). Examining the connectivity across connectivity was initially performed in animal studies before human fMRI was available. The network oscillations of interneurons were observed in basic vertebrate, such as insect olfactory system (Gelperin & Tank, 1990; Laurent & Davidowitz, 1994; Wehr & Laurent, 1996) and in more evolved species, such as cat visual system (Engel, König, Kreiter, & Singer, 1991; C M Gray & Singer, 1989; Charles M Gray, König, Engel, & Singer, 1989).

In primate, monkey studies enabled us to observe, higher cognition tasks such as attention (Moran & Desimone, 1985) and decision-making processing (Platt & Glimcher, 1999). By recording LFP and MUA, attentional modulation of neuronal synchronization was observed in sensory network, e.g., somatosensory cortex (Steinmetz et al., 2000) and visual system (Fries, Reynolds, Rorie, & Desimone, 2001).

Few studies followed these approaches and examined the neuronal oscillations synchronization even across long-range connection, such as dorsal attention network and visual network (Gregoriou et al., 2009; Noudoost, Chang, Steinmetz, & Moore, 2010; Saalmann et al., 2007). A previous MEG study also showed the gamma synchronization change by attention across long-range connections (Siegel, Donner, Oostenveld, Fries, & Engel, 2008). Additionally, a previous EcoG study

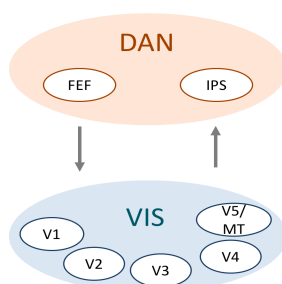


Figure 9. Neuronal synchronization during attention. Dorsal attention network (DAN) and visual network (VIS) strengthens its connectivity during attention (Maurizio Corbetta & Shulman, 2002; Harris & Thiele, 2011)

also examined neuronal synchronization across different networks during attention (Daitch et al., 2013).

4.2 Functional connectivity using fMRI: resting state

The connectivity across regions using fMRI was initially investigated by resting-state studies. Biswal and colleagues (1995) found that during resting, human motor cortex in one hemisphere correlates with the motor cortex in the other hemisphere. Alternatively, FC during rest shows where the border is in cortical region, dividing the brain functions into segments (Fox et al., 2005; M. D. Greicius, Krasnow, Reiss, & Menon, 2003).

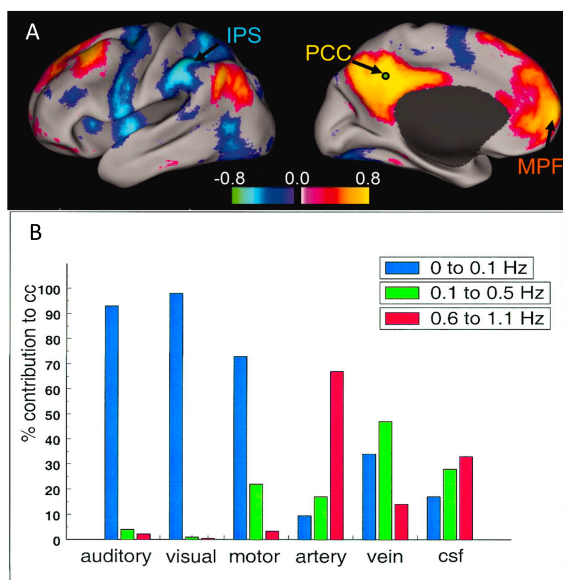


Figure 10. Resting-state functional connectivity

(a) From the resting-state connectivity that includes slow fluctuation ($<0.1\text{Hz}$), segregated human brain is revealed that distinguishes the DAN from the DMN (Fox et al., 2005). (b) Frequency dependent functional connectivity (FC). In cortex, low frequency fMRI (0-0.1Hz) has highest contribution to the FC, whereas in artery, vein, CSF relatively higher fMRI attributes to the FC (Cordes et al., 2001)

Functional connectivity, because of its sensitivity to coupling dynamics and ability to broadly survey the cortex, provides information about relations between networks (Buckner, Krienen, & Yeo, 2013). Depending on the function of the regions, they may coherently synchronize or antisynchronize with each other.

Other studies showed how the brain is segregated into diverse network structure by using resting state connectivity (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). These studies examined the connectivity using method, such as seed-to-whole analysis revealing how one region connects to the rest of the brain, such as left motor cortex specifically connects to the right motor cortex, or PCC (part of DMN) connects to other regions in the DMN (Fox et al., 2005; M. D. Greicius et al., 2003). Notably, most of these studies detected the structured connectivity while subjects lie down in the

scanner for few minutes, thus including the very slow BOLD fluctuation ($<0.1\text{Hz}$) (Biswal et al., 1995; Lowe, Dzemidzic, Lurito, Mathews, & Phillips, 2000).

When, analyzing the functional connectivity in different frequency bands in different regions (Cordes et al., 2001, Fig. 11.b), it is clear that most of the connectivity structure was driven by BOLD signal slower than 0.1Hz (Salvador et al., 2005). These studies showed that especially in sensory cortex and motor cortex, all the main FC was driven by the low frequency, and very little contribution was shown in frequencies higher than 0.1Hz (Cordes et al., 2001).

According to the resting-state FC, we learned that brain is segregated into multiple networks without presenting external stimulus. The resting-state studies has been not only conducted in healthy human brain, but as well as neuropsychiatric patients as well. A few studies using various approaches (Karl J. Friston, 1998; Zhou et al., 2007) have suggested that schizophrenia is best characterized as a disconnection syndrome (M. Greicius, 2008) and others showed that attention-deficit hyperactivity disorder (ADHD) is linked with the reduced connectivity within DMN as well as abnormal connectivity with DMN and dACC (Castellanos et al., 2008). In summary, the resting-state connectivity revealed the brain segmentation without external stimulus which has been useful tool to study in the healthy human as well as patient.

4.3. Functional connectivity: task-based

The next question is to observe the FC change during sensory perception or cognitive tasks. During visual perception, many studies observed that correlation in or across sensory regions during viewing visual stimulus, such as viewing movie using fMRI (Bartels & Zeki, 2005; Hasson, 2004) as well as watching audiovisual stimulus in MEG recording (Luo, Liu, & Poeppel, 2010). These studies indicate that visual regions interaction or auditory and visual region interaction involves with movie observation.

Further observation was conducted in attention tasks. For example, attentional coupling between V2 and V5/MT was shown to be mediated by parietal activity (K J Friston & Büchel, 2000), early visual areas enhanced correlations topographically (Haynes, Tregellas, & Rees, 2005), and early and high-level visual regions selectively coupled as function of the attended feature (Al-Aidroos, Said, & Turk-Browne, 2012). Other fMRI studies examined relations between visual and parietal regions, and found increases as well as decreases between distinct combinations of visuo-parietal regions (Lauritzen, D'Esposito, Heeger, & Silver, 2009).

Aside from attention task, memory or decision making studies also showed a modulation of correlations (Sala-Llonch et al., 2012). A few memory studies have shown how variations in working memory load modulate functional connectivity between regions of the working memory system (Honey et al., 2002; Narayanan et al., 2005), or some studies observed the interaction between working memory network and default mode network that showed increased correlation between these network in n-back task with respect to rest scans (Bluhm et al., 2011). In decision making tasks also showed the possible connections between striatum and lateral prefrontal cortex (IPFC), cerebellum (Green, Biele, & Heekeren, 2012). By observing the synaptic strength across these networks has been proposed as a candidate neural mechanism supporting decision threshold modulation (Cavanagh et al., 2011; Lo & Wang, 2006).

In summary, all these studies examined the functional connectivity change in the cognitive tasks. It led to detect not only the changes in single regions, but also interaction across network, with easily accessible techniques, such as fMRI. Yet, many of these studies compared the task and rest (Arbabshirani, Havlicek, Kiehl, Pearlson, & Calhoun, 2013; Sala-Llonch et al., 2012; Spadone et al., 2015), thus the task connectivity could be driven by sensory processing, instead of the task itself. Therefore, it requires a better control than rest. Moreover, most of the studies examined the connectivity that was designed originally to detect mean fMRI signal that each trial interval lasts from few seconds up to 20 seconds. Considering that many of the segmented connectivity structure in resting-state was revealed in their examination in slow fMRI fluctuation (<0.1Hz), some meaningful connectivity change in tasks could be missing by the fMRI experimental design.

We still do not know the exact neuronal signal behind of fMRI signal. At least, we learned that fMRI signal correlates more with synaptic input (local field potential) rather than neuronal spiking activity (multiunit activity) (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Nir et al., 2007).

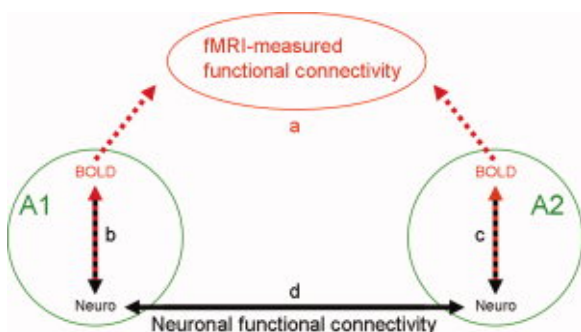


Figure 11. Can fMRI-based functional connectivity be interpreted as neuronal functional connectivity? (Shmuel & Leopold, 2008)

Much less is known about the origin of fMRI connectivity with neuronal signal (Shmuel & Leopold, 2008). Few studies examined this question (Lu et al., 2007; Schölvinck, Maier, Ye, Duyn, & Leopold,

2010; Shmuel & Leopold, 2008; G. J. Thompson, Pan, & Keilholz, 2015) and showed that certain range of LFP/EEG correlate with BOLD connectivity in low frequency range ($<0.1\text{Hz}$). However, these studies did not answer how different frequency of the BOLD correlates with LFP. Especially the relatively fast frequency fMRI ($>0.05\text{Hz}$) and its connectivity relation to the neurophysiology has not been investigated to our knowledge. Therefore, studying the functional connectivity using fast frequency ($>0.05\text{Hz}$) may require studies combined with electrophysiology studies.

5. Research Aim

In the previous section, functional connectivity (FC) has been reviewed, using electrophysiology, fMRI, MEG/EEG in resting state and task states. By using fMRI observation, one can examine its connectivity with high spatial resolution and large coverage of the brain. Yet, most prior works have investigated the FC with short trial interval (<20s) block design, which was optimal to detect mean signal relatively efficiently. However, the hemodynamic response has few seconds of delay with very dynamic shape in the initial periods with little understanding of high frequency connectivity.

For the efficiency, the fMRI experiment typically alters each trial relatively short in time to detect mean signal change. However, short interval fMRI design is more 1) difficult to take into account of dynamic shape of fMRI signal in the initial seconds, and 2) excludes the low frequency (<0.1Hz) fMRI fluctuation where resting-state connectivity structure was intensively studied (Cordes et al., 2001; Zou et al., 2008) with investigation of its neurophysiological meaning (Nir et al., 2008; Schölvinck et al., 2010). Even though some task studies were conducted with slow trial interval (Spadone et al., 2015), it compared the connectivity between task and rest that sensory effect could drive the FC as well. Therefore, this thesis introduces an ultra-long block design fMRI experiment with visually matched control that detect low frequency BOLD (<0.1Hz) and controls its task effect, in order to examine its correlation across regions in tasks, especially in various attention task conditions.

Experiment 1 examined the effects of attention on FC during precisely matched visual stimulation across visual, dorsal attention and default mode network. We aimed to examine the benefit of ultra-long block trial, the power of short and long trial fMRI experiments was compared for quantifying FC. We observed the FC in different frequencies, fast frequency (0.05-0.2Hz) and slow frequency (0.004-0.05Hz) of fMRI fluctuation. To our knowledge, the frequency specific FC analysis was first implemented in task conditions.

Experiment 2 examined the effects of attention on FC on hierarchy of visual areas V1-V5/MT. We observed the effect between dorsal attention network and visual network that showed positive correlation, as well as the connection between default mode network and visual network that showed negative correlation. Additionally, this study investigated whether the connectivity strength is modified in multiple and/or additive manner by using general linear model (GLM).

Experiment 3 examined differential effects of feature-based attention. Specifically, we examined attention to either color or to motion while attentional load was balanced. We examined FC patterns within visual cortex, DAN, and with DMN. Moreover, most previous studies in task state FC used seed-to-seed based analysis, but in this study a seed-to-whole brain connectivity method was used by

regressing out the mean signal in the whole brain. Moreover, this study investigated whether feature-based attention modifies the connectivity in regions-specific manner.

Overall, we used an ultra-long block design to detect FC change during attention task. We aim to detect the FC pattern, by using various methods that has not been heavily conducted in task conditions, such as frequency-dependency analysis, implementing GLM in the FC, seed-to-whole brain with regressing out the mean signal from the whole brain.

6. Declaration of contribution

The PhD thesis comprises of three manuscripts that are published, submitted or preparation to be submitted for publication. The detailed explanation of contribution of authors is given for each manuscript:

1. Soyoung Kwon, Masakata Watanabe, Elvira Fischer, Andreas Bartels (2017). Attention reorganizes connectivity across networks in a frequency specific manner. *Neuroimage 144*, 217-226, S.K planned, conducted the experiment, analyzed the data and wrote the manuscript, M.W helped analysis of the data and provided retinotopy data. E.F provided retinotopy data. A.B. planned, guided the experiment and wrote the manuscript.

2. Soyoung Kwon, Andreas Bartels (2017). Multiplicative and additive modulation of functional connectivity patterns by visual attention (submitted). S.K planned, conducted the experiment, analyzed the data and wrote the manuscript. A.B planned, guided the experiment and wrote the manuscript.

3. Soyoung Kwon, Andreas Bartels (2017). Feature-based attention changes connectivity in competitive and cooperative manner (in preparation). S. K. planned, conducted the experiment, analyzed the data and wrote the manuscript. A.B. planned and guided the experiment.



Attention reorganizes connectivity across networks in a frequency specific manner



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ABSTRACT

Attention allows our brain to focus its limited resources on a given task. It does so by selective modulation of neural activity and of functional connectivity (FC) across brain-wide networks. While there is extensive literature on activity changes, surprisingly few studies examined brain-wide FC modulations that can be cleanly attributed to attention compared to matched visual processing. In contrast to prior approaches, we used an ultra-long trial design that avoided transients from trial onsets, included slow fluctuations (< 0.1 Hz) that carry important information on FC, and allowed for frequency-segregated analyses. We found that FC derived from long blocks had a nearly two-fold higher gain compared to FC derived from traditional (short) block designs. Second, attention enhanced intrinsic (negative or positive) correlations across networks, such as between the default-mode network (DMN), the dorsal attention network (DAN), and the visual system (VIS). In contrast attention de-correlated the intrinsically correlated visual regions. Third, the de-correlation within VIS was driven primarily by high frequencies, whereas the increase in DAN-VIS predominantly by low frequencies. These results pinpoint two fundamentally distinct effects of attention on connectivity. Information flow increases between distinct large-scale networks, and de-correlation within sensory cortex indicates decreased redundancy.

1. Introduction

Attention is a key mechanism for optimizing adaptive behavior. It sharpens perceptual tuning (Spitzer et al., 1988), lowers perceptual thresholds (Treue and Martínez Trujillo, 1999), and shortens reaction times (Eason et al., 1969). The behavioral advantage is conveyed by a number of neural processes, many of which are not yet fully understood. One aspect involves local changes in neuromodulators, synaptic, neural and circuit properties (Herrero et al., 2008). These are accompanied by up-modulation of neural responses in sensory cortices, generally more so towards higher processing stages, as observed both in neurophysiology (Moran and Desimone, 1985) and fMRI (Kastner et al., 1998). Another aspect concerns changes in inter-regional connectivity. Sensory processing is up-modulated through long-distance projections from the dorsal attention network that is also up-modulated by attention (Corbetta and Shulman, 2002). At the same time, the default-mode network, involved in introspection and mind-

wandering, is down-modulated (Fox et al., 2005; Greicius et al., 2003). Attentional effects are therefore mediated by connectivity changes that orchestrate activity modulation across the whole brain and that are task-dependent (Gonzalez-Castillo et al., 2015; Mattar et al., 2015). Their characterization is crucial for our understanding of brain function in health and disease.

At fast time-scales, this has been done using electrophysiology. Monkey studies demonstrated that attention selectively increases synchronization in high-frequency (gamma) LFP oscillations between visual regions and those of the dorsal attention network, the lateral intraparietal area (LIP) and the frontal eye fields (FEF) (Gregoriou et al., 2009; Saalmann et al., 2007), with corresponding findings in human MEG (Siegel et al., 2008). In turn, these couplings are thought to be modulated by the dorso-frontal attention network through theta-beta frequency bands (Fries, 2015; Hanslmayr et al., 2013).

At slower time-scales, interregional interactions have been examined using fMRI. For example, attentional coupling between V2 and

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V5/MT was shown to be mediated by parietal activity (Friston and Büchel, 2000), early visual areas enhanced correlations topographically (Haynes et al., 2005), and early and high-level visual regions selectively coupled as function of the attended feature (Al-Aidroos et al., 2012). Other fMRI studies examined relations between visual and parietal regions, and found increases as well as decreases between distinct combinations of visuo-parietal regions (Lauritzen et al., 2009). Interestingly, two studies found a de-correlation among visual regions, one with attention compared to rest (Spadone et al., 2015), the other with visual stimulation compared to rest (Bartels and Zeki, 2005). But since both studies used resting state (with minimal or no visual stimulation) as comparison point, it is unclear whether visual de-correlation can be attributed to attention or to sensory processing. The distinction would be crucial, as such decorrelations may point to reduction of shared noise, and increased information, and have also been observed in noise-correlations of spiking activity within V4 (Cohen and Maunsell, 2009; Mitchell et al., 2009).

Unfortunately, there are not many studies examining whole-brain connectivity changes as a function of attention with matched visual stimulation. Most of these studies are optimized for detection of changes in activity rather than connectivity, and thus used short trials only lasting 10–20 s (Al-Aidroos et al., 2012; Friston and Büchel, 2000; Haynes et al., 2005; Lauritzen et al., 2009). However, while short trials are optimal for activity contrasts, they lead to severe limitations for connectivity measurements. In particular, condition on- and offsets induce large, long-lasting transients affecting time-courses in consequent trials. Their inconsistent nature prevents removal by mean regression. Only much longer trials allow their removal, as well as inspection of faster and slower frequency bands, introduced in resting-state connectivity analyses (Cordes et al., 2001; Salvador et al., 2008; Wu et al., 2008).

Finally, also real life scenarios frequently require deployment of attention over much longer durations, e.g. during steering tasks, focused work, or communication. Hence, the fast-paced paradigms that are optimal for neuroimaging may not optimally characterize neural processes serving longer-term attention.

For these reasons we examined connectivity across visual, dorsal-attention, and default-mode networks during identical visual stimulation but distinct attentional load. We applied the same paradigm in traditional blocks of 20 s and in ultra-long blocks lasting 2 min. Functional connectivity across and within networks was analyzed as a function of block duration and attentional state, and data of ultra-long blocks were additionally analyzed in a frequency segregated manner.

Our results indicate that massively stronger connectivity modulation can be observed during long periods compared to short trials. They also show that distinct frequency bands mediate the de-correlation among visual regions and the overall enhancement of correlations across the brain's large scale networks.

2. Materials and methods

2.1. Subjects

22 healthy volunteers (9 female, 13 male, 21–37 years) participated in the study. Two subjects were excluded from the analysis due to poor signal quality, leading to a total of 20 subjects entering connectivity analyses. All subjects provided informed consent and the study protocol was approved by the joint ethics committee of the university clinics and the Max Planck Institute. Prior to scanning, each subject participated in a psychophysics session to determine the visual noise level required in the main motion stimulus to achieve consistent performance of around 80% correct across subjects. This was achieved by adjusting the ratio of target to distractor dots in the visual flow stimulus; see below for details.

2.2. Main experimental design and task

We conducted two main experiments, one with short trials of 20 s length, and one with long trials of 120 s length, with otherwise identical parameters and conditions. Both experiments had the same two experimental conditions: one attention condition and one passive viewing condition. The visual stimulus was identical in both conditions. It consisted of a continuous stream of random dot motion that changed its state every second (with a jitter of ± 0.25 s) in a random sequence between 4 possible states: clockwise-outward, clockwise-inward, counterclockwise-outward and counterclockwise-inward. In the attention condition, clockwise-outward was set as target motion that observers needed to detect and indicate by button press. In both conditions, participants were required to fixate a central fixation cross.

Long trial runs lasted 480 s and contained four stimulus blocks (of 120 s each) such that each condition was repeated twice. Short trial runs lasted 320 s and contained 16 blocks (of 20 s each) and each condition was repeated 8 times. The trial sequence was counter-balanced across runs. Results were replicated using equal amounts of data points for comparisons between long- and short-trial experiments (see also Supplemental information).

2.3. Stimulus details

Dot-kinematograms consisted of 300 dots on a grey background of 180 cd/m² luminance. Dots were randomly black or white at 100% contrast, and were randomly positioned within a round annulus that extended to the edge of the screen (10 degrees eccentricity). Their rotation speed around the center was 3°/s (either clockwise or counterclockwise), and their contraction/expansion speed was also 3°/s. The size of the dots randomly varied between 0.35 to 0.71°. Dots were rear-projected onto a projection screen and viewed via an angled surface-mirror, with a projector resolution of 1280×1024 pixels at a refresh rate of 75 Hz. All stimuli were generated using the Matlab (Mathworks) extension Psychtoolbox (3.0.8) running on Windows XP (32 bit).

Subjects were instructed to either detect the target-motion in the attention blocks or to fixate only in passive viewing blocks. The central fixation disc displayed a 't' throughout the attention task, or an 'x' during passive viewing.

The performance level was kept around 80% correct for each subject individually as follows. In addition to each of the four presented coherent motion types a varying fraction of the presented dots moved in random directions, constituting noise. Using the QUEST procedure implemented in Psychtoolbox, the fraction of noise dots was altered according to the subject's responses. The noise-fraction was inherited for subsequent passive viewing trials to maintain matched visual stimuli across conditions. The initial noise-level was determined in each subject individually prior to scanning to ensure that only minimal adjustments had to be made during scanning.

2.4. Region of interest (ROI) definition

Regions of interest (ROIs) were defined for the task positive network (TPN) and for the default mode network (DMN). The TPN consisted of following ROIs: retinotopic areas V1-V3, hV4, V5+/MT+, and the dorsal attention network (DAN) including frontal eye-fields (FEFs) and the intraparietal sulcus (IPS). The DMN consisted of the middle frontal cortex (MFC), the posterior cingulate cortex (PCC), and the lateral parietal cortex (LP). All non-retinotopic ROIs (V5/MT+, DAN and DMN ROIs) were defined using the MarsBaR toolbox (Brett 2002) with the contrasts specified below. We used individually varying p-values ($0.05 > p > 0.001$, uncorrected) for each participant and ROI in order to maintain comparable ROI sizes across participants (Fox et al., 2009; Murray and Wojciulik, 2004).

Directly preceding the main experiment, a separate localizer experiment was conducted in each participant to identify area V5/

MT+ using conditions of moving and static dots that alternated every 20 s with 8 repetitions. The contrast motion > static allowed reliable identification of V5/MT in every hemisphere.

The retinotopic scans were conducted on a separate day for 14 subjects to identify visual regions (V1-V3, hV4) using standard mapping techniques and the FreeSurfer software package (Fischl, 2012). For 6 additional subjects, cortical folding patterns were used to predict retinotopic borders within visual regions using FreeSurfer, which has previously been shown to work with high reliability (Fischl et al., 2008).

ROIs of the DAN and DMN were identified using the short trial runs of the main experiment, contrasting attention versus visual stimulation and vice versa, respectively. DAN and DMN ROIs were identified in each participant as clusters nearest to the corresponding ROIs described in prior studies (Corbetta and Shulman, 2002; Fox et al., 2005). In addition, to keep the ROIs similar in size across participants, we restricted each ROI to a sphere with a radius of 6 mm from its center. This allowed reliable localization of DAN and DMN ROIs in 17 of the 20 participants. For the remaining 3 participants long trial data were used.

Note that the use of short-trial data for DMN/DAN ROI definition does not constitute a double-dipping problem: our analyses concerned *inter-regional connectivity within a given condition* rather than activity changes across conditions. Importantly, all analyses were conducted after regressing out mean activity, i.e. systematic condition-related changes were removed, and noise correlations within single conditions were analyzed.

If one nevertheless assumes that for connectivity there may be an advantage for the ROI-defining dataset, our use of primarily short-trial data for ROI definition was a conservative approach: the present study focused on long-trial data with the hypothesis that long-trial data deliver stronger connectivity, hence the ROI selection would have worked against this hypothesis.

2.5. Imaging parameters

Functional images were acquired in a 3 Tesla Siemens TIM scanner with a gradient echo planar imaging (EPI) sequence using a 32 channel head-coil. 36 slices positioned parallel to the calcarine sulcus were acquired in interleaved mode with the following parameters: voxel size 3x3x3 mm; repetition time (TR)=2460 ms, echo time (TE)=36 ms, flip angle: 78°, slice thickness: 2.6 mm+0.4 mm gap, FOV=192x192 mm. In addition, a high-resolution T1-weighted anatomical scan was collected for each participant.

For the long trial experiment, we recorded 6 runs for 14 subjects, and 2 runs in 8 subjects. For the short trial experiment, we recorded a single run for all 22 subjects. Note that for comparisons between long and short-trial experiments equal amounts of data for each were used, and results remained statistically the same with full or matched data samples (see also [Supplemental information](#)).

2.6. Preprocessing prior to connectivity analysis

Initial preprocessing was performed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). EPI volumes were slice-time corrected, motion-corrected, coregistered with the corresponding structural volume and normalized to the standard MNI-space template in SPM.

Data of each participant were then subjected to a regression analysis in which 6 realignment parameters were regressed out to remove global confounds. In addition, we also regressed out white matter signal of each volume (as obtained by SPM segmentation) in order to remove global signal fluctuations induced by scanner or physiological noise (Desjardins et al., 2001; Van Dijk et al., 2010).

As global signal regression can affect connectivity results (Saad et al., 2012) we repeated the connectivity analyses also without global signal regression for a supplemental analysis, and obtained virtually

identical findings (see results section and [Supplemental material](#)).

Signal was then resampled to 1 s resolution, and a temporal high-pass filter with a cut-off period of 256 s (0.004 Hz) was applied. Spatial smoothing was only applied for analyzing the localizers, but not for the correlation analysis.

Following these standard data cleaning steps, stimulus- and task-induced signal were removed from each voxel as follows. For each subject, we obtained the average time series for each condition (attention, passive viewing), separately for each subject. These trial averaged mean signals (for each condition one) were regressed out from the corresponding conditions of the subject, for each individual trial separately. Thus, following regression, the average of all trials of a given condition would be a flat line with a value of 0. This was done to reduce effects of task-induced activity on the subsequent connectivity analysis.

2.7. Functional connectivity analysis

The time courses were extracted from each ROI in each run and epoched by condition. As indicated in the results section, for trials of the long-trial experiment, the initial 20 s following trial onset were removed in order to minimize task-induced transient responses and carry-over effects from preceding trials, leaving 100 s for time-series analysis for each trial (Sadaghiani et al., 2015). For trials of the short-trial experiment, the full trial length of 20 s was used for time-series analysis following time-shifting the signal by 5 s to account for BOLD signal delay.

To obtain functional connectivity (FC) matrices, Pearson correlation coefficients between all ROIs were calculated for each trial separately. Correlation values were Fischer-Z transformed, averaged across trials, and averaged across participants.

For frequency specific connectivity analyses, band pass filters (butterworth, 2nd order) were applied to ROI time series of each run prior to calculating inter-regional correlations.

To provide average correlation measures at the network-level (e.g. VIS-VIS, or DAN-DMN), the corresponding section of the full connectivity matrix was averaged at the subject-level prior to averaging across subjects. For example, the DMN-DAN average value corresponds to the average correlation between every node of the DMN and every node of the DAN.

3. Results

3.1. Behavior

We conducted two fMRI experiments, one with short trials of 20 s length, the other with long trials of 2 minutes length. Both had identical conditions: a demanding visual attention task, and a passive viewing condition with fixation, both using identical visual displays (see [Fig. 1A](#) and [B](#)). Behavioral performance of the attentional task did not significantly differ between the two experiments (long trial rate $79.5 \pm 12.0\%$ (mean \pm SD); short trial rate $=81.6 \pm 26.5\%$, $p=0.62$).

3.2. BOLD signal time courses in long and short trials

First, we examined time course correlations within and across functional networks during visual stimulation with and without a demanding attention task. [Fig. 1C](#) illustrates anatomical locations of regions of interest (ROIs) belonging to the task positive network (TPN, i.e. regions known to positively respond to attention) and to the default mode network (DMN, negatively responding to attention). The TPN and DMN were identified in 12 different regions that were defined bilaterally, resulting 24 ROIs in total shown in the FC matrices.

[Fig. 2A](#) shows time courses after regressing out the white matter and realignment parameters from evoked BOLD signal from all ROIs, averaged across trials and participants. For clarity, groups of ROIs

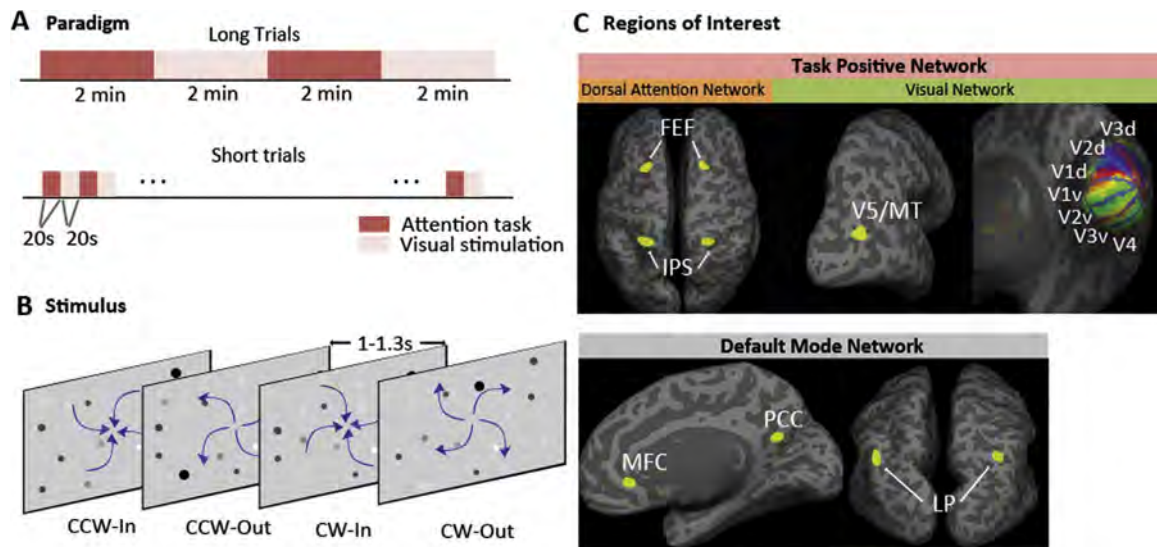


Fig. 1. Experimental design and stimuli used in attention experiments with long and short trials. (A) Experimental design with long and short trial runs, with trial durations of 2 min or 20 s, respectively. (B) The visual stimulus was identical in both, attention and passive viewing conditions. It consisted of spiral motion that could take on 4 possible motion directions: clockwise-outward, clockwise-inward, counterclockwise-outward and counterclockwise-inward. In attention tasks, participants pressed a button when a target direction appeared. (C) Illustration of regions of interest (ROIs) for the dorsal attention network (DAN), visual regions (VIS) (together forming the task positive network, TPN), and for the default-mode network (DMN). FEF: frontal eye-fields, IPS: intraparietal sulcus, MFC: middle frontal cortex, PCC: posterior cingulate cortex, LP: lateral parietal cortex.

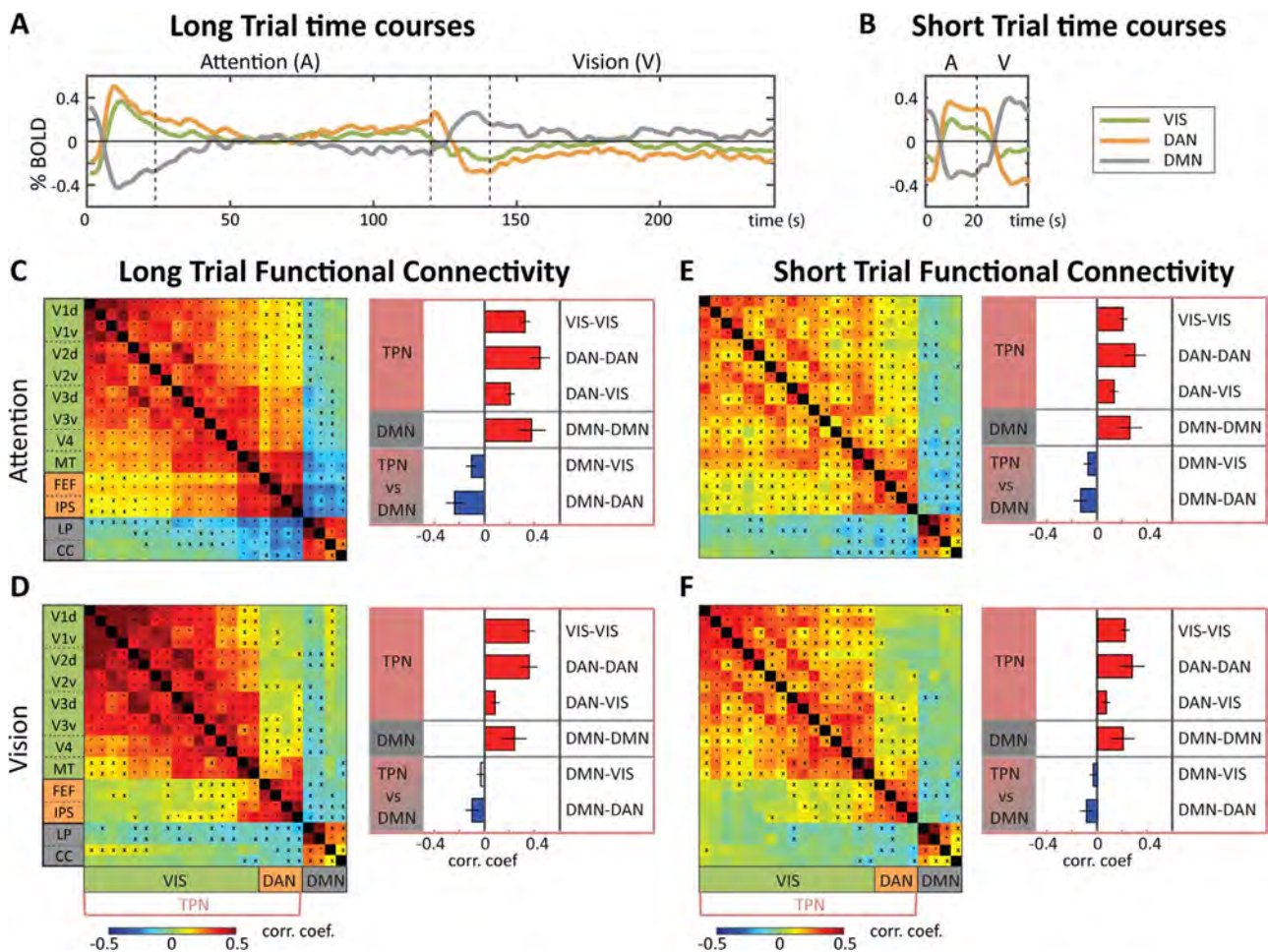


Fig. 2. fMRI time-courses and functional connectivity (FC) matrices during attention and passive viewing in long and short trials. (A) Raw BOLD signal time-courses of different ROI-networks during attention and passive vision in the long-trial experiment. Dotted vertical lines indicate 20 s post trial onsets (at 20 and 140 s), and thick dotted line indicates onset of passive viewing trial (at 120 s). (B) Same for the short-trial experiments. Note that after regressing out the mean-response all time-series were flat (not shown). (C) FC matrix and mean correlation coefficients for long trials during attention (after mean-regression and filtering) and (D) during passive viewing. (E, F) same as (C, D) but for short trials. All data are group averages. VIS: visual network, DAN, dorsal attention network, DMN: default mode network. TPN: task positive network. All corr. coeffs. were fisher-Z transformed. (* and colored bars: $p < 0.05$ Bonferroni-Holmes corrected, X and gray bars: $p < 0.05$ uncorrected). See also related control analyses in [Supplemental Figs. S1–S3](#). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

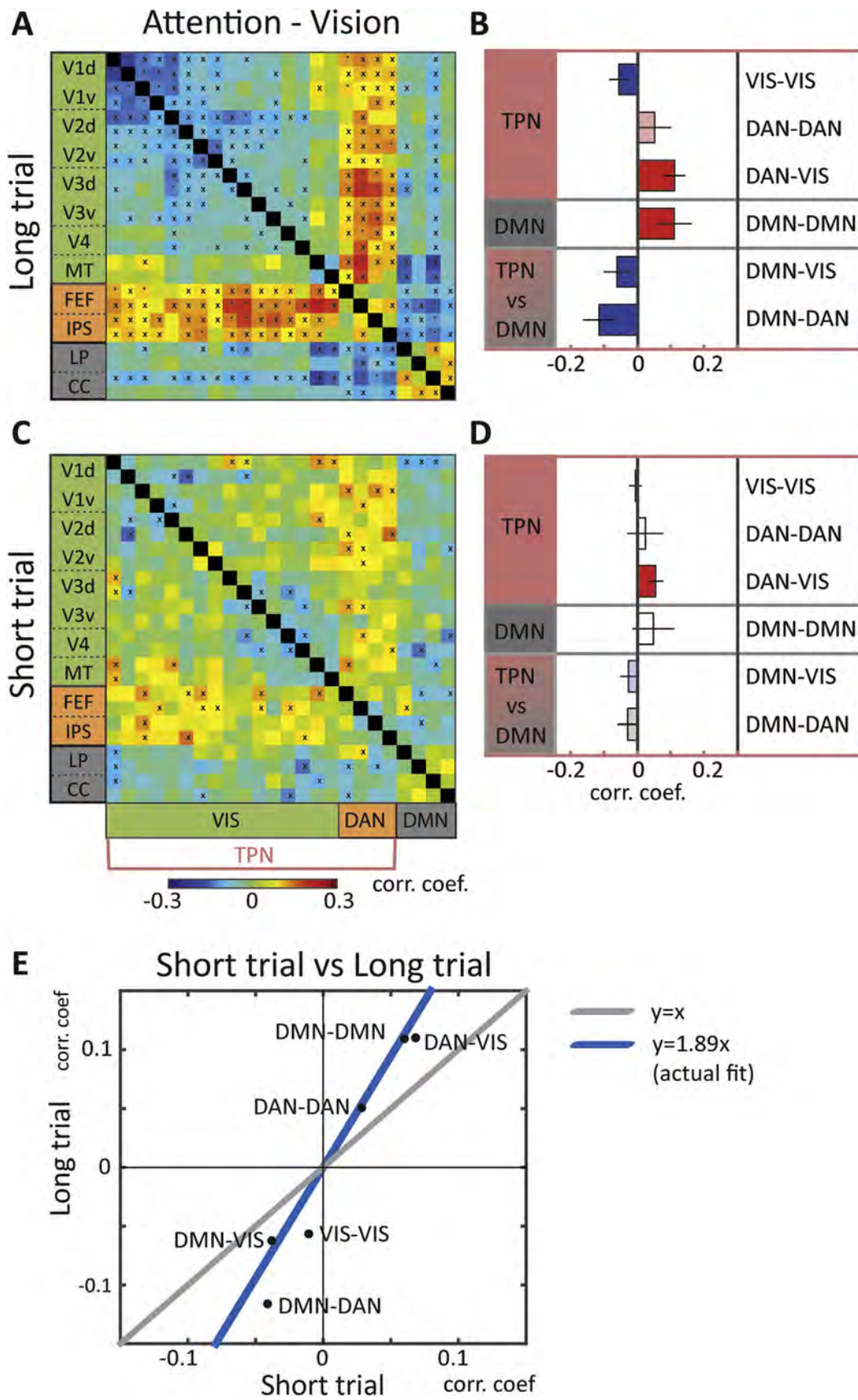


Fig. 3. Difference in FC during attention versus passive visual processing, shown for long and short trials. (A) FC difference (attention vs. passive vision) for long trial blocks for all connections, and (B) for networks. (C, D) FC difference for short trial blocks. (E) Scatterplot of differential FC for short trials versus long trials, for data-points taken from B and D. During long trials, attention effects were strongly enhanced compared to short trials, with a scaling factor=1.89, $r^2=0.93$. All data are group averages. Grey line shows slope of 1, blue line fit to data. * and dark colored bars: $p < 0.05$, Bonferroni-Holmes corrected, x and light colored bars: $p < 0.05$, uncorrected. See also related control analyses in Supplemental Figs. S4–S7. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

indicated in Fig. 1C were averaged. The time courses of the long trials (Fig. 2A) illustrate that the transients from condition-onsets affect the initial portion of any given time course well beyond the trial length of typical block designs (8–20 s). It can thus be assumed that the full duration of task-evoked time courses obtained in typical block designs are influenced by two factors: the initial task-induced transient, and history effects of the preceding condition (Fig. 2B).

To reduce effects of such transients it is common practice to calculate mean trial time courses and to regress them out of individual trials prior to connectivity analyses (Al-Aidroos et al., 2012; Haynes et al., 2005). However, this procedure is highly imperfect in achieving its aim as task-induced on- and offset transients vary in amplitude and shape from trial to trial (Sadaghiani, 2010). Thus, also trial-average regression (or related approaches) preserve considerable task-induced effects. Since the vast majority of task-related studies relies on trial lengths between 8 and 20 s in order to optimize signal-to-noise for task-related net-BOLD signal modulation, FC studies based on such data will remain affected by task-induced transient effects.

3.3. Intrinsic connectivity

To avoid possible adverse effects from task-induced transients we quantified functional connectivity during the late period (last 100 s) of extremely long trials (of 120 s), and compared results to connectivity obtained during typical trial lengths of 20 s, in otherwise matched conditions. Trial-average regression was applied to all trials (see methods).

The resulting FC matrices are shown in Fig. 2C–F for attention and passive vision during long trials (Fig. 2C and D) and during short trials (Fig. 2E and F). Overall, all patterns appeared similar. For both trial lengths and conditions, correlations within TPN and within DMN were positive, whereas correlations between DMN and TPN were generally negative ($p < 0.05$, Bonferroni-Holmes corrected). This also agrees with resting-state connectivity studies that showed a similar pattern of integration and segregation within and across TPN and DMN, respectively (Fox et al., 2005; Greicius et al., 2003). The present data suggest that this pattern is preserved during visual processing and task conditions, and that it extends to the sensory regions.

3.4. Effects of trial duration on FC

Next, we performed a three-way repeated measures ANOVA to examine effects of trial duration and of attention task on the different networks. It had the factors trial length (short and long trials), task (attention task and visual processing), and connections (six network connections as shown in Fig. 2). The ANOVA revealed significant main effects for trial length ($F(1, 39)=16.4$, $p=2.34 \times 10^{-4}$) and for connections ($F(5, 195)=65.5$, $p=7.03 \times 10^{-40}$) but not for task ($F(1, 39)=1.66$, $p=0.21$). Interactions were observed for connections and trial length ($F(5, 629)=11.4$, $p=1.60 \times 10^{-10}$) and for connections and task ($F(5, 629)=13.1$, $p=3.42 \times 10^{-12}$). Note that primarily the interactions are of interest here as we expect connection-dependent effects of trial length or of task, respectively, described in the following section. Secondly, note that the main effect of trial length was primarily driven by an increase in the *absolute* correlation strengths in long compared to short trials, with increases of 26% during passive visual stimulation and 44% during attention, respectively (see Fig. 2).

While the ANOVA presented above relied on data from long trials that contain more data points than short trials, these results remained the same when the number of long trial data points was matched to that of short trials (see [Supplementary results 1.1](#) and [Fig. S1](#)).

Conversely, when we repeated the FC analysis for attention and vision blocks of long trials, but using only the initial 6–20 s (instead of the 20–120 s used above), results become considerably weaker. In particular, nearly all differences between vision and attention got abolished ([Supplementary Figs. S2 and S3](#), and see below).

3.5. Effect of attention on FC

The ANOVA showed significant interactions involving the factor connections. This indicates that both the trial duration as well as the task modulated the connectivity for distinct networks differentially. Fig. 3 illustrates this in more detail by presenting subtracted FC matrices between visual attention and passive visual stimulation for long and short blocks. Attention had similar and systematic effects on FC in long and short blocks. However, the effects were more pronounced in long trials, in both negative and positive directions, akin a gain change. For example, the absolute of the six network-level correlation coefficients shown for long trials in Fig. 3B show an increase of 149% compared to those of the short trials in Fig. 3D ($t(5)=5.48$, $p=0.0027$). Fig. 3C quantifies the gain in a scatterplot of differential FC values between short versus long trials, revealing a scaling factor of 1.89 ($r^2=0.93$).

Overall, these results so far show that ultra-long trials led to considerably stronger FC, regardless of the task (Fig. 2), and that task-dependent effects reveal substantially higher gain during long trials. Most likely both effects can be attributed to the absence of transients from condition-onsets and of history effects from preceding conditions.

Apart from the increased gain in long trials, Fig. 3A shows a striking effect of attention compared to vision. Attention de-correlated connections within the visual network (VIS-VIS: $t(39)=-3.96$, $p=3.12 \times 10^{-4}$). Similar observations have been made before, but could not be clearly attributed to attention or vision, since the comparison was with resting state in the absence of both (Bartels and Zeki, 2005; Spadone et al., 2015). Hence, the present data are the first that can attribute visual de-correlation without confound to attention alone. Note that this was the only attention-related change going against (i.e. not enhancing) intrinsic connectivity (see Fig. 2).

In contrast to this, attention strengthened the intrinsic correlation architecture of all other networks (Fig. 3): DMN increased its anti-correlation with all other networks, and enhanced within-DMN correlations. DAN increased its correlations with VIS, but did not change within-DAN correlations. A schematic overview of these results is shown in Fig. 4.

3.6. Control analyses

We carried out several control analyses to examine robustness of the findings. First, we repeated the FC attention-vision contrast after regressing out task-related button-presses, omitted button presses and erroneous button-presses, which replicated all results in full ([Supplemental Fig. S4](#)).

Second, we examined head motion, which was within acceptable bounds for all subjects. The range of motion (max. – min. for the norm of XYZ coordinates within runs) was 0.79 ± 0.49 mm. (mean \pm SD) across subjects prior to realignment, and head motion parameters had been regressed out prior to FC analyses. However, there was a small but significant bias towards more head motion during passive viewing compared to attention across subjects (attention: 0.68 ± 0.37 mm, vision: 0.89 ± 0.57 mm, $p=0.0041$, $t(19)=-3.27$). To test whether head motion affected our FC results, we repeated FC analyses for two sets of trials that had opposite head-motion bias: we separated the trials where there was more head motion during attention in comparison to passive viewing, and vice versa, and examined the FC patterns for both sets of trials separately. [Supplemental Fig. S5](#) shows that consistent FC patterns emerged regardless of head motion bias. Head motion differences between attention and vision can hence not account for the present results.

Next, we repeated the FC analyses without applying white matter signal regression during preprocessing. While there is good evidence that global signal regression is a good way to reduce artifacts in fMRI data (Van Dijk et al., 2010), the issue is controversial (Saad et al.,

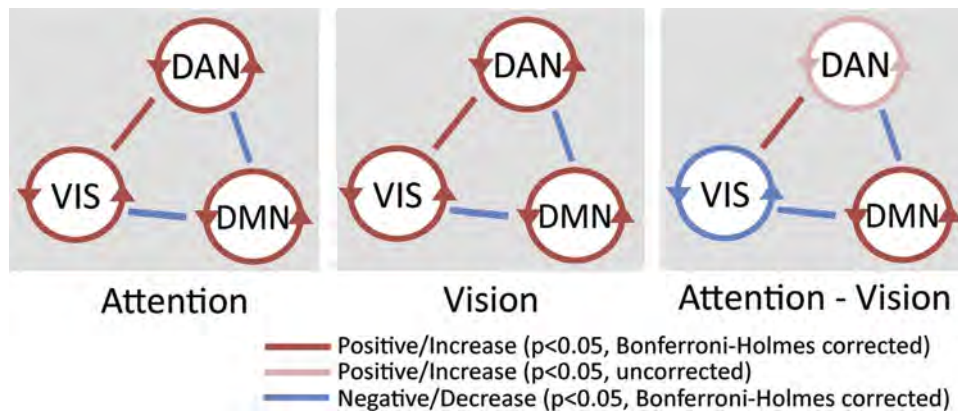


Fig. 4. Schematic representation of FC structure during attention, visual stimulation and their difference. Colored lines show significant correlations or significant changes in correlations, respectively (colored lines: $p < 0.05$, Bonferroni-Holmes corrected, grey lines: $p > 0.05$, uncorrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2012). **Supplemental Fig. S6** shows that the FC pattern without white matter regression was virtually identical to the FC after with white matter regression shown in main **Fig. 3B**. Thus, our FC patterns were consistent regardless of the white matter regression.

Finally, we attempted to remove voxels whose response may contain contributions from larger vessels. In short, we removed from each ROI the top 15% of voxels with the highest condition-driven BOLD modulation in short trials, as strongly modulated voxels have a higher likelihood of containing larger vessels (Cheng et al., 2001). **Supplemental section 1.7 and Fig. S7** show that the FC results remained the same (see also discussion).

3.7. Temporal frequency dependent effects on FC

The analyses so far included the full frequency spectrum of BOLD signal (0.004–0.2 Hz). Given that we observed drastically distinct effects of attention for connectivity within VIS, i.e. de-correlation that reduced intrinsic connectivity, and for connectivity between DAN-VIS, i.e. increase in correlation that enhanced intrinsic connectivity, we hypothesized that potentially distinct neural mechanisms may underlie the two forms of FC changes. In electro-physiology distinct frequency bands have been observed to be associated to long-range top-down modulation versus bottom-up communication from visual to higher regions (Bastos et al., 2014; Siegel et al., 2008).

We thus wondered whether we could also identify an fMRI signal property that separates short-range communication within the sensory network and long-range communication mechanisms across the distinct large-scale networks of the brain. Due to the mostly short task-

designs used in prior fMRI studies, no study was able to ask whether different frequency bands differentially underlie short-range (within VIS) and long-range (VIS-DAN) attention modulation changes in FC. To address this question, we separated BOLD signal of all trials into low frequency (0.004–0.05 Hz) and high frequency (0.05–0.2 Hz) bands, as has been done before in resting state studies (Cordes et al., 2001). For each band separately, we re-calculated the full correlation matrix for attention and passive viewing, and their difference.

Fig. 5 shows differential FC for fast and slow fluctuations induced by the attention task with respect to passive viewing. Most correlation changes were commonly driven by both frequency bands, with overall stronger contribution of the low frequency band. In particular, the increase in correlation between DAN and VIS was driven by low and high frequency fluctuations, with significantly stronger support from low compared to high frequencies ($t(39)=4.07$, $p=2.21 \times 10^{-4}$). In contrast, the decrease in correlation within the visual network was primarily driven by high frequencies (**Fig. 5B**, “High”: t -test between attention and vision for high frequencies: $t(39)=-3.96$, $p=3.12 \times 10^{-4}$), with a significantly stronger high- compared to low frequency contribution (t -test between high and low frequency values of attention versus rest, i.e. between “Low” and “High”: $t(39)=3.53$, $p=1.1 \times 10^{-3}$). These results indicate that low frequency fluctuations contribute stronger to long distance correlation increases across DAN and VIS, and high frequency fluctuations drive short distance correlation decreases within visual cortex.

The exact choice of frequency bands did not affect these results, as differential contributions to the correlation structure were maintained with 8 distinct frequency bands (**Supplementary Fig. S8**).

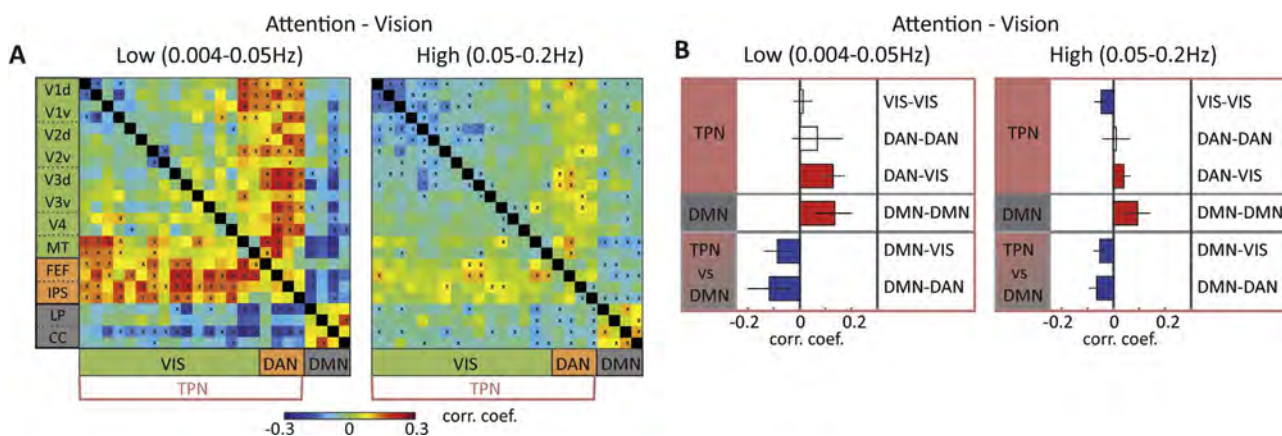


Fig. 5. Difference in FC during attention versus passive visual processing, calculated for low (0.004–0.05 Hz) and high (0.05–0.2 Hz) temporal frequencies across the group. (A) FC matrices, (B) bar-plots at the network level. See **Supplemental Fig. S8** for more frequencies. * and dark colored bars: $p < 0.05$, Bonferroni-Holmes corrected, x and light colored: $p < 0.05$, uncorrected. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

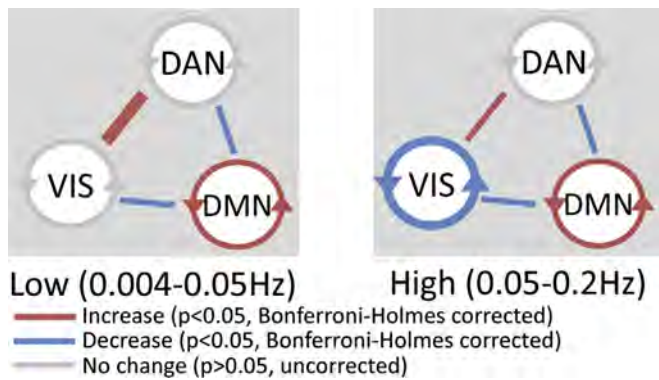


Fig. 6. Schematic representation of the changes induced by attention (i.e. attention – vision) on FC in low (0–0.05 Hz) and high (0.05–0.2 Hz) frequency bands. Colored lines show significant changes (dark: $p < 0.05$, Bonferroni-Holmes corrected, weak: $p < 0.05$, uncorrected) and thick lines reflect stronger changes in one frequency than the other ($p < 0.05$, Bonferroni-Holmes corrected). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

To our knowledge this is the first characterization of frequency band segregated FC during visual stimulation and as a function of attention. Fig. 6 summarizes these findings schematically.

4. Discussion

Our ability to engage attention during sensory processing is of fundamental importance for normal brain function. Surprisingly few studies examined brain-wide connectivity modulations that can be cleanly attributed to attention compared to matched visual processing. Of these, most used a conventional trial design with relatively short stimulus blocks (Al-Aidroos et al., 2012; Cole et al., 2014; Elton and Gao, 2014; Haynes et al., 2005; Krienen et al., 2014; Sala-Llonch et al., 2012). In contrast, our ultra-long trial design avoided trial-onset transients, picked up slow fluctuations (< 0.1 Hz) that carry important information on functional connectivity (Wu et al., 2008), and allowed for frequency-segregated analyses (Cordes et al., 2001). This led to three main findings.

First, noise correlations derived from transient-free long blocks had a nearly two-fold higher gain – in positive and negative directions – compared to correlations derived from traditional (short) block designs.

Second, attention enhanced intrinsic (negative or positive) correlations in long-distance connections, such as DMN-DAN, DMN-VIS, DAN-VIS, and within DMN. In contrast, for local connections within the visual system (VIS), attention de-correlated the intrinsically positive correlations.

Third, the de-correlation within the visual system was driven primarily by high frequencies, whereas the increase in DAN-VIS predominantly by low frequencies. All other correlations received contributions from both frequency bands. This suggests the presence of potentially fundamentally distinct mechanisms subserving within-visual and top-down network behavior.

Frequency-segregated connectivity has previously been examined for resting state (Cordes et al., 2001; Salvador et al., 2008; Wu et al., 2008), but not for visual tasks, nor for fronto-parietal and visual networks. In resting state, fMRI fluctuations in cortex have typically observed in low frequencies (< 0.1 Hz), with higher frequencies (0.1–0.3 Hz) in the limbic system (Wu et al., 2008), but also in arteries or veins (Cordes et al., 2001).

4.1. Connectivity related to DMN

The human brain can be subdivided into several interacting networks. A predominant subdivision entails two large-scale, anti-correlated neural systems: the task positive (TPN) and the default-mode

(DMN) networks, respectively (Fox et al., 2005; Greicius et al., 2003; Sala-Llonch et al., 2012). They tend to be anti-correlated across and within many task conditions, including resting state (Cole et al., 2014; Fox et al., 2005; Greicius et al., 2003; Krienen et al., 2014; Sala-Llonch et al., 2012) (see also Fig. 2). These intrinsic, task-invariant anti-correlations may indicate underlying anatomical connectivity, but they could also originate from segregated sources of vascularization (Vigneau-Roy et al., 2014), or from opposing functions, reflecting extrinsic versus intrinsic processing (Cole et al., 2014; Golland et al., 2008; Krienen et al., 2014; Sala-Llonch et al., 2012).

Despite the vast literature on these networks, it has remained unclear whether their intrinsic anti-correlation differs during passive visual stimulation and execution of an attention-demanding task. Prior studies typically examined the interaction of these networks during tasks and resting state, but either focused on similarities, or found no difference (Cole et al., 2014; Krienen et al., 2014). The latter could also be due to the limitation of short fMRI designs that carry transient effects from prior trials.

Our results show that attention enhanced the intrinsic (anti-) correlation structure of all DMN-related connections: it increased correlations within DMN and also the anti-correlation between DMN and TPN nodes. This corroborates the notion that the mutually inhibitive relationship between TPN and DMN is behaviorally relevant (Fox et al., 2005; Greicius et al., 2003). For example, their anti-correlation was associated with behavioral performance (Kelly et al., 2008), and reduced DMN suppression increased attentional lapses (Weissman et al., 2006). Here, attention to sensory stimuli required dis-engaging self-oriented processes (Spreng, 2012) and thus further dissociating the TPN from the DMN.

4.2. Dichotomy of connectivity within TPN

Attention reorganized TPNs intrinsic correlation structure in a dichotomous way: long-range connections between DAN and VIS increased, but correlations within VIS decreased. Similar observations were made in a recent study that compared resting state with visual attention (Spadone et al., 2015). Our results allow the conclusion that this dichotomy in top-down versus lateral (within-visual system) connectivity is driven by attention, as visual processing was matched.

Importantly, we found that this dichotomy had a correlate in signal frequencies. Long distance connectivity across large-scale networks – i.e. VIS with DAN, as well as all DMN-related connectivity – were primarily driven by low frequencies (< 0.05 Hz), whereas the decorrelation within VIS was primarily driven by fast frequencies (0.05–0.2 Hz). Another way to look at this is that all attention-driven correlation changes that enhanced the intrinsic correlation structure (shown in Fig. 2) were primarily driven by low frequencies. Meanwhile, decorrelation within VIS was the only correlation change that worked against the intrinsic structure and was driven by high frequencies.

4.3. De-correlation within the visual system

Hence, one of the most striking findings in this study is the de-correlation of BOLD signal between distinct visual regions during attention compared to passive visual processing. To our knowledge this is the first time that this effect has been cleanly associated to attention. Two prior studies observed de-correlation among visual regions (Bartels and Zeki, 2005; Spadone et al., 2015), but in both the comparison involved resting state, which is poorly defined and does not contain visual stimulation nor attention.

Spadone et al. (2015) correctly pointed out that the de-correlation within VIS is consistent with desynchronization of α -rhythms observed during attention and visual processing (Betti et al., 2013; Siegel et al., 2008; Thut, 2006). In the same vein, the data are also compatible with the view that de-correlation represents an increase of functional segregation of functionally specialized regions, i.e. a decrease in

redundancy (Bartels and Zeki, 2005). This is reminiscent of attentional noise de-correlation observed at the level of neural spiking (Cohen and Maunsell, 2009; Mitchell et al., 2009), but it remains to be explored how this relates to changes in BOLD activity or long-range connectivity.

4.4. Connectivity between DAN and VIS

Attention increased connectivity between DAN and VIS not only for specialized mid- or high-level regions such as V5/MT and V4 as previously reported (Al-Aidroos et al., 2012; Spadone et al., 2015), but consistently for all visual regions, including the earliest ones like V1 and V2. In early visual regions attention-related net-BOLD modulations are well-established, yet typically weaker than in higher regions (Kanwisher and Wojciulik, 2000). To our knowledge, attention-mediated connectivity changes with early visual regions have only rarely been shown before (Haynes et al., 2005).

Considering that gamma synchronization of neuronal activity is highly correlated with BOLD signal (Niessing et al., 2005; Nir et al., 2007; Scheeringa et al., 2011), it is possible that the observed increase in BOLD correlation between DAN-VIS is a low-frequency correlate of the increased communication mediated by the increase in gamma synchronization. Gamma-band synchrony is up-regulated by attention and thought to enhance signal transmission and selectivity between lower-level occipital and higher-level fronto-parietal regions (Fries, 2015; Gregoriou et al., 2009; Hanslmayr et al., 2013; Saalman et al., 2007; Siegel et al., 2008). In contrast, lower frequency bands (theta-to-beta) of the dorso-frontal attention network are thought to modulate gamma-power (Fries, 2015; Hanslmayr et al., 2013).

It is as yet unclear which exact electrophysiological mechanisms underlie the functional coupling at distinct frequencies observed here in terms of BOLD signal. However, prior evidence has shown that high- and low-frequency components in EEG contribute differentially to BOLD signal variability (Scheeringa 2011), and similarly in monkey, that ultra-slow fluctuations exist in band-limited power of local field potentials (LFPs) that are well in the time-range of both, fast and slow fluctuations observed here (Leopold et al., 2003). More recently, it was shown that distinct bands of LFP correlate with BOLD signal fluctuations with distinct lags, suggesting potentially distinct mechanisms underlying either the neurovascular coupling or the origin of the LFP signals (Schölvinc et al., 2010). However, to our knowledge, no prior study attempted to link distinct LFP frequency bands to distinct BOLD signal power bands. What is certain though is that a variety of electrophysiological signals exhibit ultra-slow fluctuations in the time scales observed here that can directly account for the distinct bands observed here.

Correspondingly, the observed fMRI dichotomy may also reflect different processes in large scale networks. De-correlation in high frequencies may indicate redundancy reduction, and low frequencies facilitation of information transfer, with both processes being reflected in non-exclusive and additive fMRI signal fluctuations.

4.5. Limitations

Due to the ultra-long trial design, and due to our comparison between two conditions differing in attentional engagement, one could argue that cardiac and respiratory signals may have confounded the observed results. If so, this critique would apply to all prior studies comparing conditions differing in attentional demand as well (Bartels and Zeki, 2005; Cole et al., 2014; Krienen et al., 2014; Spadone et al., 2015). We deem this unlikely, as these artifacts would be expected to be more wide-spread across cortex, and not co-localized to boundaries of specific functional networks, each of which showed specific and partly opposing effects in our results. Nor would the findings generally fall in line with network properties reported in a multitude of prior studies, each of which differed in paradigms and analysis techniques. Also, artifactual physiological rhythms are more prominent in higher fre-

quencies (0.3–2 Hz) and occur primarily in arteries or veins, rather than in cortex (Cordes et al., 2001), and are to a good extent removable by the analysis techniques also applied here (Desjardins et al., 2001; Van Dijk et al., 2010). In particular, only our use of ultra-long trials allowed us to fully exploit slow frequency power (< 0.1 Hz) that has been shown to correlate particularly well with neural signal (Nir et al., 2008). The fact that our main results were fully replicated in a supplemental analysis in which signal of putative vein-biased voxels was removed argues against a major contribution of vascular artifacts to our results (see Supplemental Fig. S7). Nevertheless, future work would benefit in utilizing additional scans that allow for reliable exclusion of vessels from FC analyses to more reliably rule out vessel-related contributions.

Another concern inherent to this type of interleaved paradigm using matched stimuli could be that participants still engaged – to a lesser extent and without motor response – in the attention task during passive vision blocks. This, however, would work against the differential neural results found here, as it would make conditions more similar.

5. Conclusions

Using long observation periods, we show that attention, in comparison to passive viewing with exactly matched visual stimulation, strengthened intrinsically existing long-distance correlations within and across DMN, DAN and VIS primarily by low frequencies. In contrast, within the visual system, attention de-correlated connectivity, hence working against the intrinsically positive connectivity. This de-correlation was driven primarily by high frequencies. Our long trials excluded artefacts inherent to faster designs, and yielded up to twofold higher gain in FC changes. The current results suggest that brain-wide correlations are reorganized during attention in a frequency specific manner. Importantly, these results can unequivocally be assigned to attentional effects, as visual stimulation was matched across conditions.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuroimage.2016.10.014>.

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Multiplicative and additive modulation of functional connectivity patterns by visual attention

Abbreviated title: Hierarchical modulation of attention

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Conflict of Interest

The authors declare no competing financial interests.

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Abstract

Attention improves behavioral performance by selectively enhancing neural responses to attended, task-relevant stimuli. While past studies primarily focused on modulation of activity, or of connectivity between pairs of regions, in the present study we examined attention-mediated connectivity as a function of the hierarchical organization of visual regions. We quantified connectivity between the hierarchy of visual regions (V1-V4 and V5/MT+) and individual nodes of the dorsal attention network (DAN) as well as the default-mode network (DMN). fMRI data were obtained in humans performing a demanding visual attention task throughout ultra-long blocks lasting two minutes and during passive viewing of the same stimuli. This paradigm allowed for high-quality functional connectivity measurements free of confounds related to on- and offset effects of stimulus blocks. The results revealed that during passive vision, there was a gradient of connectivity between each DAN node and visual regions, with increasing connectivity from early (V1) to higher visual regions (V3, V4, V5/MT+). Attention had an additive effect on this gradient, in that all connections increased by a similar amount throughout the visual hierarchy. Only FEF-related connectivity increased in slope across the visual hierarchy, revealing a gain effect. Connectivity with DMN during passive viewing was inversed, with strongest connectivity with early visual regions and weakest with higher regions. Attention tended to have negative gain effects for all DMN nodes with the visual hierarchy, but (negative) additive effects only for left lateral inferior parietal cortex. Finally, we found that connectivity strength correlated with change in activity induced by attention, suggesting the former mediates the latter. The current study provides a first quantification of connectivity between high-level attention and default mode regions with visual regions that takes into account the visual hierarchy. Our results suggest a hierarchical connectivity structure that is modulated by attention in both additive and multiplicative ways, with inverse effects between DAN and DMN.

Keywords

Attention, functional connectivity, default mode network, attention network, visual cortex, fMRI

Introduction

Attention is thought to selectively enhance neural processing of attended stimuli and to reduce responses to unattended stimuli. Several neural mechanisms related to attentional modulation have been proposed, each supported by experimental data from single-cell recordings as well as from fMRI (Kanwisher and Wojciulik, 2000). For example, attention enhances the gain of neural responses, i.e. exerts a multiplicative effect (Treue and Martínez Trujillo, 1999), attention increases the baseline activity, i.e. has an additive effect (Luck et al., 1997), which has also been observed in the absence of stimulation (Kastner et al., 1999), and attention reduces noise in neural responses (Bressler and Silver, 2010; Cohen and Maunsell, 2009; McAdams and Maunsell, 1999; Mitchell et al., 2009).

In addition to these effects on single locations, fMRI studies also revealed a gradient of attention-mediated net-BOLD modulation across the visual hierarchy: attention has been shown to increase activity more in higher-level regions compared to early visual cortex, with the weakest modulation in V1 (Serences and Yantis, 2006; Silver et al., 2005). In contrast to this, visual stimulation on its own, compared to no stimulation, has a reversed effect, with the strongest enhancement in early visual cortex and weaker effects in higher-level regions (Hochstein and Ahissar, 2002; Silver et al., 2005). Hence, attention enhances neural activity in a hierarchical manner, with strongest modulations in higher-level visual regions and a decreasing gradient towards V1 – a gradient whose direction is reversed to that of bottom-up stimulation effects.

One important source for attentional modulation is thought to be the dorsal attention network (DAN) that is involved in various types of attention tasks, such as controlling the location or feature of attention (Corbetta and Shulman, 2002; Kanwisher and Wojciulik, 2000). Recent TMS studies showed that stimulating DAN nodes modulates activity in visual regions, directly demonstrating the ability of DAN to exert control over sensory regions (Blankenburg et al., 2010).

Although the interaction between DAN and VIS has been heavily studied (Blankenburg et al., 2010; Bressler et al., 2008; Buschman and Miller, 2007; Gregoriou et al., 2009), the relationship of *connectivity* with hierarchical distance within the visual system is not known in detail.

Based on the fact that attention-mediated changes in *activity* follow the hierarchy in the visual system, we here tested the simple hypothesis that this is mediated by *connectivity*

between regions of the DAN and the visual system that is equally hierarchy-dependent (see Figure 1). In particular, we wanted to characterize *connectivity* in controlled conditions during passive vision and during execution of a demanding visual attention task in order to quantify baseline connectivity as well as *changes* in connectivity as a function of attention across the visual hierarchy.

In contrast to net signal modulation, there is comparably little evidence on how attention affects connectivity across the hierarchy of visual regions. Electrophysiological studies have provided some evidence that attention modulates the interaction between areas, such as between the dorsal attention network and the visual network (Gregoriou et al., 2009; Saalmann et al., 2007) with corresponding findings in MEG (Siegel et al., 2008), and fMRI (Bressler et al., 2008; Spadone et al., 2015).

Only few studies measured the strength of connection as a function of visual hierarchy, yet these studies characterized connectivity in terms of anatomical connections (Greenberg et al., 2012; Markov et al., 2014, 2012), functional connectivity during the resting state (Genç et al., 2015; Yeo et al., 2011) or during passive viewing (Heinzle et al., 2011), but not during task conditions. One study used Granger Causality analysis during extremely short trials to show modulatory influences between the dorsal attention network and visual regions, and found in some participants the attention network modulated high level visual regions more than early ones (Bressler et al., 2008).

However, to our knowledge the connectivity between the dorsal attention network (DAN) and the full hierarchy of visual regions has not been characterized systematically during prolonged periods of attention, in comparison to matched visual stimulation.

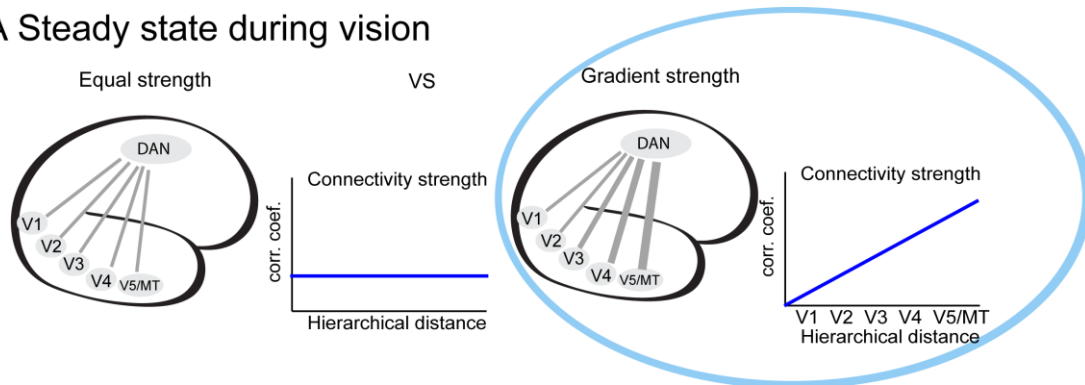
Similarly, it is not well understood how default mode network (DMN) (Biswal et al., 1995; Raichle et al., 2001) nodes interact with the hierarchy of visual regions (Shine et al., 2015), or whether DMN connectivity is related to the visual hierarchy. This would be highly relevant to understand, as there is growing evidence that the DMN also plays a role in task-execution by interacting with other task related networks (Elton and Gao, 2014; Sala-Llonch et al., 2012).

We hence also characterized connectivity between nodes of the DMN and the visual hierarchy during passive viewing and attention.

We used a linear model to test whether attention added a baseline shift and whether it exerted gain effects on connectivity between the visual hierarchy and each of the nodes of

DAN and DMN. Finally we asked whether attention-mediated changes in *activity* were correlated with attention-mediated changes in *connectivity*.

A Steady state during vision



B Effects of attention

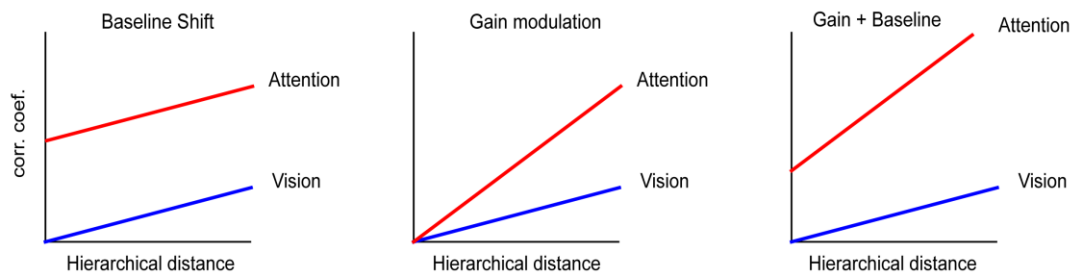


Figure 1. Hypothesis. (A) During visual processing, the connectivity between DAN and the visual hierarchy (VIS) may have equal strength across the visual hierarchy, or it may be dominated by a gradient. (B) Attention may change the baseline connectivity strength by an additive shift, a multiplicative (gain) modulation, or a combination of both. The same questions regard connectivity between the DMN and VIS.

Methods

Subjects

Twenty-two healthy individuals (aged 21-37 years; 9 females) gave informed consent and participated the study; two subjects were excluded from the analysis due to poor signal quality, so twenty subjects were used in the main analysis. The experimental protocol was approved by the joint ethics committee of the University Clinics Tübingen and the Max Planck Institute.

Experimental conditions and task

Main experiment

The fMRI experiment consisted of two conditions (attention and passive vision) presented in ultra-long blocks lasting 2 min each. In a prior study we had shown that ultra-long blocks yield more power for comparative connectivity measures between different task-conditions (Kwon et al., 2016). There were two conditions: passive viewing and attention. Both conditions contained the same visual stimuli and each condition was repeated twice in each session in a counterbalanced sequence. In both conditions, the visual stimulus was identical and consisted of a continuous stream of random dot motion. The direction of motion changed every 1 s in a random sequence between 4 possible states: clockwise-outward, clockwise-inward, counterclockwise-outward and counterclockwise-inward. Prior to each session, one direction was designated as target direction. In attention blocks only, participants had to detect the target-motion and press a button each time it was detected. In passive viewing and attention blocks they had to fixate a central fixation disc. The central fixation disc displayed a 't' throughout the attention task, or an 'x' during passive viewing. We matched the performance level across subjects to 80% by conducting a psychophysics experiment prior to scanning. For 14 participants six runs were collected, and for technical reasons for 6 subjects 2 runs. Each run contained 2 repetitions of each condition.

Attention localizer experiment

To quantify attentional signal modulation, one run was collected where the same conditions and stimuli as used above were presented, but with a block-duration of 20 s rather than 120 s. In contrast to the ultra-long block durations, 20 s blocks allow for a better quantification of net-BOLD signal modulation than 120 s blocks. Each of the two conditions (attention and passive viewing) were repeated 8 times. This measurement was conducted for all 20 subjects.

Visual localizer experiment

To quantify purely visual responses across visual regions, one run was collected where the same stimuli as used above were presented for 20 s, alternating with 20 s of blank screen. Subjects had to perform no task except for fixating a central fixation disk in both conditions. Each condition was repeated 8 times. This measurement was performed for 4 subjects.

Detailed stimulus properties

Dot-kinematograms in all experiments consisted of 300 dots on a grey background of 180 cd/m² luminance. Dots were randomly black or white at 100 % contrast, and were randomly positioned within a round annulus that extended to the edge of the screen (10 degrees eccentricity). Their rotation speed around the center was 3 degrees/s (either clockwise or counter-clockwise), and their contraction/expansion speed was also 3 deg/s. The size of the dots randomly varied between 0.35 to 0.71 degrees. Dots were rear-projected onto a projection screen and viewed via an angled surface-mirror, with a projector resolution of 1280 x 1024 pixels at a refresh rate of 75 Hz. All stimuli were generated using the Matlab (Mathworks) extension Psychtoolbox (3.0.8) running on Windows XP (64 bit).

fMRI Analysis

Region of Interest (ROI) definition

Regions of interest were defined for retinotopically mapped visual areas V1-V4, for V5/MT+, and for subregions of the DAN (frontal eye fields (FEF), intraparietal sulcus (IPS)) and DMN (lateral parietal cortex (LP), medial frontal cortex (MFC), posterior cingulate cortex (PCC)), based on separate datasets as described below.

Visual regions V1-V4 were defined using phase-encoded retinotopic mapping data collected for 14 subjects using standard mapping techniques, and analyzed using the Freesurfer software package. For the remaining 6 subjects, visual areas (V1-V4) were defined using automatic cortical parcellation provided by freesurfer (Desikan et al., 2006; Fischl et al., 2008). To identify area V5/MT+, a separate localizer experiment was conducted using a display of moving and static dots that alternated every 20 seconds with 8 repetitions. The contrast motion > static allowed reliable identification of V5/MT+ in every hemisphere.

Regions of the DAN and DMN were defined from the attention localizer experiment that alternated visual processing and attention every 20 seconds. To define DAN, the contrast attention > passive visual processing was used, allowing reliable identification of FEF and IPS in each hemisphere. For defining DMN, the opposite contrast visual processing > attention was used, allowing reliable identification of MFC, PCC and bilateral LP.

Imaging parameters

fMRI scanning was performed on a 3 Tesla Siemens TIM scanner using a 32 channel head-coil. The functional scans were acquired with a T2*-weighted echo planar imaging (EPI) sequence (echo time (TE) = 36ms, repetitions time (TR) = 2460ms, flip angle: 78 deg, FOV = 192 x 192 mm; slice thickness: 3mm, giving a voxel size of 3x3x3mm). High-resolution anatomical images were acquired with a T1-weighted ADNI sequence for each participant.

Preprocessing and mean signal Analysis using GLM

Data of each individual subject were preprocessed using SPM5 (Wellcome Department of Imaging Neuroscience), involving slice time correction, and realignment to correct for head motion, but no spatial smoothing.

Following this, ROI data were extracted for each ROI of every subject for the subsequent connectivity analysis (see below). To quantify mean signal changes associated to visual stimulation and attentional modulation in the vision and attention localizer experiments (that involved 20 s blocks), we ran a first-level general linear model using SPM5, involving regressors for each of the two conditions of the vision or attention localizer experiments, respectively. Additional six regressors modelled head-motion, and a high-pass filter with 128 s cut-off was applied. For each ROI of each subject, contrast-values for the functional contrasts (vision versus blank; or attention versus passive vision, respectively) were extracted.

Functional Connectivity Analysis

For the main experiment involving 120 s blocks, the raw time courses were extracted from each ROI in each run from preprocessed data and epoched by condition. Signal was then resampled to 1 s resolution, and a temporal high-pass filter with a cut-off period of 256 s (0.004 Hz) was applied.

For each subject and each ROI, we calculated the average time course for each condition across all blocks, and regressed this out of the raw time-course of each separate block of the same condition to remove experimentally induced gradients. Finally, the average signal from

the white matter was also regressed out to remove global noise. To minimize task-induced transient responses and carry-over effects from preceding trials (Kwon et al., 2016; Sadaghiani et al., 2015), the initial 20 s of each block were excluded, leaving 100 s for the correlation analysis. Pearson correlation coefficients between ROIs in DAN and VIS as well as between DMN and VIS were calculated, Fischer-Z transformed, and averaged across subjects.

Regression analysis between visual hierarchy and connectivity

We modelled the linear relationship between hierarchical distance and connectivity. Separate linear regression analyses were conducted for connectivity values of VIS with each of the DAN and DMN seed ROIs, separately for each condition. We used the standard equation

$$Y = G * X + B$$

with

Y=correlation values between a given DAN node and VIS, X = hierarchical distance (1-5),
G=gain, B=baseline

Then, we performed t-tests to test whether gain or baseline were significantly different from zero for each condition, and t-test were also performed on differences of these values between attention and vision conditions. To test for interactions between condition and area, 2-way repeated measures ANOVAs were performed.

Results

Mean modulation in visual regions (VIS)

Before conducting connectivity analyses, we quantified mean activity changes induced by visual stimulation and by attention. Data for these comparisons were collected in separate runs with condition trials of standard length of 20 s (rather than the 120 s used for connectivity analyses) to facilitate reliable amplitude estimates.

Figure 2A shows mean modulation of the fMRI signal evoked by visual stimulation across visual regions. Consistent with prior studies (Hochstein and Ahissar, 2002; Silver et al., 2005), we observed a negative gradient of amplitude modulation across the visual hierarchy: early visual areas exhibited the largest increase and high visual areas the smallest enhancement due to visual stimulation (pearson correlation between mean amplitude and visual hierarchy: corr. coef: -1.00, $p=0.0002$, group level $n=4$). This result was replicated in each subject measured (corr. coef: S1=-1.00, $p=0.0001$; S2=-0.99, $p=0.002$; S3 = -0.94, $p=0.018$; S4=-0.95, $p=0.013$).

In contrast to the differences in response to passive viewing, attention modulated the BOLD signal amplitude with a positive gradient across the visual hierarchy (Figure 2B): early visual areas had weak modulation that increased towards higher visual regions (corr. coef: 0.91, $p=0.030$, group level $n=20$). Again, this result is in accord with prior observations (Serences and Yantis, 2006; Silver et al., 2005).

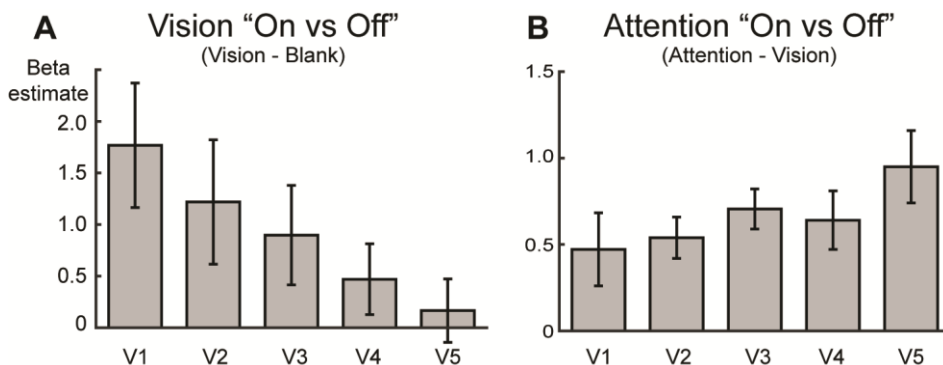


Figure 2. Responses to passive visual stimulation and to attention. (A). fMRI response increases to visual stimulation with respect to blank screen. (B) fMRI response increases to performing a visual attention task compared to passive viewing.

Connectivity between DAN nodes and VIS hierarchy

Next, we examined whether the signal strength gradients observed above may be related to corresponding gradients in *connectivity* with nodes of the dorsal attention network (DAN).

Importantly, for all connectivity analyses, we used data derived from ultra-long visual stimulation or attention blocks, respectively, lasting 2 minutes each. Such long blocks are suboptimal for estimation of net-BOLD signal modulation, but superior for examining functional connectivity (Kwon et al., 2016).

Following preprocessing (see methods), we first calculated raw connectivity values between a given DAN region with each of the five visual regions (VIS). DAN seed regions were the frontal eye fields (FEF), and the intraparietal sulcus (IPS), and VIS was defined as the five visual regions (V1-V4, V5/MT+), all bilaterally.

We then fit the connectivity values using the equation

$$Y = G * X + B$$

Y=correlation values between a given DAN node and VIS, * = hierarchical distance (1-5),
G=gain, B=baseline

This allowed estimation of the slope of connectivity across the visual hierarchy and the baseline. The slope (G) of the linear fit reflects the degree to which the DAN node interacts with VIS in hierarchical manner. The intercept of the fit (B) describes the baseline connectivity.

Connectivity during visual processing

Figure 3A shows that during passive visual processing each DAN seed region had a gradient of increasing connectivity across the visual hierarchy. The slope of the linear fit was significantly larger than zero for each DAN seed (gain G: FEF_L = 0.036, $p = 2.16 * 10^{-6}$; FEF_R = 0.031, $p = 7.46 * 10^{-6}$; IPS_L = 0.055, $p = 1.25 * 10^{-8}$; IPS_R = 0.747, $p = 5.27 * 10^{-11}$). Note that this *positive* gradient of *connectivity* with DAN for passive viewing resembled the equally positive gradient of *activity* change induced by attentional modulation rather than that induced by visual stimulation (compare Figure 3 with Figure 2).

To test for seed-specific and hemispheric effects, we performed 2-way repeated measures ANOVAs on the slopes with the factors region (FEF, IPS) and hemisphere (Left, Right). There were main effects for area ($F(1, 39)=3.18 * 10, p=1.60 * 10^{-6}$), but not for hemisphere ($F(1, 39)=1.34, p=0.25$), and an interaction between area and hemisphere ($F(1,39)= 4.69, p=0.036$). Subsequent t-tests showed that IPS connectivity with visual areas had a steeper slope than that of FEF ($t(39)=-5.65, p=1.6 * 10^{-6}$).

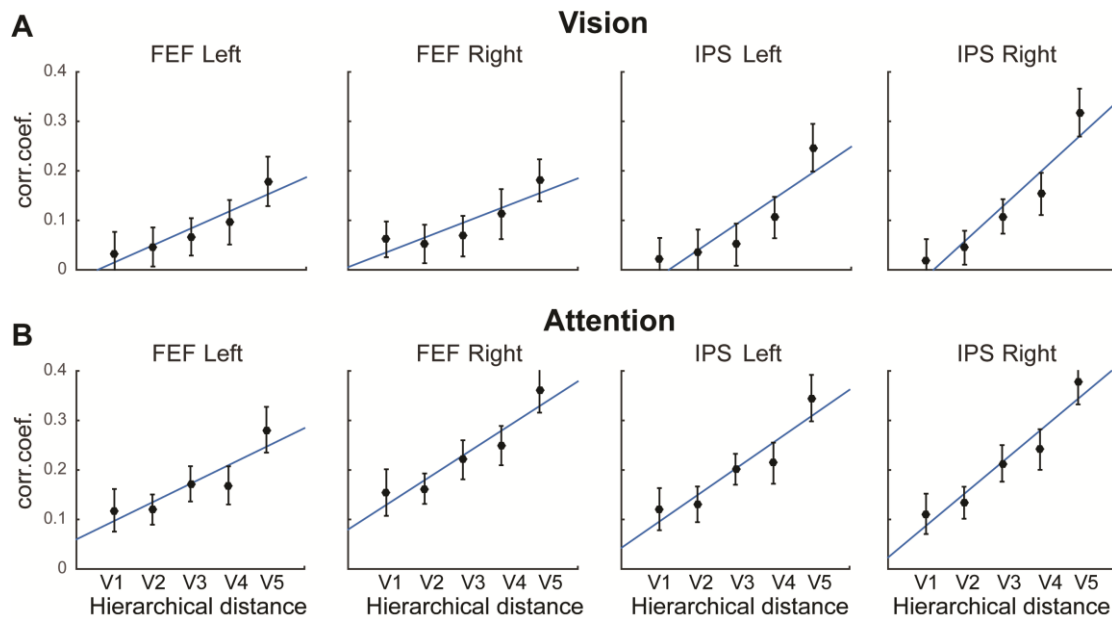


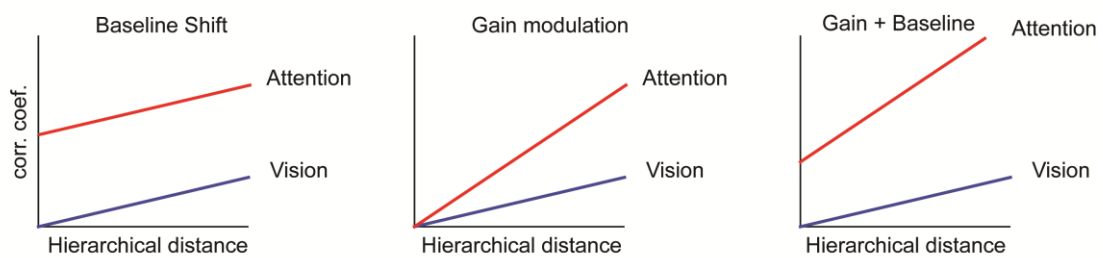
Figure 3. The relationship between the connectivity strength of a given region of the dorsal attention network (DAN) with the hierarchical distance within the visual system. (a) Connectivity of DAN nodes with VIS during visual processing. (b) Connectivity during execution of a highly demanding attention task. FEF: Frontal Eye Field, IPS: Intra-parietal Sulcus. Solid line: linear fit. Error bars: 95% confidence interval (CI).

Connectivity during attention

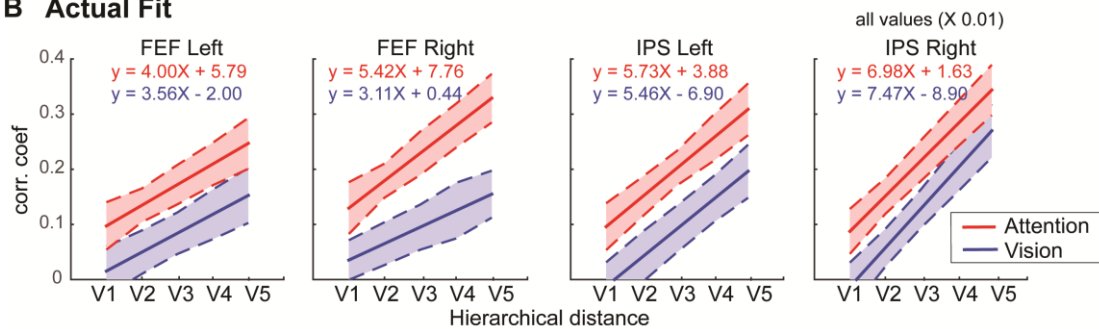
Figure 3B shows overall similar connectivity patterns when subjects performed a demanding attention task. All slopes were significant (gain G: FEF_L = 0.040, $p=2.42 * 10^{-6}$; FEF_R = 0.054, $p=1.99 * 10^{-9}$; IPS_L = 0.057, $p=1.83 * 10^{-9}$; IPS_R = 0.70, $p=8.45 * 10^{-13}$). The 2-way ANOVA on slopes revealed an effect of region ($F(1,39)=1.33 * 10, p=7.57 * 10^{-4}$), and of hemisphere ($F(1,39)=4.31, p=0.045$), but no interaction ($F(1,39)=0.325, p=0.858$). As during

visual processing, IPS connectivity with visual areas had a steeper slope than that of FEF ($t(39)=-3.66$, $p=7.57 \times 10^{-4}$) during attention. DAN connectivity was stronger for the right compared to left hemisphere ($t(39)=-2.10$, $p=0.045$). This latter result is important if one considers that numerous prior studies showed asymmetric, right-dominant effects of attention on mean activity change (Corbetta and Shulman, 2002; Mesulam, 1981). The present results extend this to connectivity, with a stronger connectivity slope in the right compared to the left hemisphere.

A Model Predictions



B Actual Fit



C Model Parameters

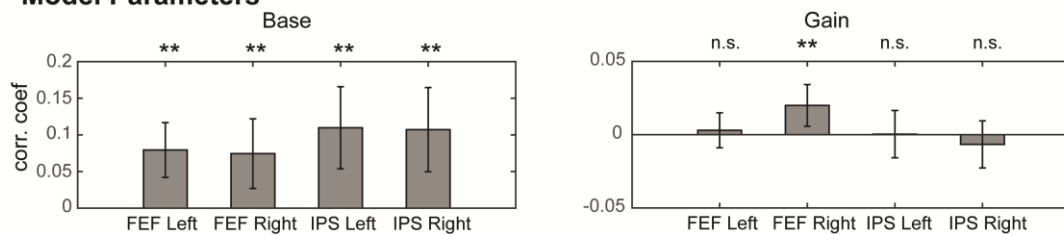


Figure 4. Additive as well as gain changes in connectivity induced by attention between DAN nodes and the visual hierarchy. (a) Schematic illustration of additive and gain modulation of connectivity by attention. Illustrated is the connectivity of a single DAN node with multiple visual nodes as a function of visual hierarchy. (b) Group connectivity fits between DAN nodes and the visual hierarchy, for passive vision and attention. Solid lines are superimposed data from figure 3, dashed lines and shaded area indicate 95% confidence interval of the fit across subjects. (c) Difference of fit parameters for gain and baseline shift between attention

and vision conditions (** $p < 0.05$, Bonferroni-Holmes corrected, * $p < 0.05$, uncorrected).
Error bars: 95% CI.

Connectivity *changes* during attention compared to vision

Having examined hierarchical connectivity separately for passive vision and attention, we next examined their difference. In analogy to attentional effects on single-cell tuning functions, we considered two independent key effects of attention, illustrated in Figure 3A. Attention could have an additive effect on existing connectivity with a given DAN node by increasing connectivity equally on each of the visual nodes, leading to a baseline shift. Independent of this, attention could amplify connectivity in a multiplicative way, so that connectivity increases as a function of existing connectivity, i.e. a gain modulation, leading to an increased slope.

To quantify both effects, we compared slopes and offsets between attention and vision for each DAN seed. Figure 4B shows group fits along with 95% confidence intervals along with the fit parameters, and Figure 4C shows the differences for slope and baseline, respectively, between passive vision and attention. For the baseline we found a significant shift for all seed regions in both hemispheres (baseline B: FEF_L=0.078, $p=2.06 \times 10^{-4}$; FEF_R= 0.073, $p=0.0050$; IPS_L = 0.108, $p=5.94 \times 10^{-4}$; IPS_R=0.106, $p=0.0011$). A gain change was observed only in right FEF (gain G: FEF_L =0.0044, $p=0.49$; FEF_R=0.023, $p=0.0043$; IPS_L = 0.0027, $p=0.75$; IPS_R = -0.0048, $p=0.589$).

Note that all of the above results were replicated when either V4, or V5/MT+, respectively, were omitted from VIS, illustrating that the somewhat arbitrary order of V4 and V5/MT+ in the current analyses did not influence the outcome (see supplemental information).

The results demonstrate a clear modulatory effect of attention on the baseline of connectivity between all DAN seeds with the visual hierarchy, and suggest a special role of right FEF that was the only region exhibiting gain effects with the visual hierarchy.

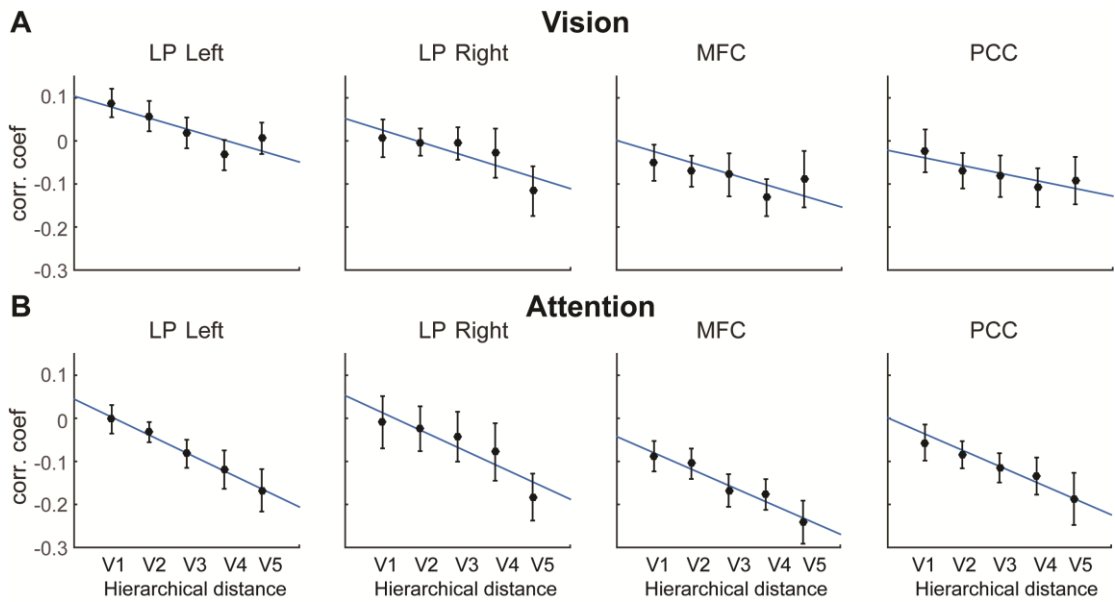


Figure 5. The relationship between the connectivity strength of a given region of the default mode network (DMN) with the hierarchical distance within the visual system. (a) Connectivity of DMN nodes with VIS during visual processing. (b) Connectivity during execution of a highly demanding attention task. LP: Lateral Parietal, MFC: Medial Frontal Cortex, PCC: Posterior Cingulate Cortex. Solid line: linear fit. Error bars: 95% CI.

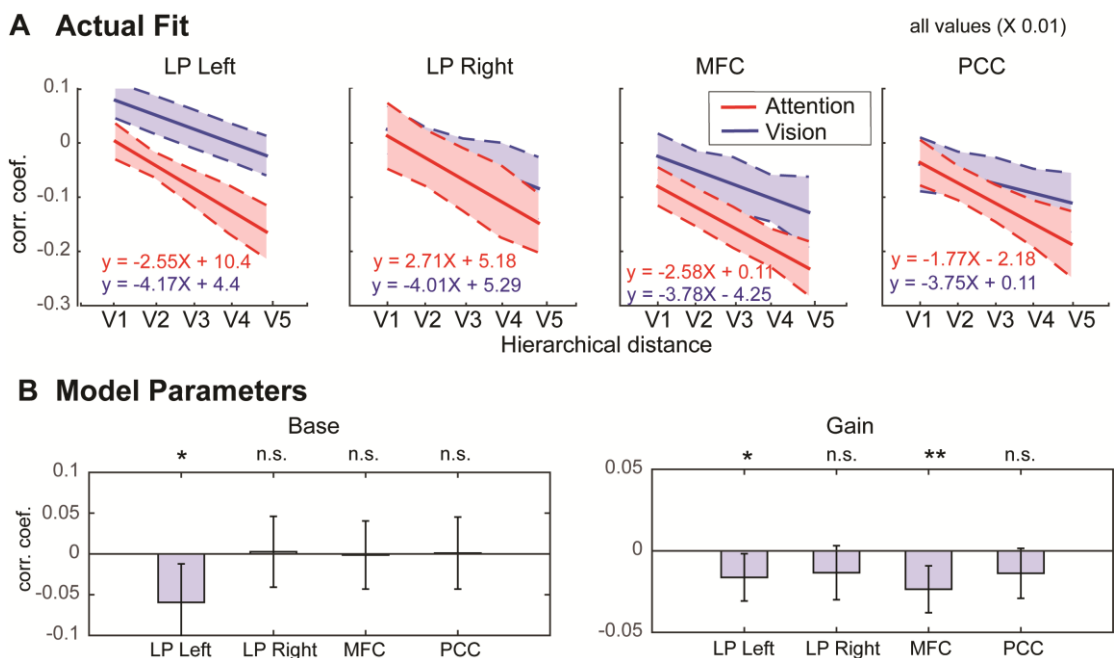


Figure 6. Additive as well as gain connectivity changes induced by attention between DMN nodes and the visual hierarchy. (a) Group connectivity fits between DMN nodes and the

visual hierarchy, for passive vision and attention. Solid lines are superimposed data from figure 5, dashed lines and shaded area indicate 95% confidence interval of the fit across subjects. (b) Difference of fit parameters for gain and baseline shift between attention and vision conditions. LP: Lateral Parietal Lobe, MFC: Medial Frontal Cortex, PCC: Posterior Cingulate Cortex (** $p < 0.05$, Bonferroni-Holmes corrected, * $p < 0.05$, uncorrected). Error bars: 95% CI.

Connectivity between DMN nodes and VIS hierarchy

While DAN is known to enhance its activity during visual attention tasks (Corbetta and Shulman, 2002), the DMN has previously been shown to decrease its activity during attention with respect to passive viewing (Raichle et al., 2001). Correspondingly, there is evidence that not only DAN actively modulates visual regions during attention (Ruff et al., 2006), but that also the DMN is directly, and inversely, related to perceptual performance (Kelly et al., 2008). We hence next extended our analysis to DMN.

Figure 5 shows that the connectivity between each node of the DMN and visual areas also reflects the visual hierarchy, but with a negative slope. This was so during passive viewing (gain G: LP_L = -0.026, $p = 1.86 * 10^{-6}$; LP_R = -0.028, $p = 8.4 * 10^{-3}$; MFC = -0.015, $p = 0.0653$; PCC = -0.018, $p = 5.4 * 10^{-3}$) as well as during the attention task (gain G: LP_L = -0.043, $p = 4.16 * 10^{-8}$; LP_R = -0.042, $p = 2.92 * 10^{-6}$; MFC = -0.039, $p = 1.55 * 10^{-6}$; PCC = -0.033, $p = 2.59 * 10^{-5}$).

Figure 6 shows the differential effects of attention modulation compared to vision on the hierarchical connectivity. The results here were overall weaker compared to those related to DAN, but nevertheless showed an overall inverted pattern with respect to gain and baseline effects: attention tended to exert negative gain modulation for every DMN node with VIS, even though not all reached significance, while only one node showed an (uncorrected) negative baseline shift.

Note again that also for the DMN the key results were replicated when either V4, or V5/MT+, respectively, were omitted from VIS, illustrating that the somewhat arbitrary order of V4 and V5/MT+ in the current analyses did not influence the outcome (see supplemental information).

Correlation between BOLD signal change and connectivity

Finally we examined whether the attentional *modulation of activity* in visual regions correlated with the *connectivity* strength between DAN and VIS (Figure 7). We found a significant correlation between activity change induced by attention in VIS with the connectivity strength of VIS nodes with DAN nodes, both for connectivity measured during visual processing (correlation: FEF_L=0.45, $p=3.73 \times 10^{-4}$; FEF_R=0.36, $p=0.0066$; IPS_L=0.73, $p=1.46 \times 10^{-7}$; IPS_R=0.66, $p=5.55 \times 10^{-6}$) and during the attention task (FEF_L=0.70, $p=2.51 \times 10^{-7}$; FEF_R=0.71, $p=6.90 \times 10^{-7}$; IPS_L=0.73, $p=5.55 \times 10^{-6}$; IPS_R=0.80, $p=1.16 \times 10^{-8}$). This result suggests that DAN connectivity towards VIS may mediate the activity change induced by attention.

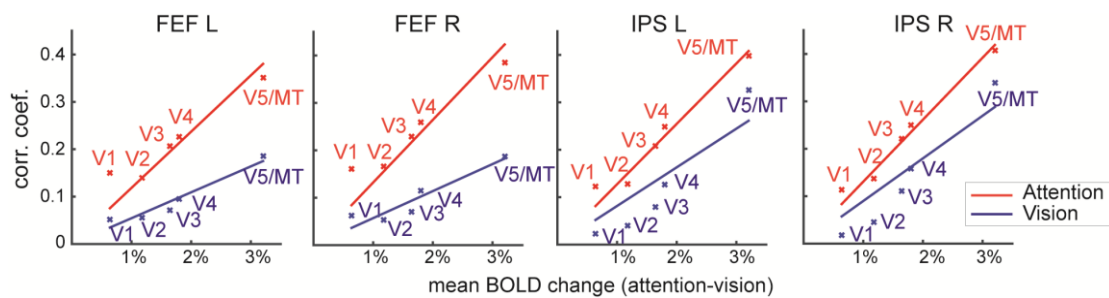


Figure 7. Correlation between activity change in VIS induced by attention with the connectivity of VIS with DAN nodes, for both, connectivity measured during passive vision (blue) and attention (red).

Discussion

We characterized functional connectivity between DAN and DMN nodes with the hierarchy of the visual system (V1-V4 and V5/MT+) as a function of attention. We used a dedicated paradigm of ultra-long trials to optimized power of the connectivity analysis, and we used precisely matched visual stimuli during passive vision and during attention to ensure a highly controlled comparison.

First, we replicated prior findings: *activity* changes induced by visual input (compared to blank) were inversely related to the visual hierarchy (strongest in V1, weakest in V4 and V5/MT+). *Activity* modulation by attention (compared to passive vision) increased with the visual hierarchy, and was thus opposite to the modulation by vision. These results were obtained using independent data of normal trial length of 20 s.

Second, we used ultra-long 2 min trial data to characterize *connectivity* across the visual hierarchy. We found that connectivity between each DAN node followed the visual hierarchy, both, during passive vision and attention: DAN had the weakest functional connectivity with V1, and increasingly higher connectivity towards V4 and V5/MT+. The task-independent connectivity structure hence closely mirrored that of the attention-induced *change in activity* along the visual hierarchy.

Next, we examined attention-related changes in connectivity. For all nodes of DAN, attention led to an additive increase in baseline connectivity. In addition, right FEF exerted a gain increase along the visual hierarchy.

Connectivity between DMN nodes and VIS had the inverse hierarchical organisation compared to DAN: DMN connectivity strength - regardless of attentional demands – was strongest with V1, and decreased towards higher-level regions. For all DMN nodes, attention tended to have negative gain effects on connectivity across the visual hierarchy, with no baseline effects except for a trend of left lateral parietal cortex.

Finally, we related *activity change* in visual regions induced by attention with *connectivity* strength to DAN nodes. It turned out that there is a strong correlation between the two measures, suggesting that DAN connectivity towards VIS may mediate the activity change induced by attention.

Our results show that there is a hierarchical structure in connectivity between the nodes of major networks and the hierarchy of early visual regions. The results suggest that attention modulates connectivity with the visual hierarchy through differential mechanisms in terms

of baseline change and gain change for DAN and DMN, respectively, and that activity changes in visual cortex are directly correlated with connectivity strength to nodes of the dorsal attention network.

Benefit of long trial design

The present study used ultra-long trials to quantify connectivity across visual regions and task positive and negative regions. Low frequency BOLD signal (<0.1Hz) has been shown to correlate particularly well with neural signal (Nir et al., 2007), and our own data demonstrated that this approach is by far more powerful to reveal functional connectivity compared to standard-length trials of around 20 s (Kwon et al., 2016). It is hence no surprise that several other studies used long-trial designs with high success to characterize connectivity-function relationships (Braun et al., 2015; Kwon et al., 2016; Spadone et al., 2015; Tambini et al., 2016).

Hierarchy

Prior studies have shown a hierarchical modulation of the neural activity in visual areas by visual stimulation: strongest enhancement in early visual areas, i.e. V1, with less modulation toward higher visual areas, such as, V4 or V5/MT (Hochstein and Ahissar, 2002; Serences and Yantis, 2006; Silver et al., 2005). Multiple studies have shown that this hierarchical modulation is reversed by attention, with the strongest attentional effects in higher-level regions and minimal effects in V1 (Greenberg et al., 2012; Hochstein and Ahissar, 2002; Serences and Yantis, 2006; Silver et al., 2005).

It has as of yet been unclear why the tendency was reversed. There are at least two possibilities that explain this modulation. First, different visual areas contain differential fractions of attention-tuned neurons, with higher visual areas having more such neurons. Electrophysiology has shown that specific subsets of neurons are modulated by attention in visual areas (Mitchell et al., 2007). Alternatively, modulatory input or connectivity could be more pronounced with higher areas. Both possibilities of course do not exclude each other. While the first possibility is difficult to examine non-invasively, the second possibility was tested in this study.

Our result of a hierarchical connectivity structure between DAN and VIS that closely mirrors the attentional *activity change*, regardless of task, clearly supports the latter hypothesis.

Anatomy points in the same direction. For example, DAN nodes have more fiber connections with higher-level visual than with early visual regions (Greenberg et al., 2012; Huerta et al.,

1987; Markov et al., 2014, 2012). Also diffusion tensor imaging in the human brain supports this evidence: fiber density between IPS and VIS followed a gradient, with weak connectedness to V1 that increased to V3 (Greenberg et al., 2012). These data still left unclear whether the same gradient would exist between FEF and VIS, and whether these gradients translated to functional connectivity, which our study shows.

Even though prior experiments examined the functional connectivity between DAN and VIS using electrophysiology (Ekstrom et al., 2008; Gregoriou et al., 2009; Saalman et al., 2007), MEG (Siegel et al., 2008), and fMRI (Bressler et al., 2008; Lauritzen et al., 2009; Spadone et al., 2015), they did not systematically quantify connectivity across the hierarchy of early visual regions. One study used Granger causality to show greater connectedness from DAN to intermediate-tier visual regions (VP and V4) compared to lower-tier regions (V1 and V2), but did not examine gradients of connectedness across the visual system, nor their modulation by attention (Bressler et al., 2008). Interestingly though, it clearly pointed to connectivity being directed top-down. A recent study examined the correlation strength as a function of retinotopic distance using fMRI, but limited their observation to visual cortex (Ryu and Lee, 2017).

Model - Gain modulation and Baseline change

Effects of attention on neural processing have for a long time been the center of interest of both computational and experimental studies. Many examined effects on tuning curves of single neurons. Attention was found to either increase the gain of selected neurons (Reynolds and Heeger, 2009; Treue and Martínez Trujillo, 1999; Treue and Maunsell, 1996) or to shift the baseline response, showing attentional enhancement of neural responses even in the absence of visual stimulation (Kastner et al., 1999; Luck et al., 1997).

In our study, we introduce the idea to apply these models to the connectivity between selected high-level nodes and the hierarchy of visual regions. The question makes sense given the pronounced gradient of connectivity across the visual hierarchy. A gain effect would imply that (a) attention acts by a mechanism that multiplies existing connectivity, or (b) that attentional effects propagate from one region (e.g. V4 or V5/MT) to the next (V3, then V2, to V1), with a loss on each step. A baseline shift on the other hand would imply that a common driver affects variability of all regions equally.

For all nodes of DAN (but not for DMN), we found clear evidence for the latter with an additional gain enhancement of right FEF with VIS. The latter could be related to

electrophysiological findings showing that the gamma oscillation synchronizes between FEF and specific cells in V4 (Gregoriou et al., 2012, 2009), whereas relatively weak connectivity was found between FEF and lower visual regions (Pooresmaeili et al., 2014). The asymmetry we found between left and right FEF in this regard fits well with asymmetry in attention, in clinical syndromes, as well as fMRI-TMS experiments that each reveal a dominant role of right-sided DAN nodes (Kastner and Ungerleider, 2000; Ruff et al., 2009a; Serences and Yantis, 2006). However, it is noteworthy that this lateralization is a population effect: for example, we have earlier found that for IPS, fMRI signal lateralization across participants varied from left-to-right dominance, and that lateralization of TMS effect sizes co-varied with it (Zaretskaya et al., 2010)

Parieto-frontal, and hemispheric differences

Another interesting observation in this study was that the gradient of connectivity across the visual network was steeper for IPS compared to FEF, regardless of task. Potentially differential roles hypothesized for frontal and parietal regions, mediating endogenously driven top-down versus bottom-up control of visual attention, respectively, may account for this (Kastner et al., 1999) In line with the present results, disruptive TMS applied over IPS, but not over FEF, also led to a gradient of activity modulation across the visual hierarchy (Ruff et al., 2008). During attention though, the gradient for right FEF also gained steepness. The latter effect could be due to endogenous attention being directed at large-scale global changes in the stimulus, that are more related to regions with larger receptive fields.

In addition to parieto-frontal differences, we found a right lateralized advantage of DAN-VIS connectivity during attention. This result mirrors that of prior attention studies showing right-dominant increases of *activity* of the DAN nodes (Corbetta and Shulman, 2002; Mesulam, 1981), and hence provides a mechanistic insight into the well-established right-hemispheric activity bias. In line with our findings, also TMS stimulation of right frontal as well as right parietal regions was associated with stronger activity modulation in visual cortex than stimulation of their left-hemispheric counterparts (Ruff et al., 2009b). Such asymmetries in activity modulation most certainly resulted from connectivity differences as observed here.

DMN connectivity

The DMN has previously not only been shown to be de-activated during attention compared to rest, but it has been shown to play a functional role during introspection, mind

wandering, or in general in self-centered tasks (Buckner et al., 2008). Typically, connectivity of most brain regions with DMN has been reported to be negative, not only during in resting state (Fox et al., 2005; Greicius et al., 2003), but also during perceptual conditions or tasks. While most studies examined connectivity across DMN and frontal parietal regions (Bray et al., 2014; DeSalvo et al., 2014; Fürtinger et al., 2015; Kelly et al., 2008; Sala-Llonch et al., 2012), some studies also examined the relationship between DMN and sensory regions (Berkovich-ohana et al., 2016; Kilpatrick et al., 2011; Lewis et al., 2009). The present study is the first to examine DMN connectivity with the different levels of hierarchy in the visual system.

The present study revealed a pronounced negative gradient of connectivity strength across the visual hierarchy for every node of DMN, regardless of task. DMN had weak or absent connectivity with V1 that turned negative towards higher visual areas. Attention tended to increase the gradient (into a more negative direction) for all DMN nodes. Considering that prior studies showed an active role of DMN with behavioral task performance (Hampson et al., 2006; Kelly et al., 2008), the present data suggest that the behavioral link of DMN could be mediated not only through its interactions with DAN, but also by changing connectivity between DMN and primarily higher-level regions of the visual system.

Together, our results imply that attention changes activity in visual regions not only by increased connectivity to DAN, but that changes in VIS are the product of influences from both, DAN and DMN that each exhibit differential hierarchical connectivity on visual cortex.

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Feature-based attention changes connectivity in competitive and cooperative manner

Abbreviated title: Functional connectivity in feature based attention

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Conflict of Interest

The authors declare no competing financial interests.

Abstract

Prior studies found that brain is segregated into multiple network; default mode network (DMN) correlated with other DMN and dorsal attention network (DAN) correlated with other DAN and these two networks anticorrelated. This segregated connectivity structure was observed in resting-state that includes slow fluctuation ($<0.1\text{Hz}$) of the BOLD. However, it is not examined whether brain segregation is observed in visual processing and changes by tasks. Prior studies have conducted functional connectivity, yet their examination was performed in traditional short trial that excludes slow fluctuation fMRI ($<0.1\text{Hz}$) fluctuation. Here introduced an ultra-long trial block design (3mins) to include the slow oscillation as well as introduced a mean signal regressing out from all brain regions. By applying such methods, we examined whether visual region correlated differentially with other regions. Interestingly, we found that visual region (V4 or V5/MT) positively correlated with large portions in DAN and other visual regions with connections of visual to parietal regions. More interestingly, the visual region negatively correlated with large portions in DMN (MFC, PCC, LP) and connection between MFC and PCC. Moreover, we observed that this correlation structure is selective depending on its feature-based attention, so that paying attention to color than motion enhances the connectivity to DAN and V4, more than DAN and V5/MT. Surprisingly, the selective connectivity was observed also across DMN and visual region, but negatively. Our result show not only visual region selectively excites together with DAN but it selectively inhibits with DMN, that suggest potential inhibitory role of DMN in attention task.

Introduction

Top-down attention enhances neural responses in the dorsal attention network (DAN), FEF and IPS. Besides, the visual areas also enhance the activation depending on the attended location or feature. For instance, face or scene attention enhances neural responses in visual regions responsive for the attended feature, FFA or PPA, respectively.

While attention selectively modulates the visual region, the underlying mechanism is still not clear. Few studies approached this issue by examining the connectivity between DAN and visual region. Monkey studies showed gamma synchronization across DAN and high-visual region, e.g, FEF and V4 (Gregoriou et al., 2009) or LIP and V5 (Saalmann et al., 2007), with corresponding MEG findings across DAN and V5/MT+ (Siegel et al., 2008). In slow time scale, fMRI studies revealed functional connectivity enhancement across DAN and VIS (Spadone et al., 2015; Kwon et al., 2016). Although these studies showed the connection between DAN and VIS, yet it is unclear whether the synchronization is selective to the attended visual regions. Some approached the selective synchronization of feature-based attention, but their observation was either limited to visual region (Al-Aidroos et al., 2012) or visual region with IFG, outside of the typical attention network (Baldauf and Desimone, 2014).

In contrast to enhanced activity of DAN and VIS during attention, the DMN reduces its activity during attention compared to rest or passive viewing or mind wandering. However, growing evidences showed that DMN involves with memory consolidation (Kaplan et al., 2016) or its connectivity with task positive network in different cognition tasks (Kelly et al., 2008). Few studies even showed the connectivity across DMN and TPN relates with the behavior (Sala-Llonch et al., 2012). Although these studies showed a possible role of DMN during cognitive tasks, to our knowledge, no study examined whether DMN interact with sensory region selectively depending on the attended feature.

Here we hypothesized that feature based attention selectively changes the synchronization across network. Paying attention to color may enhance connectivity between DAN and V4, whereas motion attention to increase the DAN and V5/MT connection. Not only DAN will selectively toggle with visual regions, but also DMN will selectively change the connectivity with visual regions. The functional connectivity between DMN and V4 may decrease by color attention, while the connection between DMN and V5/MT reduce by motion attention. We used an ultra-long block (Kwon et al., 2016), and examined its correlation structure between visual region and other regions in general. Then we examined how the correlation structure modulates by different feature-based attention,

during color, motion and no attention condition. By showing selective synchronization across visual region and DAN, DMN, we may be able to explain how the visual region modulates its activity by attention. Moreover, if DMN plays an important role in attention as an inhibitory interaction, we can examine its role in other cognitive tasks, not only in fMRI, but also with electrophysiology as well.

Result

V4 connectivity: seed vs whole brain

Connectivity in all conditions

First, we asked even the visual region (V4) segregate the brain into parts regardless of conditions (color/motion/no attention) by using seed-to-whole brain connectivity. As illustrated in Fig. 1a, we observed that some regions are positively and others are negatively connected with V4, indicating visual region V4 segregate the regions in a structural manner. More interestingly, the positive and negative correlation depends on whether the network typically shows positive or negative mean response to task even with mean-regressed out connectivity. Positive correlation was observed in network that is typically enhanced by task, task-positive network that includes IPS, FEF and visual region with surrounding of these networks. In contrast, negative correlation was observed in default mode network that includes LP and MFC/PCC. This structural connectivity extends the previous structural connectivity that segregates only the DAN and DMN in resting-state (Fox et al., 2005) to the TPN and DMN in task conditions.

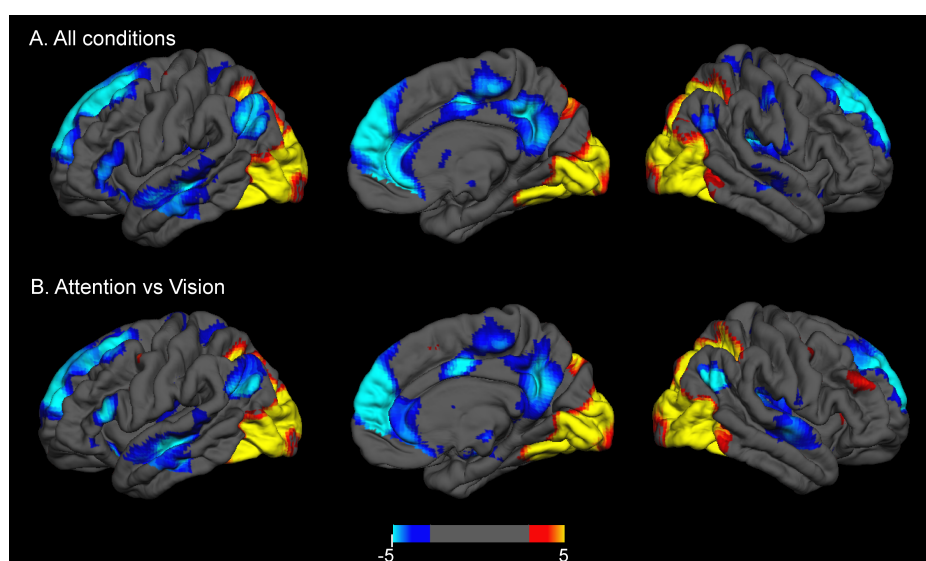


Figure 1. FC between V4 and all other voxels in the brain in (a) all conditions and (b) during attention compared to no attention. Most of the task positive networks (IPS, VIS) and connecting those networks are positively connected to V4, whereas default mode networks (LP, PCC/MFC) and connecting those networks are negatively connected to V4. T map ($p < 0.05$, FDR corrected)

Connectivity in attention compared to no attention

We then examined whether this connectivity structure differs depending on the attentional load (Fig 1b). By comparing the attention to no attention, we observed the positive correlation between V4 and DAN/VIS and negative correlation between V4 and DMN, which is basically similar to the results regardless of condition results (Fig 1a). This indicates paying attention enhances the segregation of TPN and DMN with V4 even more.

V4 connectivity: seed-vs-seed

V4 vs DAN (FEF, IPS): positive connectivity

Seed-to-whole brain connectivity led us to observe segregated connectivity structure in few networks. We then focused the examination in those networks (DAN, DMN) by traditional seed-to-seed connectivity. The FEF positively correlated with V4 during all conditions ($C_{\text{FEF-V4, color}} = 0.23$, $p < 0.001$; $C_{\text{FEF-V4, motion}} = 0.22$, $p < 0.001$; $C_{\text{FEF-V4, no}} = 0.085$, $p = 0.002$). IPS also had similar connectivity trend with V4 as in with FEF-V4 ($C_{\text{IPS-V4, color}} = 0.24$, $p < 0.001$; $C_{\text{IPS-V4, motion}} = 0.19$, $p < 0.001$; $C_{\text{IPS-V4, no}} = 0.077$, $p = 0.011$). Enhanced positive correlation was observed in any attention condition than no attention in both connections ($p_{\text{FEF-V4, color-no}} < 0.001$, $p_{\text{FEF-V4, motion-no}} < 0.001$). Feature-specific effect showed no difference in connectivity strength in these connections ($p_{\text{FEF-V4, color-motion}} < 0.001$, $p_{\text{IPS-V4, color-motion}} < 0.001$).

In summary, V4 showed stronger positive connectivity with DAN (FEF, IPS) in any attention condition than no attention, indicating the enhanced communication in the dorsal attentional pathway.

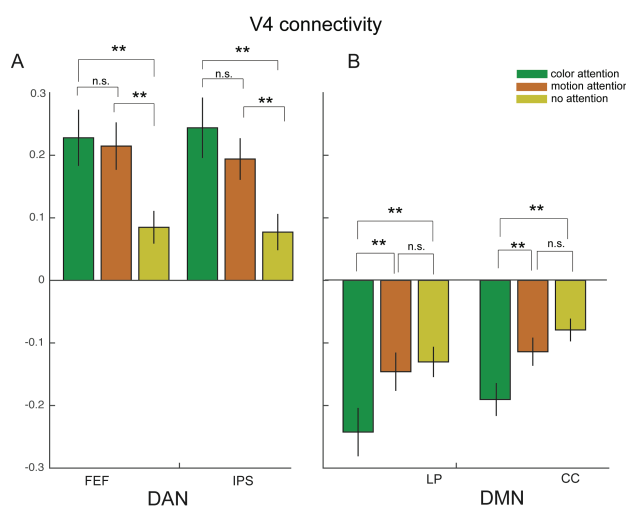


Figure 2. V4 connectivity as seed vs seed. (a) Connectivity between V4 vs DAN is positive connected, whereas (b) connectivity between V4 vs DMN is negatively connected during color, motion and no attention ($p < 0.05$, FDR corrected)

V4 vs DMN (LP, MFC, PCC): negative connectivity

In the seed-to-whole brain connectivity, the positive connectivity was observed with V4, but surprisingly negative connectivity with regions mostly in DMN. The LP negatively correlated with V4 during all conditions ($c_{LP-V4, color} = -0.24$, $p < 0.001$; $c_{LP-V4, motion} = -0.15$, $p < 0.001$; $c_{LP-V4, no} = -0.13$, $p < 0.001$). Both MFC/PCC also had similar connectivity trend with V4 as shown in LP-V4 connection ($c_{CC-V4, color} = -0.19$, $p < 0.001$; $c_{FEF-V4, motion} = -0.11$, $p < 0.001$; $c_{FEF-V4, no} = -0.079$, $p < 0.001$). Also in this negativity connectivity strength was enhanced during color than no attention ($p_{LP-V4, color-no} < 0.001$, $p_{CC-V4, color-no} < 0.001$), but not during motion than no attention ($p_{LP-V4, motion-no} = 0.53$, $p_{CC-V4, motion-no} = 0.17$). This result indicates that color attention inhibits more between V4 and DMN, but not more in motion attention. Color than motion attention also showed enhanced negativity in these connections ($p_{LP-V4, color-no} = 0.0038$, $p_{CC-V4, color-no} < 0.001$).

In summary, V4 showed not only positivity with DAN, but also negativity with DMN that is generally enhanced in attention, especially in color attention. The current result is in line with prior study showing negative connection between visual region and DMN in general (Kwon et al., 2016), and extended the finding into different feature-based attention.

V5/MT connectivity: seed vs whole brain

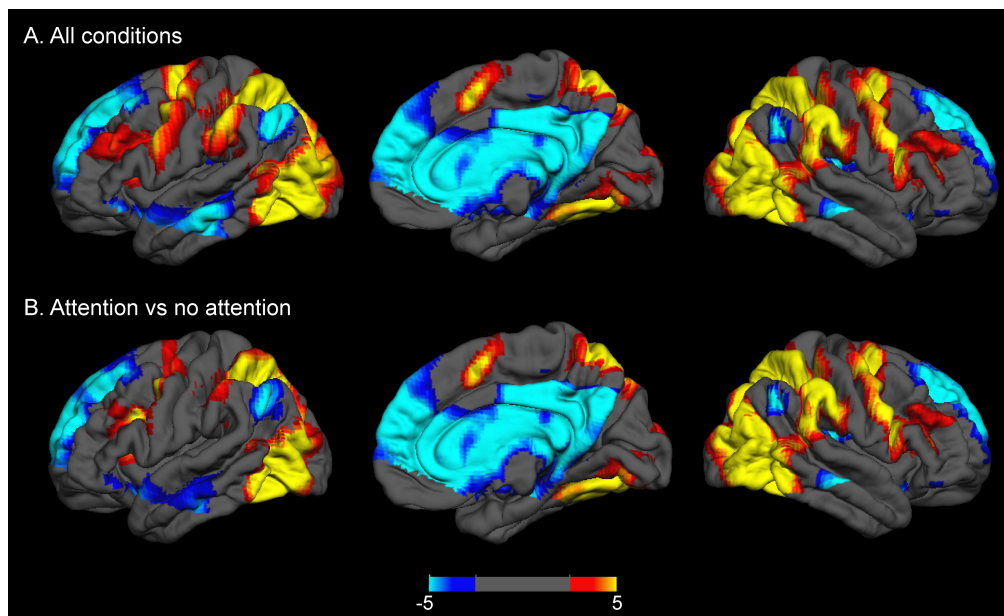


Figure 3. FC between seed region of V5/MT and all other voxels in the brain (a) in all conditions ($p < 0.05$, FDR corrected), (B) during attention compared to no attention

Connectivity in all conditions

Next, we examined the same FC map, but with seed region of V5/MT. According to the seed (V5/MT) to whole brain connectivity pattern, a similar correlation structure was observed with that of V4 seed. As shown in V4 connectivity, V5/MT also positively correlated with TPN and negatively correlated with DMN and its surroundings. In case for V5/MT, V5/MT was correlated to larger portion of FEF and V5/MT connection towards IPS ventrally also positively correlated.

Connectivity in attention compared to no attention

When this connectivity structure difference was observed depending on the attentional load (Fig 3b), we again observed similar connectivity structure shown in connectivity from regardless of conditions (Fig 3a). This indicates paying attention enhances the segregation of TPN and DMN with V5/MT even more as well.

V5/MT connectivity: seed-vs-seed

V5/MT vs DAN (FEF, IPS): positive connectivity

Seed-to-whole brain connectivity led us to observe segregated connectivity structure in connection with V5/MT as observed with V4. We again conducted the seed-to-seed connectivity focused on those networks (DAN, DMN). As similar to connectivity with V4, V5/MT positively correlated with FEF during all conditions ($c_{\text{FEF-V5/MT, color}}=0.32$, $p<0.001$; $c_{\text{FEF-V5/MT, motion}}=0.41$, $p<0.001$; $c_{\text{FEF-V5/MT, no}}=0.25$, $p<0.001$). The IPS also had similar correlation trend ($c_{\text{IPS-V5/MT, color}}=0.31$, $p<0.001$; $c_{\text{IPS-V5/MT, motion}}=0.34$, $p<0.001$; $c_{\text{IPS-V5/MT, no}}=0.27$, $p<0.001$). Enhanced positive correlation was observed in motion than no attention in connectivity between FEF and V5/MT. In summary, V5/MT showed stronger positive connectivity with DAN, especially more on the connection with FEF.

V5/MT vs DMN (LP, MFC/PCC): negative connectivity

While V5/MT positively correlated with DAN, it negatively correlated with large portions in DMN. We focused on this specific connection and observed that LP negatively correlated with V5/MT in all conditions ($c_{\text{LP-V5/MT, color}}=-0.15$, $p<0.001$; $c_{\text{LP-V5/MT, motion}}=-0.19$, $p<0.001$; $c_{\text{LP-V5/MT, no}}=-0.11$, $p=0.002$). Both MFC/PCC had negative correlation with V5/MT in all conditions as well ($c_{\text{CC-V5/MT, color}}=-0.15$, $p=0.001$; $c_{\text{CC-V5/MT, motion}}=-0.19$, $p<0.001$; $c_{\text{CC-V5/MT, no}}=-0.088$, $p<0.001$). Also in this negative connection, connectivity strength was enhanced during motion than no attention ($p_{\text{LP-V5/MT, motion-no}}=0.015$, $p_{\text{CC-V5/MT, motion-no}}=0.005$) and tends to

enhance during color than no attention ($p_{LP-V5/MT, color-no}=0.042$, $p_{CC-V5/MT, color-no}=0.03$). Feature-based attention, color versus motion attention, did not show difference in their negativity strength between any of these connections ($p_{LP-V5/MT, color-motion}=0.17$, $p_{CC-V5/MT, motion-no}=0.15$).

Not only V4 and DMN, but also V5/MT and DMN also negatively correlated and its strength is enhanced by motion attention, indicating the selective negative correlation in feature-based attention.

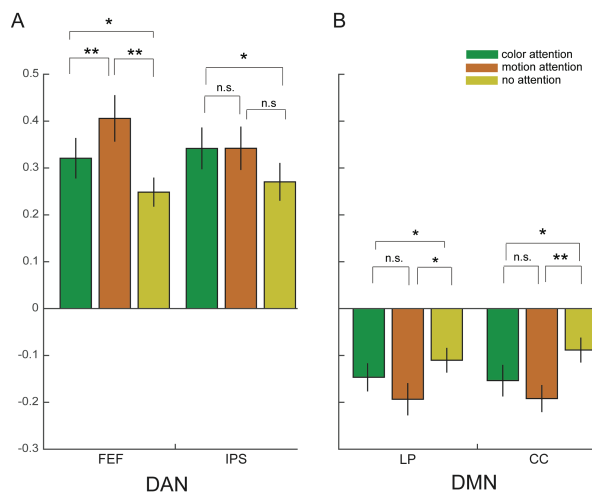


Figure 4. V5/MT connectivity as seed vs seed. (a) Connectivity between V5/MT vs DAN is positively connected, whereas (b) connectivity between V5/MT vs DMN is negatively connected during color, motion and no attention ($p < 0.05$, FDR corrected)

V4 and V5/MT comparison

Seed-to-whole connectivity: V4 vs whole – V5/MT vs whole

V4 and V5/MT showed similar, but slightly different connectivity structure with the whole brain. Therefore, we examined whether different visual regions connect with different networks. As shown in Fig 5a, we compared the V4 versus V5/MT connects to the whole brain regardless of conditions, thus positive connection indicates stronger connection to V4 and negative connection reflects stronger to V5/MT. Interestingly, these two regions differentially connected, in frontal regions and parietal regions for V5/MT and more on the subcortical structures connects with V4 as well as early visual regions. This structural connectivity is enhanced in attention than no attention, as illustrated in Fig 5b.

Interestingly, when we compared this connectivity depending on the feature, the different connectivity structure was observed (Fig 5c). Color compared to motion attention enhances the connectivity in part of DAN (FEF and rIPS) and reduces the connectivity in DMN (MFC, PCC and LPs) in V4 than V5/MT connection.

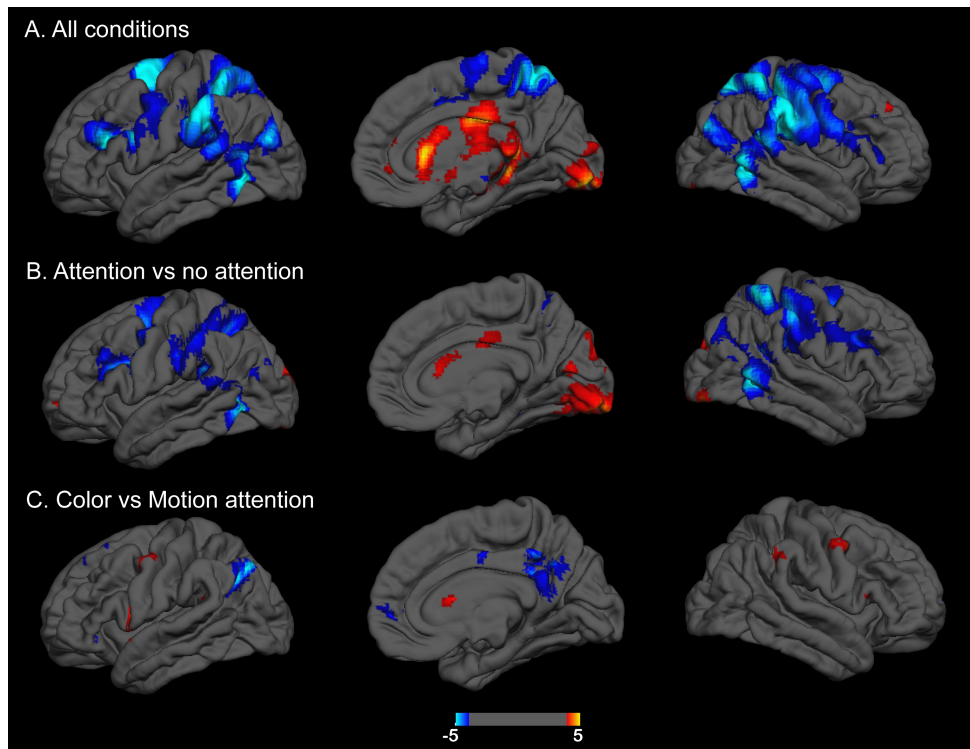


Figure 5. FC map between seed region with V4 versus whole brain and V5/MT in (a) all conditions, (b) during attention compared to no attention and (c) color compared to motion attention condition. T map ($p < 0.001$, uncorrected)

Seed-to-seed connectivity: color versus motion attention (V4 – V5)

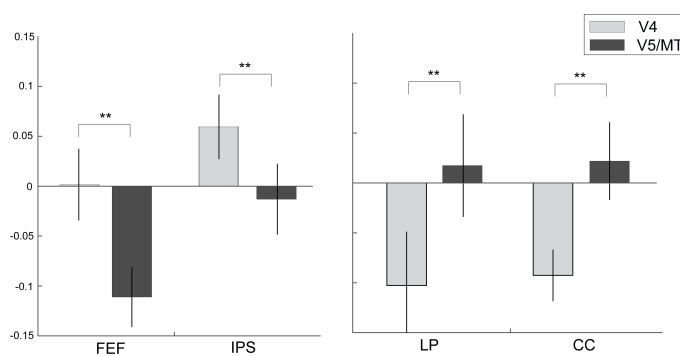


Figure 6. Color versus motion attention. (a) Connectivity between DAN and V4 or V5/MT (b) connectivity between DMN and V4 or V5/MT ($p < 0.05$, FDR corrected)

Since we observed a DAN and DMN segregation by V4 and V5/MT connectivity, we address this question in seed-based analysis more in detail. Thus, if paying attention to color than motion connects the DAN to V4 more than to V5/MT Interestingly, it was very clear that FEF strongly correlated with V4 more than with V5/MT during color versus motion attention. Similar observation with IPS as well (all $p < 0.001$). More interestingly, the LP strongly negatively correlated with V4 more than V5/MT during color versus motion attention with corresponding similar results from CC as well (all $p < 0.001$). This result indicates that DAN

selectively connects with visual regions, as well as DMN selectively negatively connects with visual regions depending on the feature-based attention.

Discussion

Correlation structure

Our current results illustrate that visual region activate/deactivate with TPN and DMN selectively in attention task. Prior studies showed the segregation of DAN and DMN in resting human brain (Fox et al., 2005). We extended this result that the segregation is not limited to DAN and DMN, but more to visual region and DAN segregate with DMN in more active state. The previous segregated brain structure was observed in seed-to-whole brain connectivity analysis, but typically performed in short-trial block design that excludes the slow fMRI fluctuation connectivity. We used an ultra-long trial block design (3mins) that led us to detect high quality connectivity (Kwon et al., 2016) as well as regressed out the mean signal from the original fMRI signal in all the brain regions. In the current study, V4 positively correlated with IPS and FEF, while negatively correlated with LP, MFC and PCC and connection between MFC and PCC. A similar correlation structure was observed with V5 and all other regions.

Feature-specific correlation dichotomy

Second prominent observation is the correlation structure observed in feature-specific attention. During color attention compared to motion attention, V4 selectively correlated positively with IPS, FEF, whereas it decorrelated with PCC, MFC, and bilateral LP. Our observation will open up a new approach on seed versus whole brain connectivity in sensory processing or cognitive tasks. One previous study showed selective connectivity by feature-based attention, but they showed a selective connectivity with V4 and higher visual regions (Al-Aidroos et al., 2012). Some EEG or MEG studies also show a selective connectivity across visual region and higher area, such as inferior frontal junction (Baldauf and Desimone, 2014) or somatosensory area and inferior frontal cortex (Sacchet et al., 2015). But, these regions do not show whether one of the major region in top-down attention, DAN and visual region interact selectively.

Few studies also showed the synchronization across DAN and visual regions during attention indicating that communication between these regions are strengthened by attention (Saalmann et al., 2007; Bressler et al., 2008; Gregoriou et al., 2009; Spadone et al., 2015;

Kwon et al., 2016) without showing selective synchronization. In our study, we showed that DAN and VIS selectively connects, e.g., attention to color, positively connects the DAN and V4, whereas attention to motion positively connects the DAN and V5/MT. This indicates that an active role of DAN in selective attention, that toggles the relevant feature area active as well.

DMN involved in selective Attention

More interestingly, we observed selective interaction of visual region and DMN. Traditionally, DMN is known to involved in resting-state conditions. But growing evidences showed that DMN is involved in tasks, such that a region in DMN is correlated with working memory performance (Sala-Llonch et al., 2012). Our previous study also showed that attention enhances the existing decorrelation between DMN and VIS. Yet these studies did not show a more specific role of DMN, such that depending on the attended feature, that DMN selectively inhibits with VIS. A previous study showed that hippocampal ripples influence selective activation of DMN, suggesting important role for episodic memory (Kaplan 2016). In our study, we show an important role for selective attention that may control the visual region activation, in inhibitory manner. By examining its electrophysiological recordings with DMN and VIS, we may understand the selective visual attention that was not shown in the synchronization between DAN and VIS.

New fMRI connectivity methods: seed-to-whole connectivity

The long trial fMRI design led us to detect the synchronization across regions that includes slow fluctuation of the fMRI (<0.1Hz). Previously, few studies examined the origin of resting-state fluctuation combining with electrophysiological recording and showed that two signals are correlated. Moreover, many resting-state studies typically examined the BOLD with slow fluctuation included, it is surprisingly task studies to examine the fluctuation connectivity did not obtained data with long trial block design. Although long trial continuous task may induce drowsing and dropping performance, it still has strong benefit of obtaining slow fluctuation. Moreover, our method cautiously considered the origin of fMRI, that needs to regress out the mean signal in examining its correlation across regions. As a result, we observed the visual region coactivate/deactivate regions depending on its function in structural way. Our study can be extended to other cognitive tasks, such as memory, decision-making or fear perception. We may observe the synchronization across regions that

were previously not detected by short trial that is optimal to detect mean fMRI signal change.

Methods

Subjects

17 (22-37 years old, 7 females) healthy participants participated in the study. All subjects provided informed consent and the study protocol was approved by the joint ethics committee of the university clinics and the Max Planck Institute.

Main experimental design and task

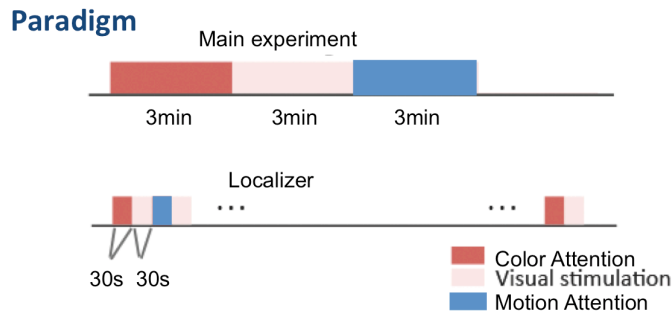
We conducted two experiments, one with short trials of 30s length to localize regions of interest, and one with long trials of 180s length, with otherwise identical parameters and conditions. Both experiments had the same three experimental conditions: color attention, motion attention and passive viewing condition. The visual stimulus was identical and central fixation was required in all conditions.

The visual stimulus consisted of a random colored dot-field moving with a spiral-like motion, changing its two different features - color and motion - simultaneously and independently at 1 Hz (see Figure 1). Each feature had four possible states. The four possible colors were: (1) red, (2) green, (3) cyan or (4) purple. The four possible dot field motion types were: (1) clockwise outward (CWOW), (2) clockwise inward (CWIW), (3) counterclockwise outward (CCWOW) and (4) counterclockwise inward (CCWIW). Each dot-field consisted of 300 colored dots on a black background. The dots were randomly positioned within an annulus that extended to the edge of the screen (10 deg eccentricity). Their rotation speed around the center was three degrees per second, and their contraction/expansion speed was also 3 deg/s. The size of the dots ranged from 0.35 to 0.71 degrees. The resolution of monitor was 1280 X 1024 pixels with refresh rate of 75 Hz. All stimuli were presented on Windows XP (64bit) generated by Psychtoolbox (3.0.8).

Prior to scanning, each subject participated in a psychophysics session to determine the visual noise level to match the difficulty constant across conditions. This was achieved by adjusting the ratio of target to distractor dots: for motion attention, CWOW versus other dots ratio were modulated; for color attention, red versus other colored dots ratio were

modulated. All four colours were set to isoluminance using the minimum flicker techniques inside the scanner for each subject individually prior to scanning.

Stimulus Design and Attention Task



Stimuli

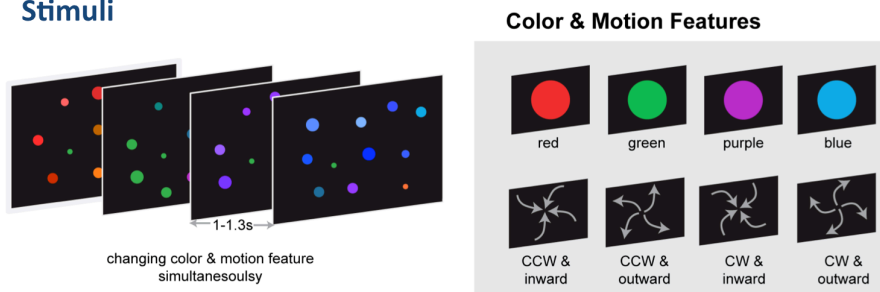


Figure 1. Stimulus presentation and design. (a) Each stimulus presentation consisted of four random-dot-fields superimposed on to each other, each presented in one of the four possible colors and moving with one of the four motion types on a black background. One of the fields contained more dots than the others, and was attended by the subject. The other three fields served as noise in the background to modulate task difficulty. Subjects had to indicate the appearance of the target color 'red' in the 'color attention' condition and a clockwise-outward motion of the dot-field in the 'motion attention' condition via a button press while fixating at the center of the screen. Stimuli were altered every one second for the duration of the whole trial. (b) The inward/outward motion direction in a counterclockwise/clockwise fashion resulted in our four motion types: (1) clockwise-outward, (2) clockwise-inward, (3) counterclockwise-outward, (4) counterclockwise-inward. (c) Each dot-cloud was presented in one of four colors: (1) red, (2) purple, (3) cyan, (4) green, all four corrected for isoluminance.

Region of Interest (ROI) definition

Regions of interest (ROIs) were defined for the dorsal attention network (DAN), default mode network (DMN) and visual region in V4 and V5/MT. The DAN includes FEF and IPS, DMN consists of MFC, PCC and bilateral LP. The ROIs were defined from a short run localizer experiment, contrasting attention versus visual stimulation for the DAN and DMN. The visual regions were defined from the same experiment, but contrasting color attention versus motion attention for V4, contrasting motion attention versus color attention for V5/MT. If not detectable, contrasting attention versus visual stimulation was used to define visual region as well. We used individually varying p-values for each participant and ROI in order to maintain comparable ROI sizes across participants.

Functional connectivity analysis

The mean signal was regressed out from the original BOLD signal averaged across trials. To avoid possible residual errors, we used time course between 20-180s that is free of task-induced transient. Data of each participant were then subjected to a regression analysis in which 6 realignment parameters were regressed out to remove global confounds. In addition, white matter signal of each volume was regressed out to removal global signal fluctuations induced by scanner (Desjardins et al., 2001; Van Dijk et al., 2010)

The initial period time that may include residual error (20s) was excluded; only time window (20-180s) was used for correlation analysis. For the seed-to-whole brain connectivity, all signals in the ROI was averaged, then this signal was correlated with all other regions in the brain. For the seed-to-seed brain connectivity, all signals in the ROI were averaged, which was correlated with other averaged ROI signal as well.

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Summary and Conclusion

The three experiments reported here investigated the neural mechanism of visual attention using fMRI connectivity. Previously, many studies examined this question, but typically used the short trial block (-20s) design that excluded the slow fMRI fluctuation ($<0.1\text{Hz}$) that carried important connectivity structure in resting brain. Even though slow fMRI fluctuation was observed to detect FC change by task, those studies did not control for the visual stimulation in their observation. Therefore, in all experiments here, we used the ultra-long block (2-3mins) that enabled us to detect the brain-wide connectivity change, during various attention tasks.

Initially, we examined the attentional FC during attention task and visually matched control condition in ultra-long block fMRI design (2mins). Prominent observation was found in its connectivity strength during long block (2mins) which had nearly two-fold FC strength over traditional short trial (20s). Besides, existing FC pattern during visual processing were modulated by attention, such that attention enhanced the positive connectivity between DAN and VIS, and decreases negative connectivity between DMN and VIS/DAN. Interestingly, attention not only enhanced the FC, but attention decreased the existing positive connectivity within VIS. More interestingly, the positive connectivity between DAN and VIS was attributed more by slow fluctuation (0.05-0.2Hz), whereas the decorrelation within VIS was contributed exclusively by fast FC fluctuation (0-0.05Hz). The results suggest that attention modulate the FC in frequency specific manner.

The next experiment examined the effects of attention on FC on hierarchy of visual areas V1-V5/MT. We found that connectivity between DAN and visual area is hierarchical, such that DAN connects strongest with high visual area V5/MT and decreases gradually towards the low visual area, V1. A reverse connection was found between the default mode network and visual network, showing DMN connects negatively strongest with high visual area V5/MT that decreases its negative strength towards low visual area. Another prominent finding was observed by implementing general linear model (GLM) in comparing the connectivity strength between attention and passive processing that demonstrated multiplicative and additive modulation by attention.

The last experiment examined the FC effect in seed-to-whole brain basis and observed the FC in feature-based attention, whether specific visual area (V4, V5/MT) correlate to the other brain region in different attention condition (color, motion). Interestingly, we found that visual regions showed segregated connectivity structure with DAN and DMN. The segregation was observed in structural way, that the visual regions (V4,

V5/MT) are positively connected with DAN and connecting regions between visual regions and DAN, whereas negative connection was observed with DMN and connecting regions in DMN. More interestingly, depending on its attended feature, the connection between DAN and visual regions were specific, such that color compared to motion attention enhances the connectivity between DAN and V4 more than the connectivity between DAN and V5/MT.

We used an ultra-long trial (2-3mins) fMRI design that detected strong FC change in attention task. The frequency dependent FC is only available by long trial, since the low frequency BOLD ($<0.05\text{Hz}$) is detected by long trial. The seed-to-whole brain FC was typically more studied in resting-state, and rarely during tasks. The long trial block also enabled us to detect such a FC change in structural manner. Although the neurophysiological meaning of the slow frequency BOLD ($<0.05\text{Hz}$) has to be still investigated, the low frequency BOLD is largely studied in resting-state, and few attempted has been conducted to study its relationship with physiology. Overall, studying the FC with long trial (2-3mins) brought us meaningful results in understanding the connections across whole human brain. This can be extended to other cognitive tasks, such as memory tasks, decision making as well as social cognition tasks.

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