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DISSERTATION

Insights into Brain Networks from Functional MRI and Graph Analysis during and following Attentional Demand

von

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Summary

The current thesis is based on three manuscripts of studies that dealt with the question of how the challenge of a demanding attentional task is mediated by brain networks *during* the task and how task demand can impact on functional organization of the brain network *following* the task. Further, the third study investigated the role of long-term nicotine consumption as a potential modulator for intrinsic brain networks. The data basis of all studies use functional MRI data acquired from healthy human subjects before, during and following an attentional task.

Within study I we investigated the effects of sustained attention on neural correlates in the human brain. Subjects performed a 32 minutes lasting vigilance task in the MR scanner and neural networks involved in sensory processing and arousal were investigated with respect to long and short periods of vigilance. Neural changes of a long period of vigilance were revealed by investigation of linear changes in neural activity over the whole task period (time on task). Widespread brain regions, especially involved in top-down modulation of attentional processing, were found to decrease in activity with ongoing time on task. Lowered activity in e.g. the posterior parietal cortex and the inferior frontal gyrus pointed to reduced top-down modulation of the attentional system towards the end of the task, which was in line with the behavioural findings of increased reaction times and reduced attentional performance in the subjects with ongoing time on task. Shorter periods of vigilance were investigated as a function of increasing time spans between the target events during the task. Several brain regions, such as the anterior cingulate cortex and esp. in subcortical regions such as the basal forebrain, the thalamus, the nucleus accumbens and the ventral tegmental area showed an increase in activity when the time span between target events was longer. A multivariate partial least squares analysis was further used to relate this activity pattern to task irrelevant motion processing during the task. The irrelevant motion processing was evoked by alternately moving and stationary dots (in cycles of 24 seconds) presented in flanker windows in the periphery which were instructed to be ignored by the subjects. The multivariate analysis yielded to answer the question whether the level of activation strength in the regions, which were recruited as a function of increasing time span between the target events, can predict the activation strength in regions that process the irrelevant motion information, area MT. The result allowed segregating these brain regions into to two functionally different networks. One group of regions, which positively correlated with the activity level in area MT, was attributed to a network involved in mediation of sensory arousal; another group of regions, which showed a negative correlation to area MT activity, was assigned to a network that mediates motivation and expectation. In summary, study I revealed different neural networks involved in mediating vigilance situations, distinct in aspects of the time period (long vs. short) and in their functional role for sensory processing.

Study II extended the scope of study I in two points: First, the effects of attentional demand on brain networks in a time window of 12 minutes following task performance were investigated. Second, by using resting state activity and a graph analytical approach, the spatial scale was increased from few, task relevant brain regions to effects on the whole brain network configuration. Resting state data before and following the vigilance task of study I was acquired and subjected to graph analysis. Measures of functional connectivity strength and network measures of global efficiency, clustering and physical distances between connected brain regions were compared between the particular resting state data sets. Main finding of study II was that task performance led to long lasting changes in brain network configuration, reflected by lowered efficiency, shorter communication path ways (physical distances) and higher clustering values. Further, in the late period of the resting state data (6-12 minutes post-task) only subjects that showed better performance within the task, respectively that were more resilient towards the demand of the task, showed recovery in these network parameters. Especially functional connectivity strength and clustering values in these subjects began to recover (approaching values as before the task has started) and showed a correlation with individual performance. These results demonstrated that intrinsic brain networks can be manipulated by task performance and that previous task demands can impact brain function for a prolonged time (up to 12 minutes). Further, the finding that some network attributes such as efficiency and clustering show performance related recovery processes point to the use of these graph metrics as biomarkers for cognitive resilience.

In study III, the same graph analytical approach was used to compare resting state data (before a task) of a group of non-smokers with a group of smokers. Goal was to identify whether smoking status, respectively long-term cigarette consumption, is a potential modulator for intrinsic brain network configuration. An existing theory about a reason of smoking as a form of self-medication for attentional deficits suggests that intrinsic network configuration in smokers might show altered – for attentional processes not beneficial – network attributes. The derived graph metrics were compared with standard test statistics, measures of effect sizes and non-inferiority testing. The results showed that smokers' brains show no significant differences in network attributes as efficiency, physical distances or clustering as compared to brains of never smokers. Comparing the measures of effect sizes and non-inferiority testing further revealed that these attributes were comparable between smokers and non-smokers and that smokers do not show reduced efficiency or higher clustering in many brain regions as compared to non-smokers. The findings of study III confirm that smoking status is unlikely to be a bias for graph analytical investigations of intrinsic brain activity.

Zusammenfassung

Die vorliegende Dissertation basiert auf drei Manuskripten von Studien, die sich mit der Frage beschäftigten, wie die Bewältigung einer Aufmerksamkeitsaufgabe von Netzwerken des Gehirns *während* der Aufgabe reguliert wird und wie die Anforderung der Aufgabe die funktionelle Organisation des Gehirnnetzwerks *im Anschluss* an die Aufgabe beeinflussen kann. Desweiteren untersuchte die dritte Studie die Rolle von Langzeit-Nikotinkonsum als möglichen Einfluss für intrinsische Gehirnnetzwerke. Die Datenbasis für alle Studien bilden funktionelle MRT Daten, die von gesunden Probanden vor, während und nach einer Aufmerksamkeitsaufgabe gemessen wurden.

In Studie I haben wir die Auswirkung von konstanter Aufmerksamkeitsleistung auf neuronale Korrelate des menschlichen Gehirns untersucht. Die Probanden absolvierten eine 32 Minuten andauernde Vigilanzaufgabe im MR-Scanner und Gehirnnetzwerke, die an sensorischer Verarbeitung und Arousal beteiligt sind, wurden in Bezug auf lange und kurze Zeitspannen von Vigilanz untersucht. Neuronale Veränderungen im Hinblick auf eine lange Zeitspanne von Vigilanz wurden mit linearen Veränderungen im Grad der neuronalen Aktivierung über die Gesamtaufgabendauer erfasst. Mehrere Gehirnregionen, insbesondere Regionen, welche bei der Top-Down Regulierung von Aufmerksamkeitsprozessen beteiligt sind, zeigten eine Abnahme in Aktivität mit fortschreitender Aufgabenzeit. Geringere Aktivität z.B. in lateral-frontalen Regionen und dem inferioren frontalen Gyrus gaben Hinweise auf eine verringerte Top-Down Regulation am Ende der Aufgabe, was mit den Befunden aus den Verhaltensdaten übereinstimmte, welche erhöhte Reaktionszeiten und verschlechterte Aufmerksamkeitsleistung mit fortlaufender Aufgabenzeit wiederspiegelten. Kurze Zeitspannen von Vigilanz wurden als Funktion der zeitlichen Abstände zwischen den Zielreizen während der Aufgabe untersucht. Mehrere Hirnareale, insbesondere in subkortikalen Regionen wie dem anterioren Cingulum, dem basalen Vorderhirn, dem Thalamus, dem Nucleus Accumbens und dem ventralen Tegmentum zeigten eine Zunahme an Aktivität mit längeren zeitlichen Abständen zwischen den Zielreizen. Eine multivariater PLS Ansatz wurde weiter benutzt, um dieses Aktivitätsmuster mit nicht- aufgabenrelevanter Bewegungsverarbeitung in Bezug zu setzen. Die nicht-aufgabenrelevante Bewegungsverarbeitung wurde durch sich im Wechsel bewegende und stillstehende Punkte hervorgerufen, die in peripheren Bereichen des Gesichtsfeldes der Probanden präsentiert wurden und die von den Probanden ignoriert werden sollten. Die multivariate Analyse sollte die Frage beantworten, ob der Grad der Aktivierung der Gehirnregionen, die als Funktion der zeitlichen Abstände zwischen den Zielreizen rekrutiert wurden, die Aktivierungsstärke im bewegungssensitiven Areal MT vorhersagen kann. Das Ergebnis erlaubte eine Aufteilung dieser Gehirnregionen in zwei funktionell unterschiedliche Netzwerke. Eine Gruppe von Regionen, die positiv mit dem Grad der Aktivierung in Areal MT korrelierten, wurde einem Netzwerk zugeordnet, das sensorische Erregbarkeit reguliert; eine andere Gruppe

von Regionen, die eine negative Korrelation mit der Aktivität in Areal MT zeigten, wurde einem Netzwerk zugeordnet, das Motivation und Erwartungshaltung reguliert. Zusammenfassend konnte Studie I verschiedene neuronale Netzwerke identifizieren, die bei der Regulierung von Vigilanzsituationen beteiligt sind: Verschieden Netzwerke für lange und kurze Zeitspannen von Vigilanz und ihre unterschiedliche Rolle für sensorische Verarbeitung.

Studie II erweiterte den Blickwinkel von Studie I in zwei Punkten: Erstens wurde der Einfluss von fordernder Aufmerksamkeitsleistung auf Gehirnnetzwerke ausgedehnt auf ein Zeitfenster von 12 Minuten *im Anschluss* an die Aufgabe untersucht. Zweitens wurde die räumliche Skala der Betrachtung von wenigen, aufgabenrelevanten Gehirnregionen auf Einflüsse auf die gesamte Konfiguration des Gehirnnetzwerkes erweitert. Dafür wurden Daten verwendet, die ohne Aufgabe, im Ruhezustand der Probanden, vor und nach der Aufgabe erhoben wurden und mit einem graphenanalytischen Ansatz ausgewertet wurden. Maße für funktionelle Konnektivität und Netzwerkmaße für globale Effizienz, Clustering und räumlichen Distanzen zwischen verbundenen Gehirnregionen wurden zwischen den einzelnen Ruhemessungen miteinander verglichen. Der Hauptbefund von Studie II zeigte, dass das Absolvieren der Aufgabe zu langanhaltenden Veränderungen in der Konfiguration des Gehirnnetzwerks führte, was sich durch verringerte Effizienz, kürzeren Kommunikationswegen (räumliche Distanzen) und erhöhten Werten für Clustering äußerte. Desweiteren zeigten in der späteren Hälfte der Ruhemessungen nach der Aufgabe (6-12 Minuten danach) nur Probanden eine Erholung in diesen Netzwerkparametern, die eine bessere Leistung innerhalb der Aufgabe erbrachten, beziehungsweise die, die sich robuster gegenüber der Anforderung der Aufgabe zeigten. Insbesondere der Grad der funktionellen Konnektivität und die Werte für Clustering fingen an sich bei diesen Probanden zu erholen und zeigten eine Korrelation mit den individuellen Leistungen. Diese Ergebnisse machten deutlich, dass intrinsische Gehirnnetzwerke durch Ausführung einer Aufgabe beeinflusst werden können und dass vorhergehende Aufgabenanforderungen nachwirkend auf die Funktion des Gehirns Einfluss nehmen (im gemessenen Zeitraum von 12 Minuten nach der Aufgabe). Der Zusammenhang zwischen der Erholung einiger Netzwerkattribute wie Effizienz und Clustering und der Aufgabenleistung der Pobanden weist zudem darauf hin, dass diese Graphmetriken als Biomarker für kognitive Belastbarkeit dienen können.

In Studie III wurde der gleiche graphenanalytische Ansatz benutzt, um Ruhemessungen einer Gruppe von Nichtrauchern mit einer Gruppe von Rauchern zu vergleichen. Ziel war es herauszufinden, ob der Status 'Rauchen', beziehungsweise langfristiger Zigarettenkonsum, einen möglichen Einfluss auf die Konfiguration intrinsischer Gehirnnetzwerke hat. Basierend auf einer bestehenden Theorie, nach der ein möglicher Grund für Rauchen eine Form von Selbst-Medikation für bestehende Aufmerksamkeitsdefizite darstellen könnte, zeigt die intrinsische Netzwerkkonfiguration von Rauchern möglicherweise veränderte – für Aufmerksamkeitsverarbeitung nicht vorteilhafte – Netzwerkeigen-

schaften. Die berechneten Graphmetriken wurden mit Standard-Teststatistik, Maßen für Effektstärke und Non-Inferiority Testverfahren verglichen. Die Ergebnisse zeigten, dass die Gehirne von Rauchern im Vergleich zu Nichtrauchern keine signifikant unterscheidbaren Netzwerkattribute, wie Effizienz, räumlichen Distanzen oder Clustering, aufweisen. Der Vergleich der Effektgrößen und das Non-Inferiority Testverfahren zeigten weiter auf, dass diese Attribute vergleichbar zwischen Rauchern und Nichtrauchern waren und dass Raucher signifikant keine geringere Effizienz oder erhöhtes Clustering in vielen Gehirnregionen aufweisen. Die Befunde von Studie III bestätigen, dass der Status 'Rauchen' kein Bias für die graphanlystische Untersuchung intrinsischer Gehirnnetzwerke darstellt.

1 Introduction

1.1 Overview

The human brain is a highly flexible and adaptive information processing system that allows us to interact with our environment and to adjust behaviour to current task demands. However, if a task demand is high, the flexibility and capability of the brain to adapt is challenged. Limitations of cognitive adjustment to a current task can be observed behaviourally by declines in task performance. The studies of the current thesis aim to shed light on *neural* mechanisms that are involved in adaptive processes of the brain in order to match task demands and on changes in brain networks that reflect consequences of demanding tasks. In particular, the current thesis focuses on neural correlates mediating attentional processing *during* and neural correlates reflecting long-term influences of attentional processes *after* a task has ended.

The following sections of this envelope introduce and provide some background of the main concepts used in the three studies.

Section 1.3 presents the phenomena of vigilance and attentional effort as investigated in study I. Section 1.4 briefly reviews findings related to resting state research and the meaning of intrinsic brain oscillation for human brain function, which are the basis for the assumptions made in study II. Section 1.5 points out the meaning of nicotine consumption for brain function and its potential role for self-medication in patients with psychological disease, which built the motivation for study III. At the end of each of these sections a short summary and concluding remarks with respect to the according study is given. Section 1.6 gives insight into two methods for network analysis on fMRI data: partial least square analysis and graph theory. One focus of the current theses was also to elaborate and apply these techniques. Especially the relatively new and promising graph theoretical approach is presented with more detail.

1.2 Experimental Approach and Aims of the Thesis

Neural data was acquired by means of fMRI which was subjected to different types of data analyses. The analytic approaches focused on identifying and describing neuronal networks and were applied to data acquired during presence and absence of a task demand. The main task was a 32 minutes lasting vigilance task. The vigilance task was used in order to challenge the attentional system of the subjects and to introduce potential

limitations of their brain's capability to perform at the same level throughout the whole task time. Resting state measurements, where subjects lie in the scanner without task, were performed for 6 minutes before the task and for 12 minutes following the task (see Figure 1.1).

Goal of study I was to identify brain networks that are involved during the vigilance task in mediating the task demand and that are related to performance decline. Neuronal networks were investigated for temporal aspects of vigilance. Networks involved in longer periods of vigilance over the total time on task and in shorter periods of vigilance, as present in 'miniature' vigilance situations immediately before target presentation within the task, were differentiated. Further, the evoked brain activity of the recruited brain regions by the main vigilance task was related to task-irrelevant stimulus processing as evoked by moving dots stimuli presented in flanker windows during the task. A multivariate analysis was used to reveal the functional roles of brain regions involved in vigilance situations for the processing of task-irrelevant stimuli. The general attributes of vigilance tasks and potential neuronal key mechanisms involved in compensating for vigilance task demands are described in sections 1.3 and 1.3.1. The modelling technique used for revealing the functional role of the identified brain regions in attentional processing, the partial least squares analysis, is introduced in section 1.6.1.

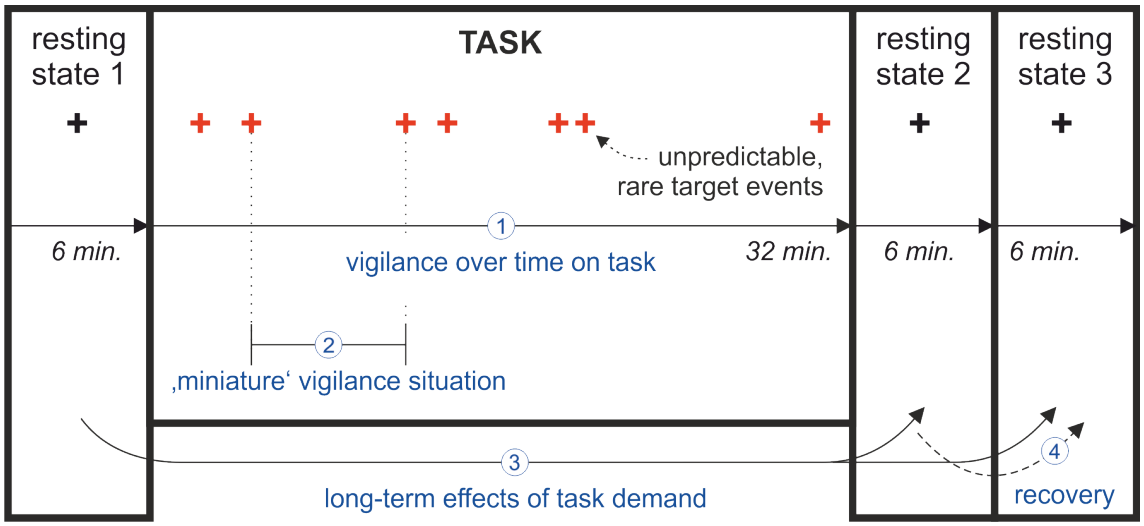

Figure 1.1: Scheme about the overall design of studies I + II. Sequence of different conditions in one functional MRI scanning session. A centre task, in which targets (red crosses, 96 targets in total) were presented with random inter target intervals to the subjects, was flanked by no-task, open eyes resting state conditions (central fixation cross only). BOLD Activity in neuronal networks involved in long and short periods of vigilance were revealed as function of time on task *(1)* and as function of time spans (in average 20 seconds) between target events *(2)*. Long term effects of task demand on intrinsic network configuration were captured by comparison of graph metrics derived from the resting state periods *(3)*. Changes of graph metrics between the two resting state periods following the task were additionally analysed with respect to network recovery *(4)*.

Study II aimed to give insight into longer-termed neuronal network changes following a task. The effects of task demand and individual performance on brain network efficiency were investigated. Functional MRI data acquired in 'no-task' or resting state conditions before and following a task were compared by use of a graph analytical approach. Measures of brain efficiency were analysed with respect to changes immediately following the task and to recovery processes later in time. An introduction about resting state research is provided in section 1.4; the measures of brain efficiency and the graph analytical approach are detailed in section 1.6.2.

Study III dealt with the question if functional brain network efficiency differs between smokers and non-smokers. Nicotine presence has been shown to alter attentional performance and to increase brain network efficiency. Study III investigated if more generally the status of smoking, in absence of acute nicotine presence, leads to reduced brain network efficiency or if network efficiency is comparable between minimal deprived smokers and never smokers. An overview about the role of nicotine as modulator for functional brain networks is given in section 1.5.

In summary, the main questions of the current thesis in particular are:

1. Are there different brain regions involved during the vigilance task in respect to longer and shorter periods of vigilance? (study I, section 1.3.2)
2. What neuronal networks are involved in mediating attentional effort during the vigilance task? (study I, section 1.3.2)
3. How does brain efficiency, respectively intrinsic brain states, change following the demand of the vigilance task? (study II, section 1.4.1)
4. How are changes of brain topology related to individual performance and how does performance affect the capability for recovery of brain attributes following the task? (study II, section 1.4.1)
5. Does smoking status impact on topological measures of brain network efficiency and represent a bias for investigating intrinsic brain function? (study III, section 1.5.1)

1.3 Vigilance Tasks and Attentional Effort

In study I, a vigilance paradigm was used in order to experimentally induce an increase in attentional effort. Vigilance tasks describe a category of tasks that are characterized by prolonged task time, low visual load and rare target events which have to be detected by the subjects. A common observed phenomenon of such tasks is the 'vigilance decrement': decreased performance with increased time-on-task reflected by increased reaction times and/or missed targets (see e.g. Parasuraman et al., 1998).

Traditionally, vigilance tests were considered to under-stimulate the attentional system due to their monotonous and repetitious nature (Nachreiner & Hanecke, 1992). With ongoing time on task subjects tend to mentally disengage from the task and begin day-dreaming (e.g. Robertson et al., 1997; Manly et al., 1999) which was seen as the main reason for the vigilance decrement. However, authors of more recent studies challenged this view of the *mindlessness theory of vigilance*. For example, Helton and colleagues (2005) pointed out, that expectations about the time course and likelihood of target appearance affect performance efficiency in vigilance tasks. Further, it was observed that aspects such as motivation or aversion to proceed in the task, which emerge during the experimental progress, decrease and increase the vigilance decrement respectively (Boksem et al., 2005; Lorist et al., 2005; Boksem et al., 2006). The latter observations suggest that these objectively simple vigilance paradigms are tasks with a high demand for the attentional system when considering their vulnerability towards individual expectation and motivation.

Consequently, a mechanism that can compensate for the demand of vigilance tasks in order to maintain performance requires considering both, the effects on sensory processing and the effects on intrinsic motivation. A promising concept of such a mechanism is *attentional effort*. In previous studies, attentional effort was only seen as a function of task difficulty. Effort is needed in order to compensate for task dependent detrimental influences. Such influences can for example be driven by prolonged time-on-task, the task load or the density of presented stimuli, the saliency of presented stimuli, the changes in stimuli features to detect, or the absence and presence of distractors. In earlier literature, attentional effort was used as a psychological concept that served as explanation for declines in performance with increases in task difficulty (e.g. Kahneman, 1973). However, the concept of attentional effort was so far only vaguely defined and a relation to neuronal correlates not illuminated. A renewal and enhancement of the concept of attentional effort was provided by Sarter et al. in 2006. Sarter and colleagues defined attentional effort as a cognitive incentive and a complex mechanism of the brain not only in response to task demands but also in response to subjects' motivation to perform a task. Beside the conceptual involvement of motivational aspects in attentional effort, Sarter and colleagues presented also a neuronal framework for top-down modulation of attentional processing as mediated by attentional effort (see next section 1.3.1).

The extension of attentional effort by motivational aspects is based on observations as e.g. from Pashler (1998), who described that subjects are capable to control their performance with different levels of motivation. Or from Tomporowski and Tinsley (1996) who could show that subjects in a 60 minutes vigilance task performed better when they were paid for performance as compared to unpaid subjects. Thus, the subjects' motivation is important to recover performance or limit performance decline in experimental tasks. If the expected reward is high, attentional effort serves to optimize goal-directed behavioural and cognitive processes.

However, literature is sparse in experimental research of investigating the influence of attentional effort on behavioural as well as on neuronal level. There is no standard test paradigm for measuring increases in attentional effort. One reason is probably given by the fact that the concept of attentional effort has remained undefined a long time until the definition of Sarter and colleagues (2006). Another reason might be the high inter-individual variability of subjects in adjusting the levels of attentional effort in experimental tasks, as attentional effort is to a bigger part driven by intrinsic motivation.

In the current thesis, attentional effort was seen as a mechanism to compensate for the demands of the vigilance task and built therefore an important concept to explain the behavioural and neuronal findings.

1.3.1 Neuronal Mechanisms of Attentional Effort

An important mechanism for stabilization and optimization of attentional processing is top-down regulation by the anterior attention network (Posner, 1994). Prefrontal and anterior cingulate regions (ACC) interact with parietal areas and build the main components of brain circuits that execute top-down control (Gehring & Knight, 2000; Hopfinger et al., 2000). Changes of receptive field properties of sensory neurons in cortical and subcortical regions (Treue & Maunsell, 1999; Corbetta & Shulman, 2002) or suppression of activity in regions which process irrelevant or competing inputs (Shulman et al., 1997) are known effects of top-down control.

Whereas top-down mechanisms are able to optimize and recover attentional processing, they themselves underlie motivational aspects and can act as a function of incentives (Small et al., 2005). Cortical cholinergic inputs to prefrontal regions play a prominent role in such top-down mechanisms. Animal studies showed that an increase in effort is accompanied by an increase in acetylcholine (ACh) efflux in the basal forebrain (BF) in attentional tasks (Kozak et al., 2006). Prefrontal regions and ACC have contact with dopaminergic regions such as the ventral tegmental area (VTA) and the nucleus accumbens (NAC) (Carr & Sesack, 2000). The functional roles of prefrontal/ACC interactions and NAC activation

are attributed to performance monitoring, conflict detection and processing of critical information about prediction errors and reward (Robbins & Everitt, 1996; Mesulam et al., 2001; Berridge, 2004; Botvinick et al., 2004); further midbrain dopaminergic neurons as in the VTA show activations in relation to reward expectation and prediction (for a review see Schultz, 2010). Efferents of the NAC and VTA as well as glutamatergic feedback loops from prefrontal/ACC regions project to the BF, which renders the BF to play a key role in linking motivational circuits with brain regions involved in top-down modulation of attentional processing.

In summary, the key mechanism of attentional effort builds an activation of the cholinergic input system that contributes to the activation of the anterior attention system and associated sensory processing (see review of Sarter et al. 2006).

1.3.2 Summary of the Main Findings of Study I

Are there different brain regions involved during the vigilance task in respect to longer and shorter periods of vigilance?

The vigilance task used in study I successfully induced a vigilance decrement to the subjects as reflected by increased reaction times towards the end of the task. Brain regions including the inferior frontal, posterior parietal, superior and middle temporal cortices, and the anterior insula showed decreases in neural activity as a function of time on task. Involvement of these regions in longer periods of vigilance was in good accordance with previous studies which investigated time-on-task effects on neural activity. This activation pattern comprises regions involved in top-down modulation of attentional processing (see previous section). A decrease in activity over time in those regions points to reduced top-down optimization of sensory processing was seen as explanation for an increase in reaction times of the subjects.

In a second step we investigated neural correlates involved in shorter periods of vigilance as a function of increasing time between targets. The time span until the next target event appeared in the task, which was unknown to the subjects, was seen as a 'miniature' vigilance situation. The longer the time span, the longer the subjects had to adjust their attention and the higher was their expectation about the appearance of the next target.

Brain regions that showed an increase in activity with longer time spans between targets were a widespread network of regions that involved lateral and medial frontal areas, temporal areas, cuneus and precuneus, right inferior occipital cortex, posterior insular cortices, the thalamus, nucleus accumbens and basal forebrain.
Main regional differences as to regions involved in longer periods of vigilance were activations of subcortical regions such as the thalamus, the nucleus accumbens and the basal

forebrain. The nucleus accumbens and the basal forebrain are key structures for attentional effort (see section above). This activation pattern pointed to enhanced acquisition of attentional effort and top-down regulation (as also evident in thalamic activations which is an effector of top-down modulation) in short-term vigilance situations.

What neuronal networks are involved in mediating attentional effort during the vigilance task?

To answer the question if functional distinguishable brain networks are involved during performance of a vigilance task, a the multivariate partial least squares approach (PLS, see section 1.6.1) was used to relate evoked brain activity patterns to task irrelevant motion processing. Simultaneously to the main centre task of relevant target presentations, flanker windows with moving dots were presented. The dots alternately moved or stood still for time periods of 24 seconds. The by the motion evoked activity in the motion sensitive area MT was functionally and regionally distinct from the brain regions involved in the processing of the target stimuli. Motion processing in the current paradigm served as a reference for task independent attentional processing, as it was previously shown that area MT activity is highly modulated by attention (see e.g. Treue & Maunsell, 1996).

The PLS approach revealed that brain regions involved in shorter periods of vigilance significantly co-varied with area MT activity. Further, the brain regions were differentiated according to their weight in which they contributed to the PLS prediction into two different networks contributing to the mediation of attentional effort. One network was attributed to arousal processes, as it showed a positive correlation with area MT activity. Regions such as the thalamus, basal forebrain, posterior cingulate cortex and the supplemental motor cortex (SMA) were part of this network. The other network, which negatively co-varied with area MT activity comprised among others regions as the nucleus accumbens (NAC), the anterior cingulate cortex (ACC) and the pre-SMA. As pointed out above, these regions are typically found to be involved in processing reward outcome, expectation and conflicts (or sensory mismatches) and were attributed to reflect parts of a motivational network.

1.3.3 Concluding Study I

Study I is one of the first studies that investigated different temporal aspects of vigilance within one paradigm. Especially aspects of vigilance over shorter time periods, such as captured in the miniature vigilance situation (time between target presentations), have not been investigated before to this extent. It is to our knowledge the first study that showed neural correlates of attentional effort in the human brain with almost all regions previously described by Sarter et al. (2006). Finally, study I provides insight into the role of functionally distinguishable brain networks (arousal and motivation), that both mediate sensory processing in a vigilance task. With these findings study I contributes to a better understanding of the complexity of neuronal processes in vigilance situations, situations that were earlier considered as 'mindlessness' and accomplishable with low demands for the brain.

1.4 Resting State and the Default Mode of the Brain

Initial resting state research based on the observation that a defined set of brain regions when contrasted to passive control conditions showed 'deactivations' across a wide array of task conditions (Raichle et al., 1994; Shulman, 1997; Petersen et al., 1998; Raichle, 1998). These regions comprised posterior cingulate regions and adjacent precuneus, medial frontal and inferior temporal regions and since were referred to as the *default network* of the brain. The default network was found to be consistent across subjects (e.g. Damoiseaux et al., 2006) and was first considered as regions showing task-induced activity decreases (Shulman, 1997; Binder et al., 1999; Mazoyer et al., 2001). However, later studies could show that the default network regions also show strong temporal coherence and spatially clustered patterns (as derived from connectivity and spatial independent component analyses) in so called *resting state* conditions, which may involve baseline conditions with either eyes open and a presentation of a fixation cross or eyes closed (e.g. Gusnard & Raichle, 2001; Raichle et al., 2001). Persistent default mode network connectivity was further observed in sedated subjects and subjects under anesthesia (Buckner & Vincent, 2007; Greicius et al., 2008). The latter findings put forward the notion of a task independent *default mode* of the brain, a brain state founded in spontaneous brain activity, supposed to be important for reallocation and organization of brain function. The role of the default mode for human brain function and its characteristics have become a major issue in nowadays resting state research, often with an extended view from the few default mode network regions to intrinsic oscillations throughout the whole brain. An interesting fact that fertilizes resting state research from a biological point of view was provided by calculations of Raichle and Mintun (2006): 60% to 80% of the brain's energy budget is used for intrinsic functional activity, whereas only 0.5% to 1% of the total energy budget is used for momentary demands of the environment. This cost-based analysis underlines the relevance of intrinsic states for human brain function, as cost efficiency is one common principle of any biologically evolved system.

In fMRI resting state data, strongest patterns of *functional connectivity*, predominantly defined as the high correlation of neuronal signal (BOLD-) time courses between two or more sources (brain regions), were observed in a frequency range below 0.1 Hz (e.g. Cordes et al., 2001; Wu et al., 2008). To date, the biological basis for this frequency range is not fully understood. Observed slow fluctuations (<0.1 Hz) in neuronal membrane polarization ('up and down' states) correspond in their frequency with the observed BOLD signal fluctuations (Petersen et al., 2003; Hahn et al., 2006) and could serve as one explanation.

Among possible functions of default mode activity, intrinsic oscillations are discussed to build a state of 'balance' between excitatory and inhibitory inputs that are continuously received by neurons (e.g. Laughlin & Sejnowski, 2003; Haider et al., 2006). This balance determines the responsiveness of neuronal networks to new, correlated inputs and thereby

constitutes communication pathways in the brain (Salinas & Sejnowski, 2001). Findings from e.g. Lim et al. (2010) revealed that RS activity prior to a task can predict task performance. Further, studies have shown that task performance can change this balance or communication pathways on functional connectivity level. For example it was shown that a language (Waites et al., 2005) and a motor task (Duff et al., 2008) can change RS attributes, and further that learning induced plasticity can affect connectivity patterns in subsequent RS measurements (Albert et al., 2009; Lewis et al., 2009; Stevens et al., 2010).

These results render RS activity to more than a task independent state. RS activity might on the one hand contain variables that work as priors and determine the 'brain readiness' for following task demands, and on the other hand build reflexive states dependent from the history of the performed tasks. Study II of the current thesis was used to pursue the latter concept and investigated how task demands change intrinsic functional networks following a task and how long it takes until a pre-existing balance, defined as the state before task performance, is recovered. The main method to describe the brain states during the resting periods was a graph analytical approach (see section 1.6.2).

1.4.1 Summary of the Main Findings of Study II

In study II topological brain measures such as network efficiency and clustering from three resting state (RS) periods were compared. One RS period was before, two RS periods followed the vigilance task from study I. The vigilance task attentionally challenged the subjects by introducing a significant vigilance decrement (see also study I) and thereby revealed limitations of the brain for upholding optimized sensory processing towards the end of the task. The graph analytical approach was used to investigate potentially changes in the topological measures immediately and later in time following the task demand.

How does brain efficiency, respectively intrinsic brain states, change following the demand of the vigilance task?

Immediately following the task (0 to 6 Min post-task) intrinsic brain network efficiency was decreased in all subjects. Further, the connectivity pattern showed an increase in clustering (cliquishness) and the physical distances between functionally connected brain regions shifted in favour to more short-distance connections. These changes in comparison to the network configuration prior to the task were further evident in the second RS period after the task (6 to 12 Min post-ask). Network attributes such as efficiency and clustering have previously been associated with the capability of cognitive performance (see section 1.6.2). The change in physical distance distribution may reflect a strategy of the brain to preserve metabolic costs. In summary the finding shows that intrinsic RS activity has reflexive attributes and can be modulated by prior task performance. A loss of global

network efficiency and a reallocation of communication pathways towards local and short-distance processing strategies were seen as a direct consequence of a challenged brain and as a biomarker for a brain approaching to cognitive limitations. A further finding was that these changes persisted for 12 minutes after the task (in both RS periods after the task).

How are changes of brain topology related to individual performance and how does performance affect the capability for recovery of brain attributes following the task?

The subjects showed a considerable amount of variability in task performance. Some subjects were able to successfully uphold their performance level (unchanged reaction times towards the end of the task) whereas others showed strong vigilance decrements. However, a relation of the individual performance levels to brain attribute changes in the RS period immediately following the task were not evident. But the change in some attributes in the post-task phase (change between the two RS periods following the task) was correlated with the individual performance. Brain networks of subjects with lower vigilance decrement showed recovery in the overall connectivity strengths between brain regions and in clustering. Even though these attributes did not reach the pre-task level (the values of the RS period prior to the task) in the latest RS period, this finding points to performance dependent variables that account for brain network recovery. Subjects that performed poorer (higher vigilance decrements) did not show recovery effects in network topology. Reason for this late recovery effects in study II were attributed to neuronal mechanisms of plasticity and cellular fatigue. Involvement of a different level of attentional effort might have lead to differently pronounced levels of neuronal plasticity and cellular fatigue, which induced longer termed changes in topology in subjects that had to invest more attentional effort in order to accomplish the task (see discussion of study II for details).

1.4.2 Concluding Study II

Long-term effects of task performance on RS activity has gained little interest so far and further was restricted to analysis on connectivity level. Study II contributed to RS research in at least two unique points. First, Study II is one of the first studies that investigated connectivity patterns on the level of the whole brain network and topological attributes such as network efficiency after task manipulation. It supports earlier ideas of a default mode of the brain that argued that the default mode of the brain is not completely task independent and that it plays a role in task post-processing, respectively in reallocation and reconfiguration of neuronal pathways following a task. Second, study II renders topological measures as efficiency, clustering and physical distance distribution between connected brain regions as valuable metrics or biomarkers for investigation of cognitive states of subjects. The relation to individual performance levels points to an important role of these metrics for measuring brain flexibility and cognitive capacity.

1.5 Smoking Status as Modulator for Intrinsic Brain Networks

One motivation that drives resting state research and especially the investigation of brain topology at rest is their use for clinical research and their potential for diagnosis of abnormal brain network configurations. Progress has been made in describing pathological network configurations in e.g. patients with Alzheimer's disease, depression, ADHD and schizophrenia. It was shown that brain networks in patients with Alzheimer's disease show generally lowered efficiency and lowered clustering attributes (de Haan et al., 2009; Stam et al., 2009); patients with depression showed more random network properties as compared to healthy control subjects (Zhang et al., 2011a); ADHD patients showed a decrease in brain efficiency but an increase in clustering (Wang et al., 2009); and schizophrenia patients showed more network hubs (brain regions with a large number of connections to other brain regions) in occipital brain regions and less network hubs in frontal brain regions as compared to healthy brain networks (Bassett et al., 2008; Lynall et al., 2010; van den Heuvel et al., 2010).

A side-effect of psychological diseases such as ADHD or schizophrenia is a very high smoking rate. Several studies have shown that the rate of smoking in these patient groups is two- to four-fold the rate seen in the general population (20-35%) (Lohr & Flynn, 1992; Pomerleau et al., 1995; Milberger et al., 1997; de Leon & Diaz, 2005). Reasons for the widespread smoking behavior in these patient groups are not completely understood, but most lines of investigation suggest that nicotine consumption serves as a form of *self-medication* in order to compensate for cognitive and attentional deficits caused by the disease and/or side effects of antipsychotic medications (for a review Sacco et al., 2004; Kumari & Postma, 2005). Binding sites of nicotine in the brain are widespread over cortical regions with a predominance in frontal and medial frontal regions as well as in cingulate and insular regions (Nyback et al., 1989; Stein et al., 1998). Beneficial effects of nicotine for performance have been reported in various tasks demands in healthy subjects as e.g. in attentional reorienting (Thiel et al., 2005; Giessing et al., 2006), in stimulus detection and vigilance paradigms (Koelega, 1993; Bates et al., 1995) or in memory tasks (Foulds et al., 1996; Rezvani & Levin, 2001). Beneficial effects of nicotine were also observed to improve performance of healthy and schizophrenic subjects in pre-pulse inhibition tasks, tasks in which subjects have to process several stimulus sources simultaneously and maintain task relevant stimuli in their attentional focus (Duncan et al., 2001; Kumari et al., 2001). The global binding sites of nicotine in the brain together with the positive effects of nicotine on performance in various, different tasks suggest that nicotine can impact on brain function on a global level and thus might lead to overall changes in the functional network configuration of the brain. A more direct line of evidence for global changes of functional network configuration under nicotine treatment was provided recently by Giessing et al. (submitted). Nicotine treatment led to higher brain efficiency and lower clustering of functional resting state networks in healthy subjects; a brain network configuration with

higher efficiency and lowered clustering has been previously suggested to be beneficial for task performance (please see chapter 1.6.2 for details).

However, one aspect that has been less investigated so far is the impact of long-term cigarette consumption on intrinsic network configuration. It was shown, that nicotine presence, on the one hand, can lead to a rapid desensitisation of nicotinic receptors in the brain (Freedman et al., 1995). On the other hand it was shown that chronic smoking leads to increases and up-regulations of nicotinic receptors, suggested as a brain's response to receptor desensitisation (Breese et al., 1997). Further it has been reported that smoking can lead to structural changes in the brain by reducing grey matter density in some brain regions (Gallinat et al., 2006; Zhang et al., 2011b). These observations suggest that intrinsic brain network configurations might also undergo changes due to prolonged cigarette consumption. If so, findings of changed brain network attributes in patient groups with high rates of cigarette consumption would be biased by the smoking status, as brain networks of these groups are most commonly compared with brain networks of healthy, non-smoking subjects. In study III it was tested if smoking status in subjects without psychological disease can lead to altered intrinsic brain network configuration.

1.5.1 Summary of the Main Findings of Study III

In study III, topological measures based on RS data from a group of smokers (slightly deprived, <2h) and a group of never smokers were compared. The same graph analytical approach as in study II was used in order to calculate measures of network efficiency, clustering and physical distances between functionally connected brain regions. In a first step, common null hypothesis significance testing was used to reveal potential differences in the graph metrics between smokers and non-smokers. As the null hypothesis could not be rejected by common testing, measures of effect size and non-inferiority testing were used in a second step in order to examine the two datasets and to explicitly test for a 'null effect' for the regional measures of efficiency and clustering.

Does smoking status impact on topological measures of brain network efficiency and represent a bias for investigating intrinsic brain function?

The results of study III confirmed that resting state topology of smokers and non-smokers do not differ in the investigated measures. With respect to the previously reported topological changes in patients with schizophrenia and ADHD in specific brain regions (please refer to introduction part of study III), findings of study III further corroborate that efficiency and clustering in these regions are not affected by the smoking status. Based on these results, the trait of smoking addiction does not state a bias for topological measures of brain networks.

1.5.2 Concluding Study III

Study III successfully helped to negate potential confounds evoked by the status of smoking addiction for research in resting state topology. The results have major relevance in two aspects: First, the validation of existing studies that previously investigated pathological brain networks of patients with schizophrenia and ADHD. In these studies typically patient groups with a high prevalence of smoking were compared to healthy, non-smoking subject groups. Prior to the findings of study III, the reported findings in these studies could have possibly not only been attributed to the disease but also to the status of smoking. Second, smoking subjects can be added to the pool of non-smoking subjects in studies that investigate resting state topology. Prior to the findings of study III, it remained unclear if long year smoking introduces changes in topological attributes of functional networks, esp. as it was recently shown that acute nicotine presence has a significant influence on these attributes (Giessing et al., under review).

1.6 Excursi: Two Approaches for Network Analysis of Functional MRI Data

The studies presented in this thesis are largely based on complex data analyses of fMRI data. In the following the two major approaches, as the partial least squares analysis and graph analysis, will be described in more detail.

1.6.1 Partial Least Squares Regression

Classification and Basic Attributes

Multivariate partial least square (PLS) methods are used to analyse the relationship between measured variables (factors, X) and explaining or predictive variables (responses, Y). In science, PLS methods were early used and established in the fields of chemistry as pioneered by Wold and colleagues in the late sixties (Wold, 1969; Wold et al., 1984). McIntosh and colleagues (1996) firstly introduced these methods to functional imaging and used them to reveal commonalities between brain activity and behaviour. In comparison to multiple linear regression analyses PLS methods are superior and more efficient when the number of factors is large (in relation to the sample size, causing the problem of 'over-fitting'), when factors are expected to be collinear, and when relationship between factors and responses is ill-understood (or there is no clear a priory expectation). All three conditions were true for the data in study I of the current thesis where the PLS regression was used to predict area MT activity (responses) from the inter-target interval related activity pattern based on several thousand voxels (factors).

In general, PLS regression shares the strategy of indirect modelling with related methods such as principal components regression (PCR) and maximum redundancy analysis (MRA).

Evoked by the problem of over-fitting, these methods avoid explaining a response space by a manifest factor space. Instead, their strategy is to extract main components or *latent variables* that account for most of the variation in the response and/or factor space. Whereas PCR is based on the spectral decomposition on the factor side (X'X) and MRA is based on the prediction of the 'responses side' (Y'Y) the PLS methods seeks to optimize *both* (X'Y) and extract latent variables that account for most variance of responses *and* predictor variables/factors (for a brief comparison of these methods see Tobias, 1995). For extraction of the latent variables the iterative NIPALS (non-linear iterative partial least squares) algorithm was used in study I (Dejong, 1993; Rosipal & Kramer, 2006). During the iteration process linear combinations of X and Y are built that show maximum covariance for each latent variable, on X as well as on Y side, by determining weights for each factor in X and response variable in Y. For instance the resulting X weights can be used for the projection of the factor space into new prediction space with maximum

covariance between X and Y space. The weights can be used to estimate the 'meaning' of each single factor considered in the PLS model for the prediction of the responses. Factors with high (absolute) weights show a high covariance with the response variables. Further, the weights are sensible for the direction of the relationship between the factors and the response variables. The weights of the first latent variable are proportional to the correlation between X and Y. The algebraic sign of the weights attributed to Y and the algebraic signs of the weights for X give information about a positive or negative correlation of the factors and the response variables.

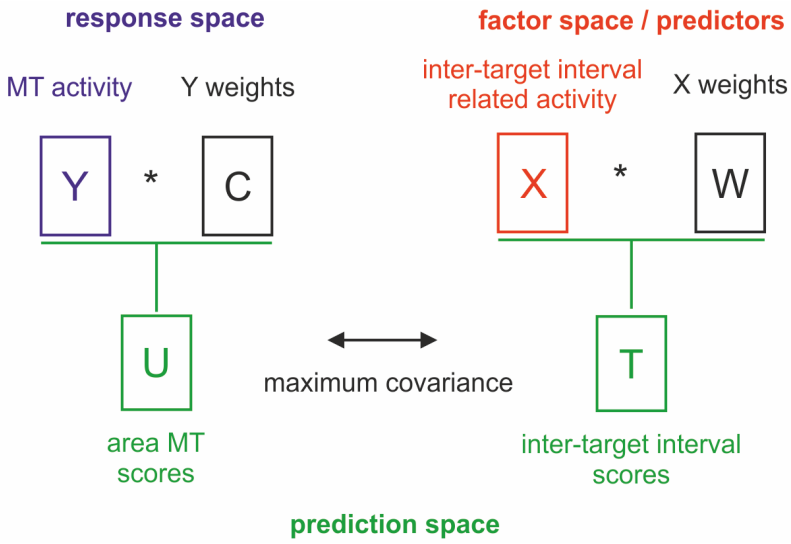

Figure 1.2: Principle of PLS Analysis. PLS generates and optimizes weights for the response space (Y, C) and for the factor space (X, W) so that the prediction space of X (T = X*W) and of Y (U = Y*C) shows maximal covariance. W correlates with U, C correlates with T. In case of study I, area MT activity was predicted with help of the activation level of brain regions that showed an increased activity with longer time spans between the presented targets.

Validation and Significance Testing

For the validation process of the PLS model and the interpretation of the weights two further steps are needed.

Model accuracy. The first step is aimed to estimate the accuracy of the extracted latent variables for the prediction of the response space. This was realized in our study by use of a randomization test suggested by van der Voet (1994) which is based on the differences in the mean squared error of prediction (MSEP) of PLS models with different numbers of latent variables. During this procedure, the number of latent variables in a PLS model is continuously increased by one (the 'full' model) and in each step compared with the previous PLS model, comprising one less latent variable (the 'reduced' model). The difference of the MSEP for all comparisons is calculated and tested two-sided with

a randomization test for the null hypothesis. Rejection of the null hypothesis would account for a significant contribution of the last added latent variable to the prediction of the response variable(s). We conducted such model comparisons for a total number of 10 latent variables in the full model with randomization tests of 500 iterations. As the sample size comprised only 20 subjects in study one, the MSEP was estimated with help of a leave-out-one-sample (LOO) cross validation approach. In this procedure the responses of one subject (defined as the test sample) were predicted by the weighted factors of the other 19 subjects (defined as the train sample). The test sample was rotated in the way that the sample of each subject was the test sample once. Resulting prediction errors built the basis for the MSEP differences for each model comparison. In study one, this model validation process revealed significance for a PLS model with up to three latent variables. Further addition of latent variables did not improve the model prediction and most of the response data could be explained by the first latent variable.

Model Validation. The second step after model validation is used in order to test the reliability of the extracted factor weights over all subjects. Even if the PLS model generally was able to significantly predict the responses by the weighted factors over the whole sample size, the factor weights can vary across subjects and a single factor can be weighted differently for different subjects. Goal of study one was to identify factors that significantly and homogenously (with the same algebraic sign) contribute to the prediction of the responses. For that purpose a bootstrap method with 500 iterations was used (Efron, 1994). In each bootstrap iteration process, a new resampled data set is created with the same sample size and with randomly picked samples out of the real sample set (sampling with replacement). Resampling allows an estimation of the factor weight distributions and calculation of Z-scores (relation of each factor weight to the standard deviation of the estimated distribution) and thus an identification of the reliable (significant) weights over all subjects. In study I bootstrapping identified different clusters of voxels that either contributed with a positive or a negative weight to the prediction of area MT activity. This allowed relating brain regions to their role in predicting sensory motion processing and helped to assign them to conceptual brain networks involved during task-unrelated sensory processing in the presented task.

Personal Conclusions and Restrictions of PLS Application

In general the PLS method has the reputation of being very solid and the fact that PLS modelling optimizes linear weighted combinations of both sides, the response and the factor side, makes it a powerful and suitable tool for data mining. In case of study I, PLS regression remarkably supported our findings and allowed an extended interpretation of the analysed BOLD response patterns. However, especially in case of using BOLD response patterns as factor and/or response space, the reliability of PLS regression is challenged. Reason for that is rather built by the applied statistical threshold for describing fMRI-data than by the PLS method itself. Based on a widely arbitrary choice of a significance threshold for describing fMRI response patterns, which is still common in the fMRI community, the number of factors introduced to the PLS model can vary from a few hundred, to thousand, to several thousands. This raises the question of which number of factors (respectively which threshold) should be chosen for PLS modelling of fMRI patterns. If there was a close relationship between responses and factors and PLS modelling is as solid as supposed to be, the choice of the description threshold for fMRI data should have minor impact on model accuracy, as key structures (or voxels) remain the same at each observation threshold, on response as well as on factor side. This is the case because only the spatial extent of their 'representation' is changed by different thresholds and not their relation to each other. This was true in case of study I, as the PLS method revealed significant relations to area MT activation for fMRI patterns at different thresholds. But this was not true for another data set (analysed by the author of the current thesis, but not related to the thesis) in which the choice of the description threshold decided if a PLS model was significant or not. The latter case calls the PLS method as a 'powerful tool for data mining' into question for exploring relationships of fMRI patterns and advises carefulness for its proper use. It can provide strong support for interpretation of fMRI response patterns but fails in the opinion of the author as to be a stand-alone approach for fMRI-data mining that is expected to deliver substantial results. Maybe an extended cross-validation approach, that takes PLS models based on fMRI-activation maps on different description thresholds into account and compares the PLS predictions for each of the different data sets, could provide an improvement for the PLS method as a more unbiased data mining tool when modelling BOLD response patterns.

1.6.2 Graph Theory

A Graph as Model of the Brain

The human brain consists of 10^{11} neurons with 10^4 synaptic connections each which results in a connectome with a total number of one Quadrillion (10^{15}) cellular connections. In order to make such a massive and complex network accessible it is inevitably necessary to reduce the amount of detailed information and to use simplified models of the brain network. One type of brain network model is provided with modern graph theory. Graph theory is a mathematical tool to analyse topological attributes of network models, namely 'graphs'. Graphs consist of only two elements: Nodes and edges. Nodes can represent functional units, information sources or brain regions. Edges represent the direct connections between them.

Important measures derived from graphs were introduced by Watts and Strogatz (1998) and base on the path lengths between network nodes. The path length between two nodes is the number of edges between them (directly neighboured nodes would have a path length of 1). So, for example, nodes that lie on a large number of paths between other nodes can be identified as network hubs, important interfaces of the network. On a more global scale, *network efficiency* can be represented as the inverse average path lengths between all pairs of nodes in the network; the more efficient the network, the shorter the average path lengths. Further, path lengths between neighboured nodes can be used to describe the *clustering* of a network; short path lengths in sub graphs with neighboured nodes are characteristic for networks with high cliquishness and modularity (see formulas of Latora & Marchiori, 2001; 2003).

One fundamental property that share brain networks in common is *small-worldness*. Small-world networks lie in between regular and random networks, but share the benefits of both configurations (see Figure 1.3). By adding only a *few random* connections to a regular network (high clustering but low efficiency), network efficiency is immensely improved while a high clustering is preserved. This small-word configuration of the brain, a network configuration with high clustering *and* high efficiency, was found to be a universal principle for brain networks across species. So small-worldness was not only shown in human brain networks (e.g. Stam, 2004; Salvador et al., 2005; Achard et al., 2006), but also in the anatomical and functional brain networks of the macaque (Hilgetag et al., 2000; Stephan et al., 2000; Sporns et al., 2004), functional coupling in the rat's brain (Schwarz et al., 2008), and also interestingly in the primitive worm brain of *C. elegans* (Chen & Stein, 2006). Main reason for the evolutionary success for small-world configuration in brains was supposed to be its *cost-efficiency*, as axonal wiring is expensive in terms of metabolic costs and maintenance. So Watts and Strogats (1998) pointed out that with increasing the number of random connections in a regular network by only 4% the network efficiency can be increased by 40%.

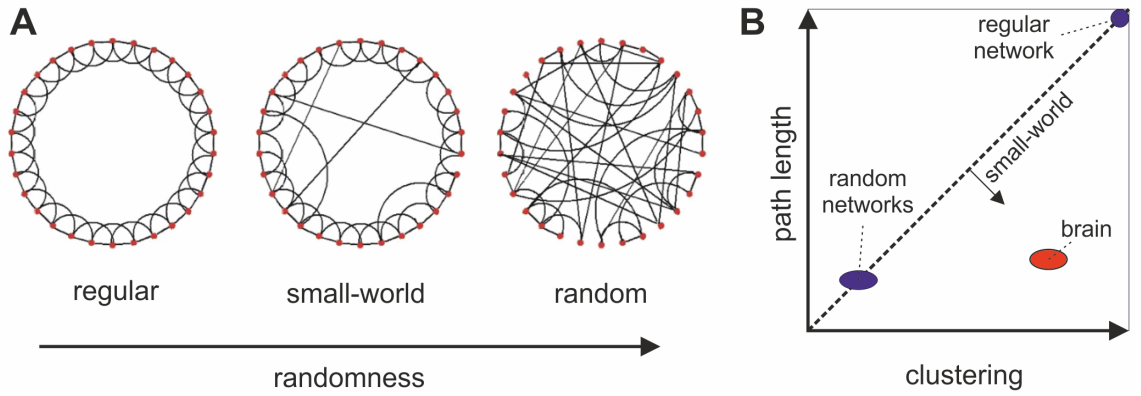

Figure 1.3: Small-world network configuration. A. Networks with different levels of random wiring. *Left:* Regular networks show a very high local efficiency with short path lengths between neighboured nodes; but a very low global efficiency with long path lengths between distant nodes. *Right:* Random networks show the opposite attributes: very low local, but very high global efficiency. *Middle:* By adding a few random connections to a regular network, the so called small-world configuration is achieved: Networks that show both, a high local efficiency and – in comparison to completely regular networks – high global efficiency (figure adopted from Hamill & Gilbert (2009), JASSS). **B.** Schematic illustration of the ratio between global efficiency (path length) and local efficiency (clustering). Brain networks show small-world properties, characterized by short path lengths (=high global efficiency) *and* high clustering.

Findings from graph based models of the brain gained also broad acceptance in the field of neuroscience because the identified attributes of high integrity (global efficiency) and clustering map to some of our fundamental ideas of the brain we have. The first idea is based on the fact that the brain needs to gather and integrate information from different kind, such as e.g. information from perceptual, attentional, evaluative or memory systems. Integration of these different kinds of information is necessary for controlled and complex behaviour. This idea was formerly conceptualized by Baars (1997) and Dehaene (1998) in 'the global workspace theory of the brain'. Information are stored and made accessible throughout a highly efficient and integrated network system. The other idea of the brain is based on the observation that the brain consists of anatomically and functionally distinguishable brain regions. Information is segregated and split up according to different features and are further processed in different brain regions. So for example visual information is, after it is first processed in the primary visual cortex, sent to different brain regions that process distinct features such as object shape, category, motion or location. Thus, the second idea of the brain is a very hierarchically and modular idea of the brain. Graph theoretical findings of a high integrity and high clustering describe an architecture of the brain that supports both kinds of processes, integrated and segregated processes, which renders graphs as models of the brain as a plausible and promising way to access brain topology.

Building a Brain Graph

For building a graph, answers to three basic questions are needed: What is the data basis? What are the nodes? And what are the edges?

Graph theory was adopted from economics, ecology and computer sciences that delivered the concept and the mathematical framework for graph statistics. Transferred to neuroscience, graph theory finds growing interest for analysing anatomical networks, such as derived from grey matter density maps from voxel based morphometry or axonal fibre bundles from diffusion tensor imaging, and functional networks, as based on EEG, MEG or fMRI data (for a review see Bullmore & Sporns, 2009). Depending on the data basis, graphs can have different meanings, their nodes represent different sources and their edges represent different metrics of connectivity.

The data bases for the analyses in the current studies were BOLD signal time courses acquired during resting state periods. Resting state brain activity is driven by intrinsic spontaneous oscillations; in resting state research it has been shown that these oscillations show strong and robust (across individuals and different analysing methods) functional coherence patters in a frequency range below 0.1 Hz (see also previous section X). Thus, the metric of connectivity were the correlation values of the BOLD signal time courses in this frequency range; high correlation values reflect high functional coupling between the signal sources. The resulting graphs built on this data basis represent functional network configurations of the brain at rest. A scheme about the major steps for creating functional brain graphs is given in Figure 1.4.

Graph theory is to most parts a relativistic analysing method, which means that single, complex graphs alone are not meaningful. Only the comparison to other graphs of networks with known attributes (such as regular or random networks) or the comparison to graphs based on the same data basis allow interpretations about their characteristics. Therefore it is essential to use the same number of nodes and the same number of edges for the graphs that are used for comparison. The number of nodes and the number of edges are crucial for the most derived graph parameters (as e.g. path lengths and hence resulting measures of efficiency and clustering).

The choice of nodes in the current studies was based on randomly generated seed regions. A parcellated grey matter standard atlas (the AAL-template from the wfu-pickatlas toolbox for SPM (http://www.nitrc.org/projects/wfu_pickatlas/)) build the template for all subjects to extract the average BOLD time courses for each of the seed regions (please find more details about the template in study II). Goal was to investigate functional brain networks, so the restriction to grey matter tissue assured that BOLD signal sources based on neuronal activity only. The number of about 500 seed regions/nodes was chosen as a good trade-off between a sufficient number of nodes for a fine-grained cortex coverage – in order to allow more region-specific assumptions – and a reasonable upper limit of nodes for preserving computing time. A study from Zalesky et al. (2010) showed that basic topological attributes, such as network efficiency and clustering, are preserved across a range of nodes between 100 and 5000.

More complex is the definition of the number of edges used for the graph and the question of what edges between which nodes to use in the graph. More recent approaches define the number of edges by different cost levels of a network. The cost level represents the density of the graph and is defined in the current framework as the number of nodes as percentage of all possible edges. So for example a graph with N=500 nodes has 124,750 ((N*N-1)/2) possible edges; at a cost level of 10% this graph uses 12,475 of all possible edges. Such a definition helps to control the number of edges and make graphs which are built at the same cost level comparable. But how many connections are functional brain networks supposed to have? As brain networks are dynamic, coherence patterns are shaped spontaneously and the number of sources vary (on biological side as from smaller to larger neuronal populations as well as on methodical side as based on the choice of seed regions) this question cannot be answered. Hence, the current strategy is to describe graphs for functional brain networks on a cost *range*. Reasonable lower and upper limits about the number of edges are given by two considerations: The brain is a coherent network in which no brain region operates alone and is not fragmented. This sets the lower limit of the number of edges to the number that is necessary to at least *connect all nodes* to the rest of the network. The upper limit is set by the observation that networks/graphs above a cost level of 50% show widely random properties. Widely random properties are unlikely for the human brain, as it supports directed and controlled behaviour. Thus, the plausible cost range used in the current thesis to describe the attributes of the brain networks was set between 2.5% and 50% (sampled in 2.5% steps in the lower range and 5% in the higher range).

For definition of which of all available edges to use at certain cost levels, first a priority order of the edges in which they should be added to the graph has to be defined. There is currently no gold standard of how to order the edges, except that the ordering is based on the correlation values (as captured in the connectivity matrix) and that the graph always should be fully connected, as fragmented brain networks are not plausible and more difficult to compare. So the first edges added to the graph are the edges that are needed to fully connect all the nodes and assure that each node has at least one connection to the rest of the nodes. The first edges used for each node were the edges with the highest correlation values between this node and another node. Then further edges according to the second highest correlation value were added, and so on until the graph was fully connected. Such a configuration builds the *minimum spanning tree* (MST) of a network. So for example, the MST could be built in study II averaged over all subjects at a cost level of 1.74% (with a small deviation); hence by using the lowest cost level of 2.5% in study II it was assured that all individual graphs were fully connected. Finally, adding of further edges to the graph followed the same strategy. For each node further edges were added according to the height of the correlation values between this node and all others. This strategy (the k-nearest neighbour graph (k-NNG) growing, with k as the number of edges per node) assured an equal graph growing and was described by Alexander-Bloch et al. (2010). In the end, the edges between nodes used in a graph at a certain cost level, are the percent number of edges with the highest order. Graphs with higher cost levels always comprise the edges from the graphs at the lower cost values. As a consequence, when averaging graph parameters over a cost range, as done so in study II and III, connections or edges with relative higher correlation values gain more weight.

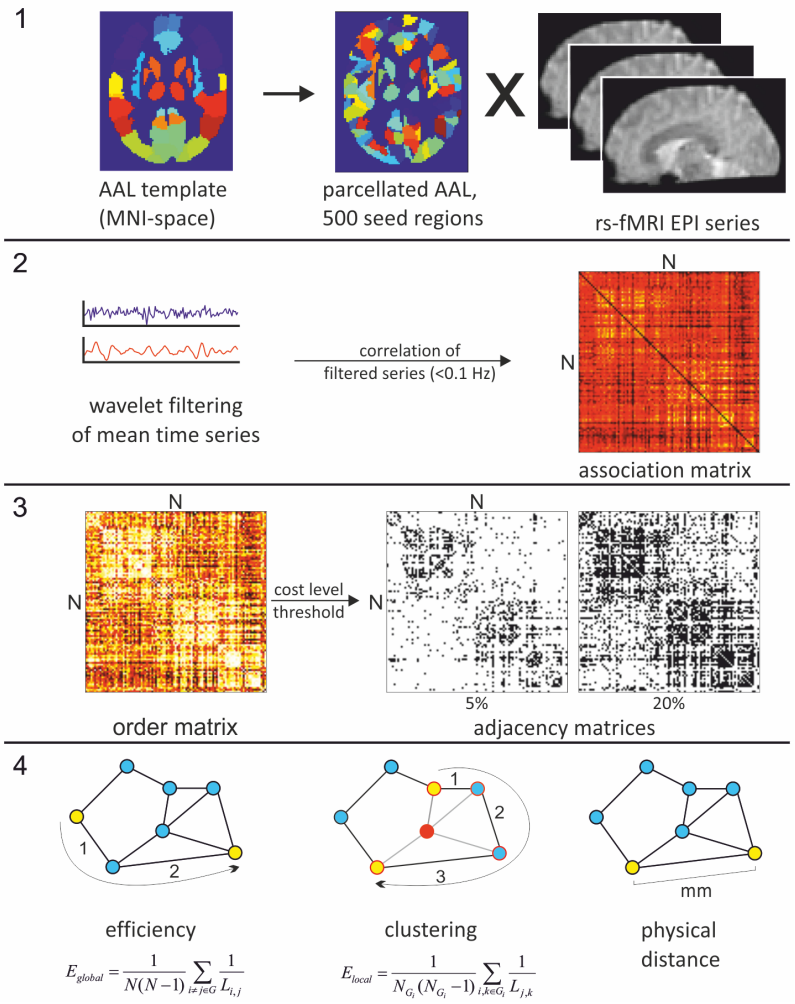

Figure 1.4: Scheme for creating of the graphs. Step 1: Anatomical subregions from the AAL standard grey matter brain atlas (SPM toolbox wfu-pickatlas) are further randomly parcellated in smaller subregions. Result is a template with 500 seed regions that is used to extract the mean BOLD time series (mean of time courses of all voxels inside each seed region). The datasets for each RS period analysed in study II and III consisted of 256 functional scans. Scans were prior spatially realigned, slice-time corrected and normalized to MNI-space. **Step 2:** The extracted mean time series of each seed region get first corrected for head motion by only further using the residuals after multiple regression with the six motion parameters from spatial realignment. Wavelet filtering is then used to access frequency ranges below 0.1 Hz. The resulting wavelet coefficients are used to determine the functional coupling between the particular seed regions (correlation values) in this frequency band(s) and stored in an N by N association matrix with N = number of seed regions. **Step 3:** A sorting algorithm is used to determine the order in which edges are added to the graph. The ordering process bases on the height of the correlation values but further assures that i) the graph is fully connected and that ii) graph growing is homogeneous (respectively the degrees of the nodes do not vary much). The order matrix is then used to build adjacency matrices at different cost levels. Adjacency matrices determine which nodes/brain regions are treated as functionally connected for the calculation of the graph metrics. The cost levels determine the number of edges that are used in a graph. E.g. a graph at 5% uses the 5% of all edges with the highest orders from the order matrix. In studies II and III 15 different cost levels in the range from 2.5% to 50% were investigated. **Step 4:** Formulas from Watts & Strogats and Latora & Marchiori are used to calculate the graph metrics of efficiency and clustering. These values base on the inverse, harmonic mean of the path lengths between all pair of nodes in the graph (efficiency) or between all pair of nodes in subgraphs as separately built for all nodes in the graph (clustering). Physical distances base on the Euclidean distance between connected nodes. These state only three of many graph metrics that can be potentially derived from graphs, but are the mainly used measures in studies II and III.

Graph Parameters and their Meaning for Cognitive Performance

With established graphs many different graph parameters can be computed. Some are more region specific/based on nodal relations, such as the degree (defined by the number of edges leaving a node) or the hubness of a node (determined by the number of paths going through a node), some refer to sub-graphs such as modularity (groupings of more densely connected nodes which show distinguishable less dense coherence to the rest of the graph) or clustering (path lengths between neighboured nodes), and finally measures that relate to the whole network such as efficiency (average path lengths between all pairs of nodes) and physical distances (Euclidian distances between nodes). Goals of studies II and III were to capture brain attributes on more global scales, as there were a priory no regional assumptions.

Two of the graph parameters addressed in the current thesis were global efficiency and average clustering over all nodes (Figure 1.4); a number of recent studies provided evidence that both measures are associated with cognitive capacity and attentional performance. It was shown that scores in intelligence tests (based on performance in various tasks) correlated positively with global efficiency (Li et al., 2009; van den Heuvel et al., 2009). Other studies revealed that aged subjects show lowered global efficiency and increased clustering (Gong et al., 2009; Wang et al., 2010) which is a indirect piece of evidence for the relation of maleficial network configuration and task or cognitive performance, as it is known from other studies that aged subjects typically show poorer performance in tasks (Berardi et al., 2001; Gazzaley et al., 2005). Wang et al. (2009) could also identify maleficial network configuration for attentional performance (lowered global efficiency, increased clustering) in a patient study with children suffering from attention deficit hyperactivity disorder (ADHD). In summary, the two graph metrics of nodal efficiency and clustering may represent a biomarker for cognitive capacity and reflect measures of the brain's capability to adjust and adapt behaviour.

A third graph parameter investigated was physical (Euclidian) distances between connected nodes. As different to the measure of efficiency, which is dimensionless and based on the *number* of edges between nodes, physical distances describe the lengths of communication pathways between nodes (edges) in physical space. Communication via short physical pathways was earlier considered as a strategy of the brain to preserve metabolic costs (Niven & Laughlin, 2008; Kitzbichler et al., 2011). Communication over long distance fibers affords to maintain more ion channels over wider membrane surface and more metabolic energy in order to restore and uphold the membrane potential (Laughlin et al., 1998; Attwell & Laughlin, 2001). So in study II a shift towards more short-distance communication after the demanding task, more pronounced in subjects with poorer performance, was seen as a consequence of the challenged brain that needed to preserve energy for upholding intrinsic states.

Conclusions and Restrictions of Graph Theory Application

With extending the view from regionally restricted activation patterns to the whole brain network and comparing network attributes related generally to cognitive capacity a step backwards is made in revealing the true mechanisms underlying these changes. The question if changes as e.g. in efficiency or clustering underlie global mechanisms and strategies of a challenged (or 'fatigued') brain or if they are triggered by specialized neural circuits, responsible for reconfiguration and reallocation of communication pathways, remains unanswered. As pointed out in study II, thalamic regions could fulfil a key role in functional reorganization of functional networks, but further proof is needed in order to consolidate this finding.

As a method in progress, graph theoretical techniques to date provide no sufficient empirical support for such kind of more specific analyses esp. with regard to task involved network modules or network hierarchy. Main reason is the lack of a gold standard of these methods and hence the missing opportunity to compare graph specific findings with findings from other studies. As pointed out above, graph theory is a very relativistic technique; graph parameters are only meaningful in comparison. Progress has to be made in defining rules about graph building, such as choice of nodes and the way edges should be ordered when added to a graph. Further, for the investigation of more specific roles of brain regions or sub-networks for the whole brain network topology, algorithms for identifying and classification of such sub-graphs or network modules must be elaborated and normalized.

A further restriction of most graph theoretical studies in the field of fMRI to date is the restriction to a data basis of resting state measurements and thus the limited access to the dynamic of brain networks. The brain in a resting state condition is from a perspective directed functional processing in order to perform a task in a relative 'static' network configuration. Low frequency fluctuations below 0.1 Hz, the only range that is reasonable and accessible by temporally low sampled BOLD time series, are not representative for fast changes in the range of milliseconds as they would be necessary for successful task performance. The relation between high frequency and low frequency coherence patterns in the brain is to date merely understood (as e.g. discussed in Bullmore & Bassett, 2011). As a consequence, the amount to which graphs built on the correlation basis of functional MRI time series acquired *during* a task are affected by task related high frequency correlation changes is not clear and will probably be a key focus of future work. So far, conclusions about brain network dynamics can only be made indirectly by use of data from several resting state periods in an experiment that are separated by manipulative treatments, as also used in study II.

1.7 The Future of Brain Network Analysis

Drawing a more complete picture. The brain is a complex and coherent information processing system. Within the last few years more and more studies have started to use additional analysis with respect to connectivity measures between brain regions and brain networks analysis. It has come into awareness that describing single brain regions involved in experimental task processing might only represent the 'tip of the iceberg' of a working brain and that information about more widespread network interactions, either in between task involved regions or in subliminal, 'background' network processes, might play a key role for the understanding of brain function. The observed increasing frequency of studies that report measures of brain connectivity and network attributes will further push forward the development of tools for brain network analysis that will provide more insight in such network processes. The current thesis contributes with the application of two techniques that allowed qualitatively different insights into neuronal networks. *The partial least square analysis* allows deriving main covariance components between two sets of active brain regions during task performance and helped to identify different functional roles of the brain regions for stimulus processing. This multivariate approach was an elegant way to cope with inter-individual variability and further relate the many different activity levels captured on small-volume (voxel) level to each other by circumventing problems of multiple comparison testing and over-fitted models. Partial least squares analysis can help to understand complex interactions of neuronal activation patterns such as revealed with fMRI and is valuable for neuroscientists who investigate neuronal network-network or network-behaviour interactions. *Graph analysis* gives new insights into how the brain network is configured and how it assures efficient information flow. Graph models allow to access many aspects of brain network attributes from the level of single brain nodes to whole network efficiency and organization. Only global measures derived with graph theory were focus of the current thesis, but these measures as e.g. global efficiency and clustering were successfully related to a representation of subjects' cognitive states and their limitations or resilience towards the challenges of the performed task. Graph analysis is still a method in development and more studies about new techniques and algorithms for analysing brain graphs are expected in future days. However, the current graph analytical framework as described in the current thesis can be seen as a solid start with this technique and a good basis on which future frameworks can build on.

Graph theory as a diagnostic tool. Graph theory for functional brain data has become one of the driving forces for the renaissance of resting state research within the last few years. One major reason is given by the potential for its application in clinical research. The progresses made in describing pathological brain networks in patients with psychological diseases clear the way for using graph metrics as an additional or supportive tool for diagnosis of psychological diseases. However, future work is necessary to further elaborate the graph analytical method and to investigate variables that impact or change graph analytical results, respectively intrinsic brain network configurations. The current thesis contributed with the investigation of two potential modulators for intrinsic brain states, task demand and smoking status. Whereas smoking status might only have minor impact on intrinsic brain states, as based on the findings of the current thesis, task demand was observed to lead to widespread changes in intrinsic network configuration. Future research will be needed that evaluates the tolerated dynamic range in which derived network parameters are understood as 'normal' or 'healthy' and at which point network metrics can be seen as 'abnormal' or 'pathological'. Without a better understanding about such dynamic ranges of network metrics, as also caused by the individual history of tasks performed by potential patients before brain scanning, a reliable diagnosis is hardly possible.

Exploring complex networks during tasks. Further perspectives of future studies that work with the graph analytical approach are also given by the current limitations of the graph theory application, such as the predominant focus on analysis of resting state data only and the restriction to low frequency bands when based on fMRI data, which is currently the most frequently used data basis for graph theoretical studies in the field of neuroscience. In order to get insight into dynamic network configuration changes during task performance, more knowledge is needed about how task induced high correlations between task involved brain regions relate to task unrelated 'background' brain networks and how to potentially separate these processes (as e.g. discussed in Giessing & Thiel, 2012). As it is a crucial part of brain function to quickly react to demands of the environment and tasks in order to adjust behaviour, such investigations also have to take into account dynamic processes in higher frequency ranges. During task performance, the brain needs to adapt and reconfigure its functional networks in the ranges of milliseconds, reconfiguration processes that cannot be accessed by temporally poor sampled fMRI data. Consistent attributes of neuronal signals over different frequency bands, such as the self-similarity or fractal properties of neuronal signals, and mathematical frameworks in order to reveal common attributes of brain network communication at different frequency scales have been elucidated (Bullmore et al., 2009; Meunier et al., 2010), however, it is subject to future studies to adopt these approaches and to show how brain networks or modules are dynamically shaped in response to task demands.

1.8 References

Achard, S., Salvador, R., Whitcher, B., Suckling, J. & Bullmore, E. (2006) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. The Journal of neuroscience : the official journal of the Society for Neuroscience, 26, 63-72.

Albert, N.B., Robertson, E.M. & Miall, R.C. (2009) The resting human brain and motor learning. Curr Biol, 19, 1023-1027.

Alexander-Bloch, A.F., Gogtay, N., Meunier, D., Birn, R., Clasen, L., Lalonde, F., Lenroot, R., Giedd, J. & Bullmore, E.T. (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. Frontiers in systems neuroscience, 4, 147.

Attwell, D. & Laughlin, S.B. (2001) An energy budget for signaling in the grey matter of the brain. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism, 21, 1133-1145.

Baars, B.J. (1997) In the theater of consciousness : the workspace of the mind. Oxford University Press, New York.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R. & Meyer-Lindenberg, A. (2008) Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci, 28, 9239-9248.

Bates, T., Mangan, G., Stough, C. & Corballis, P. (1995) Smoking, processing speed and attention in a choice reaction time task. Psychopharmacology, 120, 209-212.

Berardi, A., Parasuraman, R. & Haxby, J.V. (2001) Overall vigilance and sustained attention decrements in healthy aging. Experimental aging research, 27, 19-39.

Berridge, K.C. (2004) Motivation concepts in behavioral neuroscience. Physiology & behavior, 81.

Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S., Rao, S.M. & Cox, R.W. (1999) Conceptual processing during the conscious resting state. A functional MRI study. Journal of cognitive neuroscience, 11, 80-95.

Boksem, M.A., Meijman, T.F. & Lorist, M.M. (2005) Effects of mental fatigue on attention: an ERP study. Brain Res Cogn Brain Res, 25, 107-116.

Boksem, M.A., Meijman, T.F. & Lorist, M.M. (2006) Mental fatigue, motivation and action monitoring. Biol Psychol, 72, 123-132.

Botvinick, M.M., Cohen, J.D. & Carter, C.S. (2004) Conflict monitoring and anterior cingulate cortex: an update. Trends in cognitive sciences, 8, 539-546.

Breese, C.R., Marks, M.J., Logel, J., Adams, C.E., Sullivan, B., Collins, A.C. & Leonard, S. (1997) Effect of smoking history on [3H]nicotine binding in human postmortem brain. The Journal of pharmacology and experimental therapeutics, 282, 7-13.

Buckner, R.L. & Vincent, J.L. (2007) Unrest at rest: default activity and spontaneous network correlations. NeuroImage, 37, 1091-1096; discussion 1097-1099.

Bullmore, E., Barnes, A., Bassett, D.S., Fornito, A., Kitzbichler, M., Meunier, D. & Suckling, J. (2009) Generic aspects of complexity in brain imaging data and other biological systems. NeuroImage, 47, 1125-1134.

Bullmore, E. & Sporns, O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems (vol 10, pg 186, 2009). Nature Reviews Neuroscience, 10.

Bullmore, E.T. & Bassett, D.S. (2011) Brain graphs: graphical models of the human brain connectome. Annual review of clinical psychology, 7, 113-140.

Carr, D.B. & Sesack, S.R. (2000) Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. J Neurosci, 20, 3864-3873.

Chen, N. & Stein, L.D. (2006) Conservation and functional significance of gene topology in the genome of Caenorhabditis elegans. Genome research, 16, 606-617.

Corbetta, M. & Shulman, G.L. (2002) Control of goal-directed and stimulus-driven attention in the brain. Nature reviews. Neuroscience, 3, 201-215.

Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A. & Meyerand, M.E. (2001) Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. American Journal of Neuroradiology, 22, 1326-1333.

Damoiseaux, J.S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M. & Beckmann, C.F. (2006) Consistent resting-state networks across healthy subjects. P Natl Acad Sci USA, 103, 13848-13853.

de Haan, W., Pijnenburg, Y.A., Strijers, R.L., van der Made, Y., van der Flier, W.M., Scheltens, P. & Stam, C.J. (2009) Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory. BMC neuroscience, 10, 101.

de Leon, J. & Diaz, F.J. (2005) A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res, 76, 135-157.

Dehaene, S., Kerszberg, M. & Changeux, J.P. (1998) A neuronal model of a global workspace in effortful cognitive tasks. P Natl Acad Sci USA, 95, 14529-14534.

Dejong, S. (1993) Simpls - an Alternative Approach to Partial Least-Squares Regression. Chemometrics and Intelligent Laboratory Systems, 18, 251-263.

Duff, E.P., Johnston, L.A., Xiong, J., Fox, P.T., Mareels, I. & Egan, G.F. (2008) The power of spectral density analysis for mapping endogenous BOLD signal fluctuations. Human brain mapping, 29, 778-790.

Duncan, E., Madonick, S., Chakravorty, S., Parwani, A., Szilagyi, S., Efferen, T., Gonzenbach, S., Angrist, B. & Rotrosen, J. (2001) Effects of smoking on acoustic startle and prepulse inhibition in humans. Psychopharmacology, 156, 266-272.

Efron, B., Tibshirani, R.J. (1994) An Introduction to the Bootstrap. Chapman & HALL/CRC.

Foulds, J., Stapleton, J., Swettenham, J., Bell, N., McSorley, K. & Russell, M.A. (1996) Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology, 127, 31-38.

Freedman, R., Hall, M., Adler, L.E. & Leonard, S. (1995) Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry, 38, 22-33.

Gallinat, J., Meisenzahl, E., Jacobsen, L.K., Kalus, P., Bierbrauer, J., Kienast, T., Witthaus, H., Leopold, K., Seifert, F., Schubert, F. & Staedtgen, M. (2006) Smoking and structural brain deficits: a volumetric MR investigation. Eur J Neurosci, 24, 1744-1750.

Gazzaley, A., Cooney, J.W., Rissman, J. & D'Esposito, M. (2005) Top-down suppression deficit underlies working memory impairment in normal aging. Nature neuroscience, 8, 1298-1300.

Gehring, W.J. & Knight, R.T. (2000) Prefrontal-cingulate interactions in action monitoring. Nature neuroscience, 3, 516-520.

Giessing, C. & Thiel, C.M. (2012) Pro-cognitive drug effects modulate functional brain network organiza-

tion. Frontiers in behavioral neuroscience, 6, 53.

Giessing, C., Thiel, C.M., Alexander-Bloch, A.F., Patel, A.X., Bullmore, E.T. (under review) Human brain functional network changes associated with enhanced and impaired attentional task performance.

Giessing, C., Thiel, C.M., Rosler, F. & Fink, G.R. (2006) The modulatory effects of nicotine on parietal cortex activity in a cued target detection task depend on cue reliability. Neuroscience, 137, 853-864.

Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z.J., He, Y. & Evans, A.C. (2009) Age- and gender-related differences in the cortical anatomical network. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 15684-15693.

Greicius, M.D., Kiviniemi, V., Tervonen, O., Vainionpaa, V., Alahuhta, S., Reiss, A.L. & Menon, V. (2008) Persistent default-mode network connectivity during light sedation. Human brain mapping, 29, 839-847.

Gusnard, D.A. & Raichle, M.E. (2001) Searching for a baseline: functional imaging and the resting human brain. Nature reviews. Neuroscience, 2, 685-694.

Hahn, T.T., Sakmann, B. & Mehta, M.R. (2006) Phase-locking of hippocampal interneurons' membrane potential to neocortical up-down states. Nature neuroscience, 9, 1359-1361.

Haider, B., Duque, A., Hasenstaub, A.R. & McCormick, D.A. (2006) Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. J Neurosci, 26, 4535-4545.

Helton, W.S., Hollander, T.D., Warm, J.S., Matthews, G., Dember, W.N., Wallaart, M., Beauchamp, G., Parasuraman, R. & Hancock, P.A. (2005) Signal regularity and the mindlessness model of vigilance. Br.J Psychol, 96, 249-261.

Hilgetag, C.C., O'Neill, M.A. & Young, M.P. (2000) Hierarchical organization of macaque and cat cortical sensory systems explored with a novel network processor. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 355, 71-89.

Hopfinger, J.B., Buonocore, M.H. & Mangun, G.R. (2000) The neural mechanisms of top-down attentional control. Nature neuroscience, 3, 284-291.

Kahneman, D. (1973) Attention and Effort. Prentice Hall, Englewood Cliffs, NJ.

Kitzbichler, M.G., Henson, R.N., Smith, M.L., Nathan, P.J. & Bullmore, E.T. (2011) Cognitive effort drives workspace configuration of human brain functional networks. The Journal of neuroscience : the official journal of the Society for Neuroscience, 31, 8259-8270.

Koelega, H.S. (1993) Stimulant drugs and vigilance performance: a review. Psychopharmacology, 111, 1-16.

Kozak, R., Bruno, J.P. & Sarter, M. (2006) Augmented prefrontal acetylcholine release during challenged attentional performance. Cerebral cortex, 16, 9-17.

Kumari, V. & Postma, P. (2005) Nicotine use in schizophrenia: the self medication hypotheses. Neuroscience and biobehavioral reviews, 29, 1021-1034.

Kumari, V., Soni, W. & Sharma, T. (2001) Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. Human psychopharmacology, 16, 321-326.

Latora, V. & Marchiori, M. (2001) Efficient behavior of small-world networks. Phys Rev Lett, 87.

Latora, V. & Marchiori, M. (2003) Economic small-world behavior in weighted networks. European Physical Journal B, 32, 249-263.

Laughlin, S.B., de Ruyter van Steveninck, R.R. & Anderson, J.C. (1998) The metabolic cost of neural information. Nature neuroscience, 1, 36-41.

Laughlin, S.B. & Sejnowski, T.J. (2003) Communication in neuronal networks. Science, 301, 1870-1874.

Lewis, C.M., Baldassarre, A., Committeri, G., Romani, G.L. & Corbetta, M. (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci U S A, 106, 17558-17563.

Li, Y.H., Liu, Y., Li, J., Qin, W., Li, K.C., Yu, C.S. & Jiang, T.Z. (2009) Brain Anatomical Network and Intelligence. Plos Computational Biology, 5.

Lim, J., Wu, W.C., Wang, J.J., Detre, J.A., Dinges, D.F. & Rao, H.Y. (2010) Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect. NeuroImage, 49, 3426-3435.

Lohr, J.B. & Flynn, K. (1992) Smoking and schizophrenia. Schizophr Res, 8, 93-102.

Lorist, M.M., Boksem, M.A. & Ridderinkhof, K.R. (2005) Impaired cognitive control and reduced cingulate activity during mental fatigue. Brain Res Cogn Brain Res, 24, 199-205.

Lynall, M.E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., Muller, U. & Bullmore, E. (2010) Functional connectivity and brain networks in schizophrenia. The Journal of neuroscience : the official journal of the Society for Neuroscience, 30, 9477-9487.

Manly, T., Robertson, I.H., Galloway, M. & Hawkins, K. (1999) The absent mind: further investigations of sustained attention to response. Neuropsychologia, 37, 661-670.

Mazoyer, B., Zago, L., Mellet, E., Bricogne, S., Etard, O., Houde, O., Crivello, F., Joliot, M., Petit, L. & Tzourio-Mazoyer, N. (2001) Cortical networks for working memory and executive functions sustain the conscious resting state in man. Brain research bulletin, 54, 287-298.

McIntosh, A.R., Bookstein, F.L., Haxby, J.V. & Grady, C.L. (1996) Spatial pattern analysis of functional brain images using partial least squares. NeuroImage, 3, 143-157.

Mesulam, M.M., Nobre, A.C., Kim, Y.H., Parrish, T.B. & Gitelman, D.R. (2001) Heterogeneity of cingulate contributions to spatial attention. NeuroImage, 13, 1065-1072.

Meunier, D., Lambiotte, R. & Bullmore, E.T. (2010) Modular and hierarchically modular organization of brain networks. Frontiers in neuroscience, 4, 200.

Milberger, S., Biederman, J., Faraone, S.V., Chen, L. & Jones, J. (1997) ADHD is associated with early initiation of cigarette smoking in children and adolescents. J Am Acad Child Psy, 36, 37-44.

Nachreiner, F. & Hanecke, K. (1992) Vigilance. In Smith, A.P., Jones, D.M. (eds) Handbook of human performance. Academic Press, London, pp. 261-288.

Niven, J.E. & Laughlin, S.B. (2008) Energy limitation as a selective pressure on the evolution of sensory systems. The Journal of experimental biology, 211, 1792-1804.

Nyback, H., Nordberg, A., Langstrom, B., Halldin, C., Hartvig, P., Ahlin, A., Swahn, C.G. & Sedvall, G. (1989) Attempts to visualize nicotinic receptors in the brain of monkey and man by positron emission tomography. Progress in brain research, 79, 313-319.

Parasuraman, R., Warm, J.S. & See, J.E. (1998) The attentive brain. In Parasuraman, R. (ed) Brain systems of vigilance. MIT Press, Cambridge, pp. 221-256.

Pashler, H.E. (1998) The Psychology of Attention. MIT Press, Cambridge, MA.

Petersen, C.C., Hahn, T.T., Mehta, M., Grinvald, A. & Sakmann, B. (2003) Interaction of sensory responses with spontaneous depolarization in layer 2/3 barrel cortex. Proc Natl Acad Sci U S A, 100, 13638-13643.

Petersen, S.E., van Mier, H., Fiez, J.A. & Raichle, M.E. (1998) The effects of practice on the functional

anatomy of task performance. Proc Natl Acad Sci U S A, 95, 853-860.

Pomerleau, O.F., Downey, K.K., Stelson, F.W. & Pomerleau, C.S. (1995) Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. Journal of substance abuse, 7, 373-378.

Posner, M.I. (1994) Attention: the mechanisms of consciousness. P Natl Acad Sci USA, 91, 7398-7403.

Raichle, M.E. (1998) Behind the scenes of functional brain imaging: a historical and physiological perspective. Proc Natl Acad Sci U S A, 95, 765-772.

Raichle, M.E., Fiez, J.A., Videen, T.O., MacLeod, A.M., Pardo, J.V., Fox, P.T. & Petersen, S.E. (1994) Practice-related changes in human brain functional anatomy during nonmotor learning. Cereb Cortex, 4, 8-26.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. & Shulman, G.L. (2001) A default mode of brain function. P Natl Acad Sci USA, 98, 676-682.

Raichle, M.E. & Mintun, M.A. (2006) Brain work and brain imaging. Annual review of neuroscience, 29, 449-476.

Rezvani, A.H. & Levin, E.D. (2001) Cognitive effects of nicotine. Biol Psychiatry, 49, 258-267.

Robbins, T.W. & Everitt, B.J. (1996) Neurobehavioural mechanisms of reward and motivation. Current opinion in neurobiology, 6, 228-236.

Robertson, I.H., Manly, T., Andrade, J., Baddeley, B.T. & Yiend, J. (1997) 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia, 35, 747-758.

Rosipal, R. & Kramer, N. (2006) Overview and recent advances in partial least squares. Subspace, Latent Structure and Feature Selection, 3940, 34-51.

Sacco, K.A., Bannon, K.L. & George, T.P. (2004) Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. J Psychopharmacol, 18, 457-474.

Salinas, E. & Sejnowski, T.J. (2001) Correlated neuronal activity and the flow of neural information. Nature reviews. Neuroscience, 2, 539-550.

Salvador, R., Suckling, J., Schwarzbauer, C. & Bullmore, E. (2005) Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philosophical Transactions of the Royal Society B-Biological Sciences, 360, 937-946.

Sarter, M., Gehring, W.J. & Kozak, R. (2006) More attention must be paid: the neurobiology of attentional effort. Brain Res Rev, 51, 145-160.

Schultz, W. (2010) Dopamine signals for reward value and risk: basic and recent data. Behavioral and brain functions : BBF, 6, 24.

Schwarz, A.J., Gozzi, A. & Bifone, A. (2008) Community structure and modularity in networks of correlated brain activity. Magnetic resonance imaging, 26, 914-920.

Shulman, G.L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M. & Petersen, S.E. (1997) Top-down modulation of early sensory cortex. Cerebral cortex, 7, 193-206.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, L., Miezin, F.M., Petersen, S.E. (1997) Common Blood Flow Changes across Visual Tasks. Journal of Cognitive Neurosicence, 9, 648-663.

Small, D.M., Gitelman, D., Simmons, K., Bloise, S.M., Parrish, T. & Mesulam, M.M. (2005) Monetary incentives enhance processing in brain regions mediating top-down control of attention. Cerebral Cortex, 15, 1855-1865.

Sporns, O., Chialvo, D.R., Kaiser, M. & Hilgetag, C.C. (2004) Organization, development and function of complex brain networks. Trends in cognitive sciences, 8, 418-425.

Stam, C.J. (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci Lett, 355, 25-28.

Stam, C.J., de Haan, W., Daffertshofer, A., Jones, B.F., Manshanden, I., van Cappellen van Walsum, A.M., Montez, T., Verbunt, J.P., de Munck, J.C., van Dijk, B.W., Berendse, H.W. & Scheltens, P. (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. Brain : a journal of neurology, 132, 213-224.

Stein, E.A., Pankiewicz, J., Harsch, H.H., Cho, J.K., Fuller, S.A., Hoffmann, R.G., Hawkins, M., Rao, S.M., Bandettini, P.A. & Bloom, A.S. (1998) Nicotine-induced limbic cortical activation in the human brain: a functional MRI study. The American journal of psychiatry, 155, 1009-1015.

Stephan, K.E., Hilgetag, C.C., Burns, G.A., O'Neill, M.A., Young, M.P. & Kotter, R. (2000) Computational analysis of functional connectivity between areas of primate cerebral cortex. Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 355, 111-126.

Stevens, W.D., Buckner, R.L. & Schacter, D.L. (2010) Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cereb Cortex, 20, 1997-2006.

Thiel, C.M., Zilles, K. & Fink, G.R. (2005) Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. Neuropsychopharmacol, 30, 810-820.

Tobias, R.D. (1995) An Introduction to Partial Least Squares Regression. SAS Institute Inc., Cary, NC.

Tomporowski, P.D. & Tinsley, V.F. (1996) Effects of memory demand and motivation on sustained attention in young and older adults. The American journal of psychology, 109, 187-204.

Treue, S. & Maunsell, J.H. (1996) Attentional modulation of visual motion processing in cortical areas MT and MST. Nature, 382, 539-541.

Treue, S. & Maunsell, J.H. (1999) Effects of attention on the processing of motion in macaque middle temporal and medial superior temporal visual cortical areas. J Neurosci, 19, 7591-7602.

van den Heuvel, M.P., Mandl, R.C., Stam, C.J., Kahn, R.S. & Hulshoff Pol, H.E. (2010) Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J Neurosci, 30, 15915-15926.

van den Heuvel, M.P., Stam, C.J., Kahn, R.S. & Pol, H.E.H. (2009) Efficiency of Functional Brain Networks and Intellectual Performance. J Neurosci, 29, 7619-7624.

van der Voet, H. (1994) Comparing the Predictive Accuracy of Models Using a Simple Randomization Test. Chemometrics and Intelligent Laboratory Systems, 25, 313-323.

Waites, A.B., Stanislavsky, A., Abbott, D.F. & Jackson, G.D. (2005) Effect of prior cognitive state on resting state networks measured with functional connectivity. Human brain mapping, 24, 59-68.

Wang, L., Li, Y., Metzak, P., He, Y. & Woodward, T.S. (2010) Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. NeuroImage, 50, 862-872.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., Zhong, Q. & Wang, Y. (2009) Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Human brain mapping, 30, 638-649.

Watts, D.J. & Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. Nature, 393, 440-442.

Wold, H. (1969) Econometrics as Pioneering in Nonexperimental Model Building. Econometrica, 37, 369-381.

Wold, S., Ruhe, A., Wold, H. & Dunn, W.J. (1984) The collinearity problem in linear regression. The partial least squares (PLS) approach to generalized inverses. SIAM Journal of Scientific and Statistical Computing, 5, 735-743.

Wu, C.W., Gu, H., Lu, H., Stein, E.A., Chen, J.H. & Yang, Y. (2008) Frequency specificity of functional connectivity in brain networks. NeuroImage, 42, 1047-1055.

Zalesky, A., Fornito, A., Harding, I.H., Cocchi, L., Yucel, M., Pantelis, C. & Bullmore, E.T. (2010) Whole-brain anatomical networks: does the choice of nodes matter? NeuroImage, 50, 970-983.

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y. & Gong, Q. (2011a) Disrupted brain connectivity networks in drug-naive, first-episode major depressive disorder. Biol Psychiatry, 70, 334-342.

Zhang, X., Salmeron, B.J., Ross, T.J., Geng, X., Yang, Y. & Stein, E.A. (2011b) Factors underlying prefrontal and insula structural alterations in smokers. NeuroImage, 54, 42-48.

Study I

Impact of Brain Networks Involved in Vigilance on Processing Irrelevant Visual Motion

Short title: Long- and short-term aspects of vigilance

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Research highlights

- Different brain networks involved in short-term and long-term aspects of vigilance
- Processing of motion distractors functionally related to short-term network
- Short-term network can be functionally segregated into two components
- Motivation and arousal components of short-term network mediate distractor processing

Keywords: fMRI, neuroimaging, sustained attention, vigilance, time on task, partial least square, distractor

2.1 Abstract

The ability to sustain attention over prolonged periods of time is called vigilance. Vigilance is a fundamental component of attention which impacts on performance in many situations. We here investigate whether similar neural mechanisms are responsible for vigilant attention over long and short durations of time and whether neural activity in brain regions sensitive to vigilant attention is related to processing irrelevant information. Brain activity was measured by means of functional magnetic resonance imaging (fMRI) in a 32 Min visual vigilance task with varying inter-target intervals and irrelevant peripheral motion stimuli. Changes in neural activity were analysed as a function of time on task to capture long-term aspects of vigilance and as a function of time between target stimuli to capture short-term aspects of vigilance. Several brain regions including the inferior frontal, posterior parietal, superior and middle temporal cortices and the anterior insular showed decreases in neural activity as a function of time on task. In contrast, increasing inter-target intervals resulted in increased neural activity in a widespread network of regions involving lateral and medial frontal areas, temporal areas, cuneus and precuneus, inferior occipital cortex (right), posterior insular cortices, the thalamus, nucleus accumbens and basal forebrain. A partial least square analysis revealed that neural activity in this latter network co-varied with neural activity related to processing irrelevant motion stimuli. Our results provide neural evidence that two separate mechanisms are responsible for sustaining attention over long and short durations. We show that only brain areas involved in sustaining attention over short durations of time are related to processing irrelevant stimuli and suggest that these areas can be segregated into two functionally different networks, one possibly involved in motivation, the other in arousal.

2.2 Introduction

The capability to sustain attention over prolonged periods of time is called vigilance. Vigilance is crucial in many work environments such as airport security controls or vehicle operations where humans have to continuously monitor and react to rare signals while ignoring irrelevant stimuli. A variety of experimental tasks have been designed to study vigilance over prolonged periods of time. These range from the classic vigilance tasks with rare, highly salient signals (e.g. Dinges and Powell, 1985; Mackworth, 1948) on the one hand to more difficult tasks with high event rates, low signal saliency and high memory load on the other side (e.g. Helton et al., 2010; Smit et al., 2004). The common finding in these tasks is a decline in detection rate and an increase in reaction time with time on task.

Despite these common findings it is still unclear what the underlying reasons for these effects are and under which task conditions a vigilance decrement can be observed. Vigilance decrements can often be found after 15 minutes of task performance, but in tasks with high cognitive demands they can occur much faster (Parasuraman et al., 1998). Posner and Boies (1971) pointed out, that short- and long-term situations both involve the ability to increase readiness and proposed that phasic increases in alertness following a warning cue may be considered as a 'miniature vigilance situation'. Yet, there are hardly any studies which explicitly addressed the question whether similar mechanisms underlie vigilance decrements over the range of several seconds as opposed to several minutes.

On the basis of patient and neuroimaging studies it has been postulated that a right lateralised fronto-parietal network contributes to sustained attention (for review see Posner and Petersen, 1990). To investigate brain regions involved in vigilance different approaches have been used. Many neuroimaging studies focussed on brain regions involved in task performance per se (e.g. Coull et al., 1998; Sturm et al., 2004) or described brain regions associated with slow as opposed to fast reaction times (Drummond et al., 2005). Only few studies investigated changes in neural activity over time which paralleled the vigilance decrement behaviourally. Studies analysing changes in neural activity as a function of time on task reported mainly decreases in neural activity in several brain regions including the right inferior parietal cortex, the right dorsolateral prefrontal cortex, the thalamus and the posterior cingulate cortex (Coull et al., 1998; Lim et al., 2010; Paus et al., 1997). However, the functional meaning of these results is still a matter of debate. It has been hypothesised that these changes in neural activity reflect a decrease in arousal and a shift from controlled to automatic processing (Coull et al., 1998; Paus et al., 1997).

Behaviourally, there is some evidence that false alarms to irrelevant stimuli increase with time on task (e. g. Boksem et al., 2005). Neurally it has been shown that processing of irrelevant stimuli is modulated by varying attentional load. Rees and colleagues asked subjects to perform a linguistic task with low or high load while ignoring irrelevant visual motion in the periphery. They found that processing irrelevant motion was decreased in the motion sensitive area MT if the processing load of the primary task engages full attention (Rees et al., 1997). Thus, if brain regions that are related to vigilance decrement over short or long durations reflect a decrease in attentional control as suggested previously, neural activity in this network should impact on processing irrelevant stimuli in motion sensitive area MT.

We here aimed to answer the question whether vigilance decrements over long and short durations activate similar brain networks and might therefore also reflect similar functional processes. We assumed that both, short-term and long-term aspects of vigilance involve a shift from controlled to automatic processing modulating neural activity related to processing of distractors. We used functional magnetic resonance imaging (fMRI) and a monotonous visual vigilance task with rare signals and irrelevant visual motion. The display was composed of a central target and peripheral motion stimuli. Time between two consecutive target stimuli varied unpredictably. We analysed vigilance decrements as a function of time on task and as a function of time between consecutive target stimuli (inter-target intervals). To investigate whether time dependent changes in neural activity predict the level of processing task-irrelevant visual motion we used a multivariate partial least square (PLS) regression approach.

2.3 Material and Methods

2.3.1 Subjects

Twenty healthy, right-handed subjects (11 female, 9 male; mean age = 27.0 years, range = 24 to 39 years) participated in the experiment. The study was approved by the ethics committee of the German Psychological Association and subjects signed written informed consent. Subjects received a monetary compensation for participation.

2.3.2 Experimental Design and Stimuli

Subjects performed a 32 Min visual vigilance task with irrelevant visual motion stimuli. The baseline display consisted of a central black fixation cross and two flanker windows (6° wide and 7° 12′ eccentric in each visual field). Each window contained five dark grey dots (diameter 36′) on a light grey background (see Figure 2.1). The target stimulus was a colour change of the fixation cross from black to red for 300 ms. In total 96 targets were presented in 32 minutes. The targets were equally distributed over the experiment by presenting three target stimuli per minute. The intervals between the target stimuli were randomized within each minute and not predictable for the subjects (the hazard function was flat over a wide range of inter-target intervals (see supplementary Figure 2.7)), mean inter-target interval = 20 seconds, which is comparable to previous work (Coull et al., 1998). The smallest possible inter-target interval was set to 3 seconds. Thus, the duration of the inter-target intervals used in our experiment was slightly longer than the duration of inter-target intervals usually used in the psychomotor vigilance task (PVT) (Dinges and Powell, 1985; Drummond et al., 2005) which is between 2 to 10 seconds and slightly shorter than the inter-target intervals used in the Mackworth's Clock-Test (Mackworth, 1969; Mackworth, 1948) where 12 targets are presented in 20 minutes. Motion stimuli were presented in the two flanker windows. In these windows, five dots randomly moved with low speed (motion on phase) or were hold constant (motion off phase) (dot-speed 5° 52′ 10″ visual angle per second). Both phases alternated every 24 seconds. A similar amount of target stimuli was presented during both phases. Subjects were instructed to report the colour change of the fixation cross by pressing a response button as fast as possible and to ignore dot movement. For response time acquisition an MRI-compatible optical response keypad ("LUMItouch", Photon Control Inc., Burnaby, BC, Canada) was used. Stimulus presentation was programmed with the Psychophysics Toolbox Version 3 (http://psychtoolbox.org/) for Matlab (The MathWorks, Inc.).

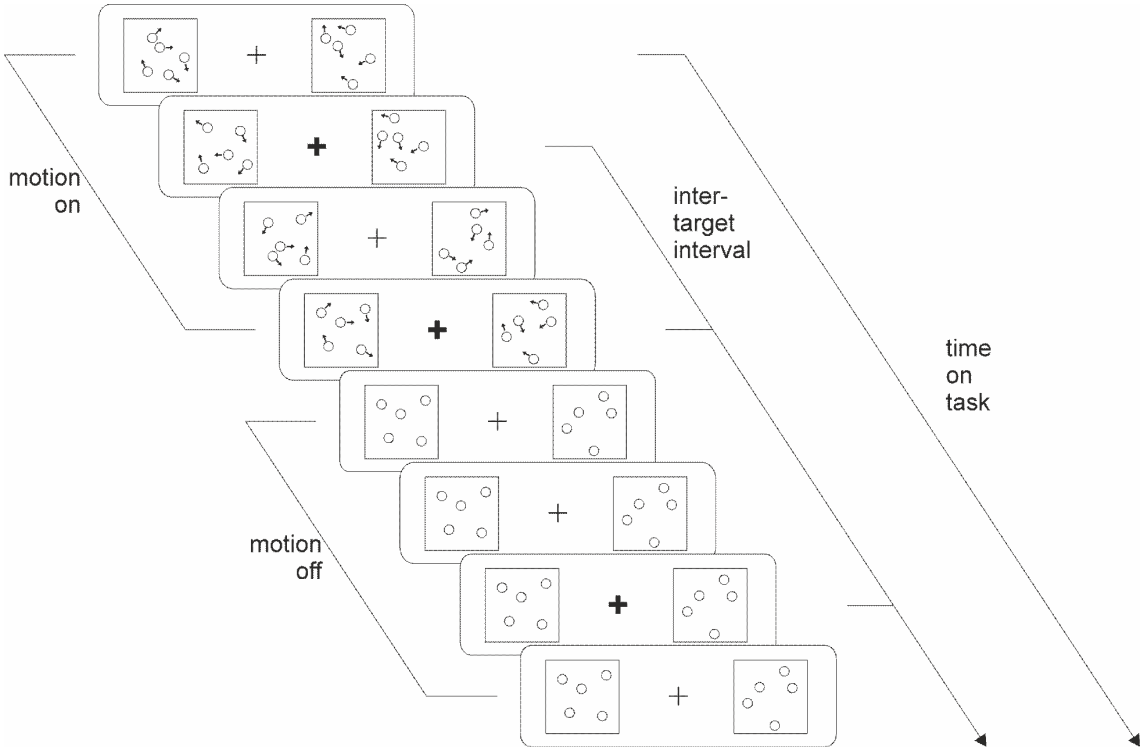

Figure 2.1: Illustration of experimental paradigm. Subjects were instructed to detect a colour change of the central fixation cross from black to red (here indicated as a bold fixation cross). Three target stimuli per minute were presented with randomized inter-target intervals. Motion stimuli were presented in two flanker windows. Each window contained dark grey dots on a light grey background (here both illustrated in white). Dot motion on and off phases alternated every 24 seconds.

2.3.3 Analysis of Behavioural Data

In order to analyse reaction times (RTs) as a function of time on task and inter-target interval, a linear mixed-effects (LMER) model was applied. Calculations were conducted with the software packages 'lme4' and 'languageR' (Baayen, 2008; Baayen et al., 2008; Pinheiro and Bates, 2000) of the statistics software R (see http://www.r-project.org/). The model was fitted using restricted maximum likelihood (REML) estimation. Note, that there is currently an intensive debate on how to estimate the correct degrees of freedom of denominators in F ratios in context of mixed effects models (see Baayen et al., 2008 for further information). Therefore, Markov chain Monte Carlo (MCMC) samples for the posterior distribution of the parameters in the fitted mixed-effects model were used to estimate the models' significance (Baayen et al., 2008). The MCMC sampling was carried out with 10,000 samples to estimate the p-values. Reaction times over 1500 ms and missed targets were defined as outliers and excluded.

Reaction times were modelled by the fixed effect factors 'time on task', 'motion phase' and 'inter-target interval' and their respective interactions. In addition, for each subject a random intercept term was added into both models. A modified Stanford Sleepiness Scale (SSS, the seven point scale of the original SSS was extended to a 10 point scale) was used prior and after the experiment to capture subjective vigilance decrements. Individual test scores were compared using a two-tailed t-test.

2.3.4 fMRI Data Acquisition

Functional and structural images were acquired on a 1.5 Tesla MRI-scanner (Siemens MAGNETOM Sonata, Siemens AG, Erlangen, Germany). Functional images were obtained using a multislice T2*-weighted gradient echo planar imaging method (EPI). Each volume consisted of 17 axial slices (voxel size 3x3 mm, 4 mm slice thickness, slice gap 40%, FoV = 200 x 200 mm^2, TR = 1,500 ms, TE = 50 ms 90° flip angle). During each experiment, 1280 whole brain scans (32 Min) were acquired. Additionally resting state measurements were obtained prior (6 Min 24 sec) and after (12 Min 48 sec) the experiment (data not presented). Structural T1-weighted images were obtained after the experiment, using magnetization frequency pulse and rapid gradient-echo (MP RAGE) sampling (1 mm isotropic, 176 slices, FoV = 256 x 256 mm^2, TR = 2,130 ms, TE = 3.93 ms and 15° flip angle).

2.3.5 fMRI Data Processing and Univariate Analysis

FMRI data were analysed using SPM5 (FIL, Wellcome Trust Centre for Neuroimaging, UCL, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). Functional images were spatially realigned and unwarped to compensate for subjects' head movements during the experiment. Slice-time correction was used for temporal realignment to the middle slice of the volumes. After coregistration of the structural and functional images, the structural T1-image was segmented into grey and white matter tissue maps and registered to the tissue probability maps of SPM5 which are spatially normalised to standard stereotaxic MNI space (Montreal Neurological Institute, Quebec, Canada). The resulting parameters of this registration were then used to normalise the functional images to MNI space. Finally, the functional images were spatially smoothed with a three-dimensional isotropic Gaussian filter of 8 mm full-width-at-half-maximum to compensate for interindividual anatomical variability.

FMRI data were statistically analysed in a two-level random effects analyses. At first level, seven regressors (three 'main' regressors modelling the average signal increase during events and four parametric regressors) went into the design matrix. Two of the 'main' regressors coded for detected target stimuli during either 'motion on' (regressor i) or 'motion off' phases (regressor iv). These two 'main' regressors were each expanded by two parametric regressors that modelled signal increases or decreases linearly related to time on task (parametric regressors ii and v) and the time lag related to each previous target presentation (parametric regressors iii and vi). These parametric regressors model changes of BOLD signal as a function of time on task or inter-target interval over and above the changes elicited by the target presentations per se. The last regressor (vii) coded for missed targets in both motion phases and had no parametric expansion. All regressors were modelled as stick functions convolved with a canonical hemodynamic response function. Data were high-pass filtered at 1/128 Hz to account for non-physiologically induced slow noise drifts. An AR(1) model was used to correct for temporal autocorrelation over scans.

At first level, four contrasts were computed for each subject and were tested for significance on the second level with one-sample-t-tests: The first contrast captured the difference between target processing during 'motion on' and 'motion off' phases, i.e. the effect of processing irrelevant visual motion at the points of time when correctly identified target stimuli appeared (for simplicity we refer to this contrast as 'motion'). The second contrast reflected the effect of task performance, i.e. target detection during motion on and motion off phases ('task performance'). The third contrast modelled signal decreases and increases linearly related to the time on task, i.e. the parametric regressors that weighted the events of the 'main' regressors with respect to time on task ('time on task'). The fourth contrast captured signal decreases and increases linearly related to the time lag between target presentations, i.e. the parametric regressors that weighted the events of the 'main' regressors with respect to inter-target interval ('inter-target interval'). Additional contrasts were used to test for the effect of motion phase on neural activity related to 'time on task' and 'inter-target intervals'. At group level, the significance threshold used for all statistical analyses was $p<0.01$ FDR corrected (one-tailed, cluster extent threshold of $k\geq 40$ voxels) (Genovese et al., 2001). The only exception was the main effect of task which is reported at $p<0.00001$ FDR corrected.

2.3.6 Multivariate Partial Least Square Regression Analysis

Overview. Partial Least Square (PLS) regression is a multivariate data analysis method which basically predicts one set of data from another set of data. PLS analyses have been introduced to the analysis of neuroimaging data by McIntosh et al. (1996) and have since been applied to a variety of questions, such as the prediction of behavioural data from brain activity (for review see Krishnan et al., 2010). Here we used a PLS regression approach to answer the question whether we can predict neural activity in area MT from neural activity in the network related to time on task effects and/or effects of inter-target interval. From a methodological perspective, PLS regression is a multivariate analysis that predicts multiple correlated response variables Y (here: neural activity in area MT) with multiple highly correlated predictor variables X (here: neural activity related to time on task and inter-target interval) by extracting latent factors. Thereby, PLS regression balances two objectives. It seeks for factors or linear combinations of X and Y that explain both, a high amount of variation in the predictor and response variable. Other statistical multivariate approaches like e.g. principal component regression optimize only for one of both criteria. Assuming that factors in the predictor space that are well sampled should provide a good prediction also for new observations, PLS factors can be expected as robust and predictive. The PLS analysis was performed in three steps: i) The model was established and the latent factors were extracted. ii) The prediction accuracy of the model was tested and iii) it was screened for predictor variables with reliable contribution to the model.

Model Definition. Two PLS models were defined, one to test whether neural activity related to time on task effects can predict neural activity in area MT, the other to test whether neural activity related to effects of inter-target intervals can predict neural activity in area MT. To define a predictor matrix X of the model, we isolated 'time on task'- and 'inter-target interval'-related networks respectively from the random effects analysis over all subjects (group-level, $p \leq 0.01$, FDR corrected, $k \geq 40$, see above) and used these as a mask to extract the mean 'time on task'- and 'inter-target interval'-related networks in each subject and voxel. Data were then entered into the predictor matrix X where each row coded for one subject and each column for the contrast estimate of one voxel. By using contrast or beta images, we averaged over the time dimension. This was done to reduce error variance and the dimensionality of the dataset (compare Caplan et al., 2006). To establish the response data matrix Y (the same in both models), spherical regions around the activation peaks in the areas MT (both hemispheres) of the motion-related activation of the random effects analysis on group level served as mask. These masks were used to extract the mean motion-related activation (i.e. the mean of the contrast estimates of all voxels within each sphere) of each subject. The radius of the sphere was set to 8 mm in order to match the size of the smoothing kernel. Each row of the response data matrix

Y represented one subject and the two columns coded for the mean contrast estimates over voxels in both areas MT (one column for each hemisphere). Both, predictor (X) and response matrices (Y) were mean centred and scaled to unity. To assure independence of the extracted activations of the two time contrasts from the motion-related network, voxels that were found active in both of the compared networks were removed. In a second step latent factors were extracted by building linear combinations of X and Y that show maximum covariance (using the algorithms of de Jong (1993), Rosipal and Kramer (2006) as implemented in the Statistics Toolbox of Matlab,Version R2008b).

Prediction Accuracy. The significance and prediction accuracy of the extracted latent factors were tested with a leave-out-one-sample (LOO) cross validation approach in combination with the randomization test of van der Voet (1994). The test of van der Voet (1994) compares the capabilities of different models to predict responses by comparing the residuals of the cross-validation procedure. The model comparison starts with a 'null model' in which Y is predicted by the means of Y (the left and right MT activations) assuming that the variables in X have no predictive value. It adds then stepwise latent factors and compares each model with the previous 'reduced' model. To explain the predictive power of the models we computed the root mean PRESS for each latent factor (MPRESS, mean predicted residual sum of squares) (Cook and Weisberg, 1982; Wold et al., 1984).

Screening for Reliable Predictor Variables. While the cross validation approach described above tests whether the extracted latent factors significantly predict MT activation a bootstrapping approach was used for each significant latent factor to identify those voxels that reliably contribute to the prediction. The bootstrapping approach identifies voxels with high and consistent voxel weights in all subjects. By sampling different subsets of subjects, we estimated for each voxel the bootstrap distribution of each X weight of the linear combination using 500 iterations. Assuming that this distribution follows a Gaussian distribution Z-scores were thresholded on a significance level of $p \leq 0.05$, two-tailed (this procedure was already described by Giessing et al. 2007).

2.4 Results

2.4.1 Behavioural Data

On average, the rate of misses was low (mean=1.95, STD=±0.94) reflecting the undemanding nature of the task. Statistical analysis of behavioural data therefore focussed on reaction times. We found a significant increase of the RTs as a function of time on task (t=2.71, MCMC sampling test p≤0.05). RTs were increased by 10.44% at the end of the task, reflecting a raw RT increase of 39.84 ms (see Figure 2.2 A). Similarly, the subjective ratings in the Stanford Sleepiness Scale after the experiment indicated a decrease in alertness (p≤0.001, mean increase=2.23, STD=±1.25).

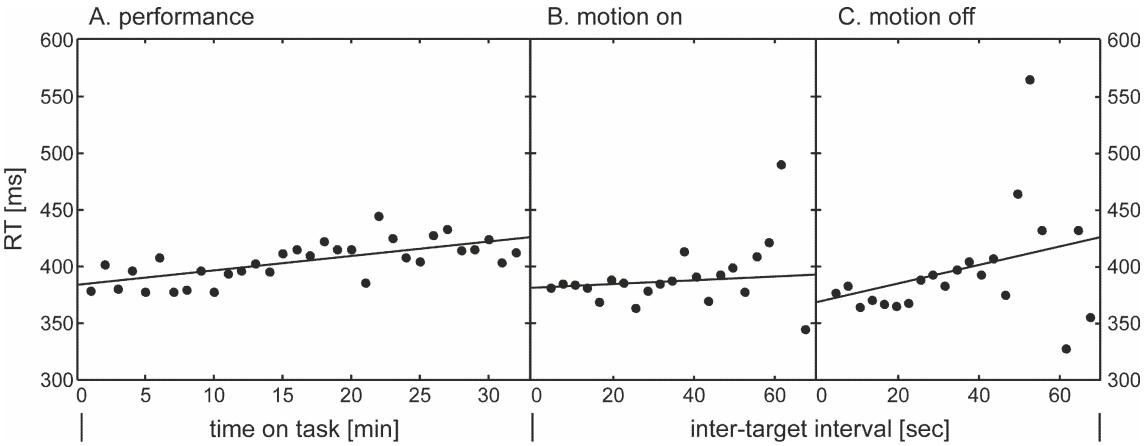

Figure 2.2: Behavioural data. A. Reaction times as a function of time on task. Each dot represents the mean over the median RT of each of the 20 subjects (all values binned to minutes of task time). Solid line represents result of regression over all median values (see text). The regression predicts an RT increase of 39.84 ms after 32 minutes of task time. **B.** Median RTs as a function of inter-target interval during motion was on. **C.** Median RTs as a function of inter-target interval during motion was off. RTs were binned to inter- target intervals of 3 seconds (for illustration only). Solid lines represent result of LME regression (post hoc analysis, see text).

The reaction time analysis as a function of inter-target interval revealed no significant main effect, but a significant interaction of inter-target interval and motion phase (t=2.22, MCMC sampling test $p \leq 0.05$). To explore this interaction, data were split up according to the motion phase (i.e. motion on vs. motion off). Using two mixed effects models the effects of inter-target interval on RTs were calculated separately for both conditions. Significant effects of inter-target interval were only found when visual motion was off and evident as increased RTs when targets were far apart in time (t=3.90, MCMC sampling test $p \leq 0.01$) (Figure 2.2 C). This effect was not present during periods of visual motion (motion on phases) (Figure 2.2 B). Note that the inter-target intervals were not equally distributed throughout the experiment. This was especially the case for longer inter-target intervals (longer than 40 seconds) and accounts for the larger variance of reaction times at these intervals as there were fewer target presentations. There was neither a significant interaction of 'time on task' and 'inter-target interval' nor a significant interaction of 'time on task' and 'motion phase'.

2.4.2 fMRI Data

Task Performance. Detecting unpredictable targets in a classic vigilance task with rare, highly salient target stimuli increased neural activity in a widespread network comprising bilaterally the middle frontal gyri, the supplementary and pre-supplementary motor area (SMA and pre-SMA, medial), the left precentral gyrus (sensorimotor areas), the left calcarine gyrus (BA17), the superior temporal gyri, bilaterally, the cuneus, the precuneus, the supramarginal gyri and bilaterally inferior occipital cortices. Further activations were found bilaterally in the anterior insular cortices, the anterior and posterior cingulate cortex (ACC and PCC) and in subcortical structures such as the striatum, thalamus and brainstem. Activations are depicted in Figure 2.3 A (a detailed list is included in Table 2.1).

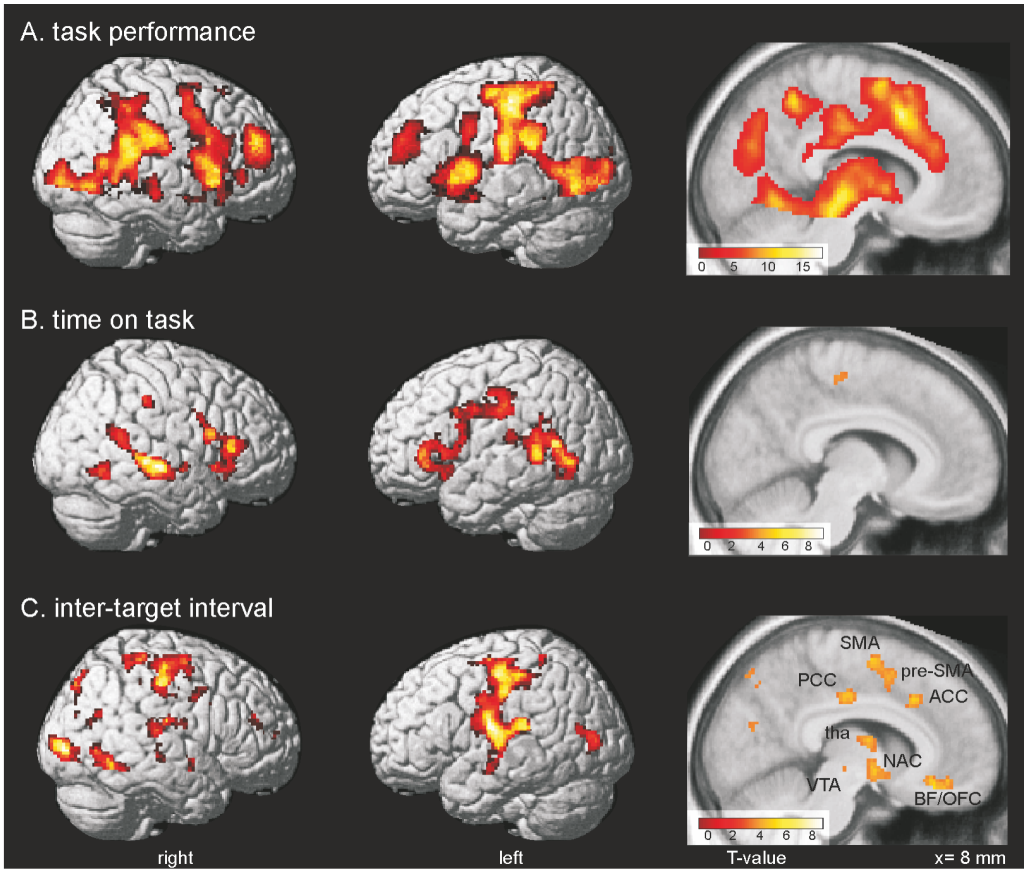

Figure 2.3: Neural activity related to task performance (A), time on task (B), and inter-target interval (C). Note that brain areas depicted in B show a linear decrease, while brain areas in C show a linear increase. All contrasts superimposed on a single subject rendering (left and middle column, SPM5 template) and on a normalised mean T1-image of the 20 subjects (right column). ACC=anterior cingulate cortex; BF=basal forebrain; NAC=nucleus accumbens; OFC=orbito frontal cortex; PCC=posterior cingulate cortex; SMA=supplementary motor cortex; tha=thalamus; VTA=ventral tegmental area.

Table 2.1: List of peak voxel activations comparing different task conditions.

	region of peak activation	left hemisphere				right hemisphere			
		MNI coord.			Peak Z	MNI coord.			Peak Z
		x	y	z		x	y	z	
	task performance (<0.00001, FDR corrected, k≥40)								
frontal cortex	L/R middle frontal gyrus	-28	44	22	6.19	32	42	20	6.88
	supplementary motor area	-6	-8	58	7.18				
	pre-supplementary motor area	-6	2	48	6.95				
	L/R precentral gyrus (BA6)	-54	2	32	6.38	48	-2	44	5.84
	L precentral gyrus (sensorimotor)	-44	-24	50	6.39				
parietal cortex	L/R precuneus	-8	-50	54	6.33	10	-50	52	6.12
	L/R cuneus	-14	-70	32	5.98	10	-76	24	5.79
	L/R supramarginal gyrus	-56	-40	26	6.49	54	-24	30	6.35
occipital cortex	L/R inferior occipital cortex	-42	-70	-6	6.52	38	-88	-4	6.32
	L calcarine gyrus (BA17/V1)	-14	-66	8	5.84				
temporal cortex	L/R superior temporal gyrus	-32	-20	0	6.36	38	-18	-2	6.27
allocortex	L/R anterior insular cortex	-32	22	8	7.22	34	20	8	7.13
	anterior cingulate cortex					6	14	44	7.00
	posterior cingulate cortex					8	-22	36	5.97
subcortical	L/R thalamus	-14	-24	8	6.28	16	-18	4	6.16
	L/R striatum (putamen)	-14	6	0	6.09	12	4	2	6.15
	brainstem					6	-24	-6	7.27
	time on task related decrease (p≤0.01, FDR corrected, k≥40)								
frontal cortex	L/R inferior frontal gyrus	-42	30	-6	4.71	54	30	10	4.13
	supplementary motor area					4	-24	58	4.49
	L supplementary motor area	-20	-8	60	4.19				
parietal cortex	L/R inferior parietal cortex	-58	-16	32	4.32	54	-26	40	3.93
occipital cortex	R inferior occipital cortex (BA19/V3)					48	-58	-8	4.29
temporal cortex	L/R superior temporal gyrus	-56	-42	16	3.83	60	-18	-4	5.74
	L/R middle temporal gyrus	-48	-60	4	4.94	62	-46	16	4.64
allocortex	L/R anterior insular cortex	-32	20	-8	4.92	28	16	-10	4.85
	inter-target interval related increase (p≤0.01, FDR corrected, k≥40)								
frontal cortex	R medial frontal gyrus					30	42	16	4.11
	R middle frontal gyrus					36	10	30	4.25
	orbito frontal cortex					8	34	-16	4.27
	supplementary motor area					6	-2	58	4.37
	pre-supplementary motor area					6	8	48	3.88
	L/R precentral cortex	-46	-16	54	4.53	42	-12	62	4.89
parietal cortex	R cuneus					20	-80	46	4.1
	L precuneus	-10	-60	38	3.99				
occipital cortex	R inferior occipital cortex					38	-88	-2	4.64
	R superior occipital lobe (BA31)					24	-70	18	4.34
	L middle occipital cortex (BA19/V3)	-46	-80	8	4.34				
temporal cortex	L/R superior temporal gyrus	-52	-32	18	4.56	52	-24	-4	3.65
	R heschl gyrus					40	-28	16	4.7
	R inferior temporal gyrus					46	-54	-12	4.75
	L fusiform gyrus					-16	-36	-16	4.24
allocortex	L/R posterior insular cortex	-32	8	12	3.91	40	-4	-6	4.22
	anterior cingulate cortex	-6	14	34	4.58				
	posterior cingulate cortex					12	-20	36	4.39
subcortical	basal forebrain	-6	22	-10	4.28				
	L/R nucleus accumbens	-6	-2	-6	5.17	6	-2	-6	4.03
	L/R ventral tegmental area	-4	-22	-8	4.12	12	-22	-6	3.98
	R thalamus					12	-14	14	3.67
	motion > no motion (p≤0.01, FDR corrected, k≥40)								
frontal cortex	L supplementary motor area	-32	-4	50	4.75				
parietal cortex	L/R superior parietal cortex	-22	-56	52	4.65	20	-56	62	4.04
occipital cortex	L/R middle occcipital cortex	-22	-80	36	4.47	30	-78	36	5.82
	L/R lingual gyrus	-20	-74	-6	4.31	16	-76	-6	4.71
temporal cortex	L/R area MT	-42	-72	10	7.78	48	-68	2	6.28

Effects of Time on Task. In contrast to the rather unspecific analysis above this parametric analysis isolates brain regions showing further increases or decreases in neural activity as a function of time on task. Significant decreases in neural activity were found bilaterally in cortical regions such as the inferior frontal gyri, the lateral somatosensory cortices, the superior and middle temporal gyri, the anterior insular cortices, the SMA and the right inferior occipital cortex (Fig. 2.3 B and Table 2.1). There was no brain area showing increases in neural activity as a function of time on task. Further, no brain area showed significant activation when comparing time on task effects between motion on and motion off phases.

Effects of Inter-Target Intervals. In contrast to the decreases in neural activity found above, increases in neural activity were found when analysing parametric changes in neural activity as a function of inter-target interval. Frontal cortical regions whose activity increased with increasing inter-target intervals were localised to the right middle frontal gyrus, the orbitofrontal cortex and the precentral cortices (motor areas) bilaterally. Further cortical activations were found bilaterally in the superior temporal gyri, the right inferior temporal gyrus, the right Heschl gyrus and the left fusiform gyrus. Smaller activation clusters were evident in the right cuneus, the left precuneus, the right inferior occipital cortex, the right superior occipital lobe, the left middle occipital cortex and the posterior insular cortices bilaterally. Increased neural activity was found in several medial structures such as the supplementary and pre-supplementary motor area (SMA and pre-SMA) and the anterior and posterior cingulate cortices (ACC and PCC). Increases in subcortical neural activity with increasing inter-target intervals was found in the nucleus accumbens bilaterally, the ventral tegmental area, the right thalamus and the basal forebrain. Activations are depicted in Figure 2.3 C and listed in Table 2.1. There was no brain area showing decreases in neural activity as a function of inter-target interval. Further, no brain area showed significant activation when comparing effects of inter-target intervals between motion on and motion off phases.

To answer the question, whether neural activity related to increases in inter-target intervals is further modulated by time on task, a second post hoc analysis was performed. In that model we separately coded motion on and off phases and linear effects of inter-target intervals in four different time periods covering the time of the entire experiment. This analysis revealed no significant effects of time on task on neural activity related to inter-target intervals.

Effects of Irrelevant Motion. Motion-related activity was present in areas MT, the middle occipital cortices, and the superior parietal cortices in both hemispheres. Smaller activation clusters were found in the lingual gyri and the left SMA (see Figure 2.4 and Table 2.1).

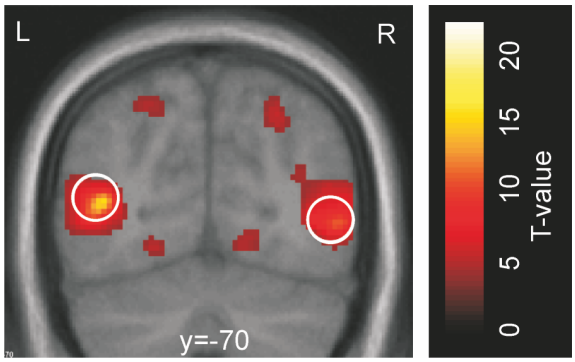

Figure 2.4: Motion-related activity (display threshold p≤0.01, FDR corrected, k≥40). Spherical regions around the group-level peak-voxel activations in the areas MT (r=8 mm, white circles) were used as mask to extract mean beta values in areas MT on single subject level for the PLS analysis.

Predicting Processing of Irrelevant Motion by Neural Activity in Networks Related to Time on Task and Inter-Target Interval. We used two PLS analyses to investigate whether the changes in neural activity in the networks shown above (Fig. 2.3 B and C) are able to predict motion-related activity in area MT. In other words, we investigated whether these time dependent neural changes have a functional impact on processing behaviourally irrelevant distractors. In our first PLS analysis, where we related decreases in neural activity as a function of time on task to neural activity in area MT, we found no evidence that such decreases predict motion-related neural activity. In contrast, the second PLS analysis revealed that increases in neural activity as a function of inter-target interval was able to predict motion-related activity in area MT. This suggests that the latter network has a functional impact on processing distractors. The results of the LOO cross validation approach and the randomization test of van der Voet (1994) showed that the first three latent factors of the PLS analysis were significant (first factor p≤0.002; second factor p≤0.04; third factor p≤0.03) and were able to explain most of the variance in the MT activations (see Figure 2.5 A). Put more intuitively, each of these latent factors reflects a network of brain regions which is able to explain variance in neural activity in area MT. In order to show the direction of the correlation between X and Y scores (the weighted sums of X and Y) and the goodness of model fit we plotted these scores for the first latent factor in Figure 2.5 B. To get further information which brain regions reliably contribute to the prediction of neural MT activations we further focussed on interpreting the weights of X.

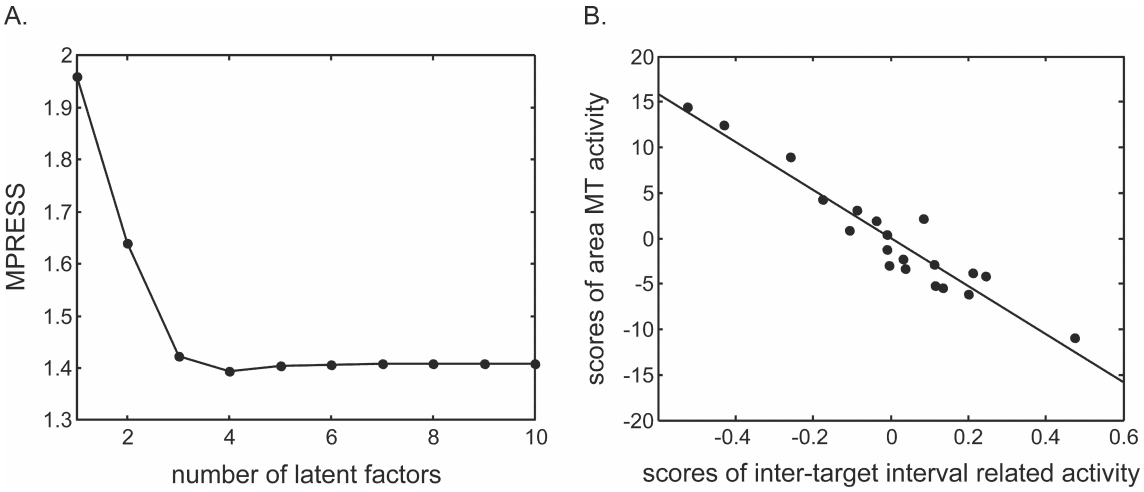

Figure 2.5: Goodness of fit of the PLS model. A. Mean predicted error sum of squares (MPRESS) of PLS models with one up to ten latent factors considered. Most of the variance in MT activity can be explained by the first three factors. B. First latent factor of PLS analysis: Correlation of the scores of the 'inter-target interval'-related network and area MT activity for each of the 20 subjects.

To identify those voxels of the network that robustly contribute over all subjects to the latent factors of the PLS analysis we used a bootstrap approach. This approach revealed significant voxel weights only for the first latent factor. For the second and third latent factor no discrete voxels turned out to be reliable over subjects. Therefore, only the first latent factor will be described further.

The first latent factor predicts the average of the MT activations bilaterally (y weights for the first factor MT left=3.33 and MT right=3.9). Thereby some brain regions correlate negatively and some positively with the averaged MT activations which results in positive and negative weights in the linear combination of X. A positive weight would indicate that increased brain activity in this area predicts increased activity in area MT; a negative weight would indicate that increased activity in this area predicts decreased activity in area MT. Thus, different weights reflect areas of the network with functionally distinct contributions (see Figure 2.6 and Table 2.2). Brain regions such as the ACC, the left pre-SMA, the nucleus accumbens (bilateral), the left lateral SMA, the left precentral cortex (motor area), the left insular cortex and the right precuneus are negatively weighted which implies that high neural activity in these regions predicts low activity in area MT. On the other hand, regions such as the basal forebrain, the right thalamus, the PCC, the right middle frontal gyrus, right precentral cortex (motor area), middle temporal gyrus (bilateral) and medial right SMA were positively weighted which implies that high neural activity in these regions predicts high neural activity in area MT. Thus our PLS analysis suggests for one that neural activity increases with increasing inter-target intervals impact on processing distractors and are composed of two functionally different networks.

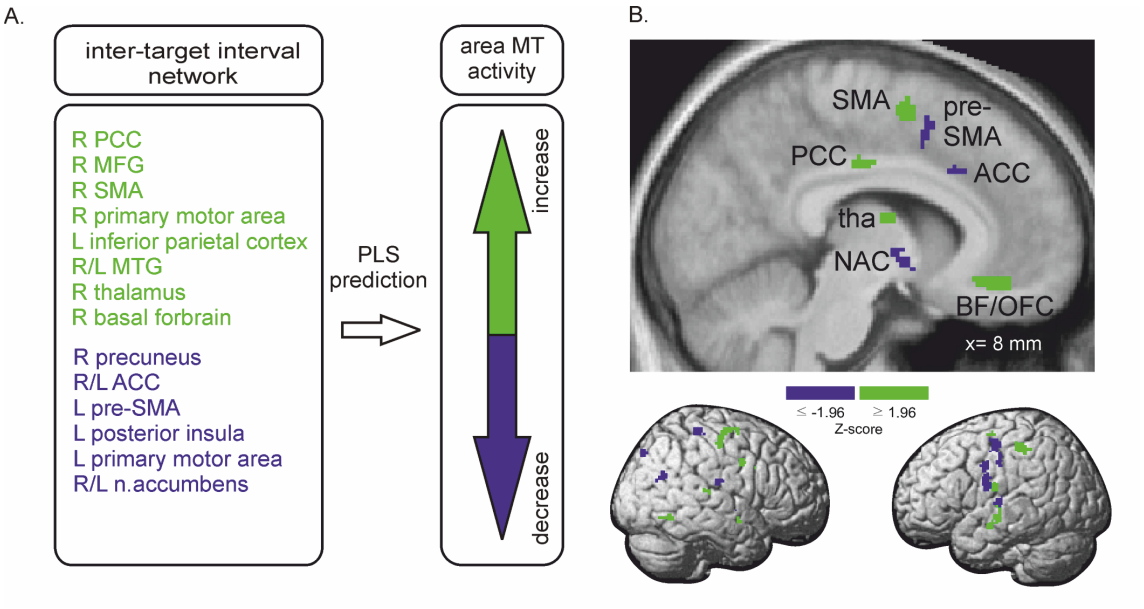

Figure 2.6: Brain regions of 'inter-target interval'-related network contributing reliably over all subjects to the prediction of area MT activity. A. Regions with positive Z-scores (green) predict an increase of MT activity; regions with negative Z-scores (blue) predict a decrease of MT activity. B. Regions superimposed on a MNI- normalized mean T1-image of the 20 subjects for medial view and superimposed on a rendered, MNI-normalized single subject T1-image for the lateral views. Abbreviations of medial view see Figure 2.3.

Table 2.2: PLS analysis: List of peak voxels of clusters that contribute significantly to the prediction of the PLS model over all subjects.

	region of peak voxel	left hemisphere				right hemisphere			
		MNI coord.			Peak Z	MNI coord.			Peak Z
		x	y	z		x	y	z	
	negative weights: predicting low area MT activity ($p \leq 0.05$, $k \geq 10$)								
frontal cortex	L lateral supplementary motor area	-50	-2	36	-2.64				
	L pre-supplementary motor area	-10	4	44	-2.52				
	L primary motor area	-44	-14	48	-2.1				
parietal cortex	R precuneus					16	78	36	-2.45
allocortex	L/R anterior cingulate cortex	-4	20	32	-2.5	4	22	34	-2.39
	L posterior insular cortex	-44	-18	6	-2.64				
subcortical	L/R nucleus accumbens	-4	0	-4	-2.42	6	0	-6	-2.43
	positive weights: predicting high area MT activity ($p \leq 0.05$, $k \geq 10$)								
frontal cortex	R basal forebrain					16	24	-12	2.64
	R supplementary motor area					8	8	48	2.46
	R primary motor area					50	-18	52	2.38
	R middle frontal gyrus					38	10	34	2.56
parietal cortex	L postcentral cortex	-40	-34	52	2.52				
allocortex	R posterior cingulate cortex					10	-20	32	2.58
temporal cortex	R middle temporal gyrus					40	-4	-14	2.59
	L middle temporal gyrus	-58	-8	-16	2.58				
subcortical	R thalamus					8	-10	14	2.58

2.5 Discussion

The main finding of this fMRI study is that different brain regions and mechanisms underlie short-term and long-term aspects of vigilance. Short-term aspects, which were gauged by analysing neural activity related to increasing inter-target intervals were evident as increases in neural activity in a widespread network of regions involving lateral and medial frontal areas, temporal areas, cuneus and precuneus, inferior occipital cortex (right), posterior insular cortices, the thalamus, nucleus accumbens and basal forebrain. Neural activity in these brain regions co-varied with neural activity related to processing irrelevant motion stimuli and can be further subdivided into two functionally distinct networks. Long-term aspects, which were gauged by analysing neural activity related to increasing time on task, were evident as decreases of neural activity in inferior frontal, posterior parietal, superior and middle temporal cortices and the anterior insular cortices. Neural activity in these brain regions did not impact neural activity related to processing irrelevant motion stimuli.

2.5.1 Behavioural Data

Vigilance decrements were evident as a function of time on task and to a weaker extent as a function of inter-target interval. The increase in reaction times as a function of time on task and the increased ratings of sleepiness after task performance are in line with prior vigilance studies demonstrating an overall performance decline and increased fatigue experience over time (Langner et al., 2010b; Lim et al., 2010; Paus et al., 1997). Increasing the inter-target intervals had a significant impact on reaction times, however only when motion was absent. It may be speculated that the monotony of the vigilance task was further increased when no motion was present, making it harder to sustain attention until the (unpredictable) appearance of the next target. This would be in line with findings from vigilance tasks where a decline in performance increased with increased monotony and 'monotony-induced' stress-level (e.g. Thackray, 1981).

2.5.2 Brain Regions Active During Task Performance

Our main effect of task performance revealed several brain regions, such as the dorsolateral prefrontal cortex, ACC, pre-SMA, SMA and PCC and thalamus previously found to be involved in vigilance and sustained attention (e.g. Coull et al., 1996; Lim et al., 2010; Sturm et al., 2004, Paus et al., 1997, Posner and Petersen, 1990). For example, bilateral increases in neural activity in middle frontal cortex were also found by Lim and colleagues (2010) in the psychomotor vigilance task. Additionally Lim and colleagues (2010) described that pre-task resting state measurements suggest that neural activity in this region is predictive of a vigilance decline.

2.5.3 Different Brain Networks Related to Long-Term vs. Short-Term Aspects of Vigilance

Our results demonstrate that the network of regions showing short-term effects of vigilance (reflected by increased neural activity with increasing inter-target intervals) was different from the network related to long-term effects of vigilance (reflected by decreased neural activity as a function of time on task), providing neural evidence that two separate mechanisms are responsible for sustaining attention over seconds as compared to sustaining attention over minutes. Research in sleep deprived subjects also supports the idea that two separate mechanisms are responsible for sustaining attention over minutes as usually measured in vigilance tasks as compared to sustaining attention over seconds in between two rare signals. While the first process was shown to be degraded by sleep deprivation, the latter was not affected by the manipulation (Tucker et al., 2009). A recent study by Langner and colleagues (2010a) also points to a dissociation between cue induced phasic alertness and vigilance over prolonged periods of time. While decrements in reaction times were seen with time on task, phasic alertness was not decreased with time on task (see however Rueckert and Levy (1996) who argue for similar mechanisms).

Several of the brain areas showing activity decreases during target detection as a function of time on task such as the inferior frontal, the posterior parietal and the superior temporal cortex were previously shown to exhibit time-dependent decreased tonic activity as measured with positron emission tomography and arterial spin labelling (Lim et al., 2010; Paus et al., 1997). Our results on long-term aspects of vigilance are thus in good accordance with studies investigating effects of time on task. Compared to other studies (Coull et al., 1998; Lim et al., 2010; Paus et al., 1997) our decreases in frontal activity were however restricted to inferior parts of the frontal cortex. Note that our decrease of neural activity in posterior parietal cortex is located in a region which has recently been shown to contribute to vigilance decrements in spatial attention tasks if lesioned (Malhotra et al., 2009).

In contrast to the effects of time on task which were evident as decreased neural activity, the short-term effects of increasing inter-target intervals yielded increases in neural activity in a different network of brain regions, including lateral and medial frontal areas such as the right middle frontal gyurs, the SMA, pre-SMA and the ACC, temporal areas, cuneus and precuneus, posterior insular cortices, and subcortical regions such as the thalamus, nucleus accumbens and basal forebrain.

Neural activity related to varying inter-stimulus intervals in vigilance tasks has not been investigated before. There are however some studies which focused on neural mechanisms of preparation over variable time intervals. It has been shown that brain regions sensitive to a variable fore-period are located bilaterally in the middle frontal gyrus and in the anterior and posterior cingulate cortex which resembles some of the activations

found here (Vallesi et al., 2009). Note however that the intervals in variable fore-period tasks are usually much shorter than the average inter-target intervals in the task used here.

Several of the subcortcial regions, such as the ventral tegmental area, the nucleus accumbens and the thalamus which showed a main effect of task performance yielded further increases in neural activity as a function of increasing inter-target interval. One region showing increased neural activity as a function of inter-target interval was the basal forebrain. The activation encompassed the septum (Ch1-Ch2), the horizontal limb of the diagonal band (Ch3) and the sublenticular part of the basal forebrain (Ch4) (Zaborszky et al., 2008). These findings are in line with experiments in rats that showed increased prefrontal acetylcholine (ACh) release during performance of attentional tasks in general (Himmelheber et al., 2001; Passetti et al., 2000) or with increasing attentional demand (Himmelheber et al., 2001).

Our results indicate that target processing is modulated by different, independent processes that either emerge during shorter time scales ('inter-target intervals') or longer time scales ('time on task'). Note, that the neural activity we report here is the modulation of target processing as a function of 'time on task' or preceding inter-target interval rather than neural activity emerging over the entire experiment or neural activity emerging during two target stimuli. Nevertheless these long and short term processes may differ. Cognitive fatigue and more emotional and motivational aspects of fatigue like boredom, aversion to go on in the task or enhanced daydreaming which continuously accumulates with time on task could be responsible for long-term modulation of target processing (e.g. Pattyn et al, 2008). In contrast, the short-term process may be related to increasing expectations of the subjects about target appearance or increasing effort to focus attention with increasing inter-target intervals. Some of these processes may reset after target presentation.

Potential Confounds. It is known that time series of fMRI data acquired over a long scan duration are affected by low frequency drifts attributed to scanner instabilities. This is especially critical for fMRI studies that rely on the investigation of long-term processes in the brain whose frequencies potentially overlap with these noise components (frequencies below 0.015 Hz, see Smith et al., 2002). To test this possible confound we performed a frequency analysis of the parametric regressors capturing 'time on task' related brain activations which underlines that most parts of the modelled frequencies lie above potential low frequency drifts. A power spectrum of the modelled frequencies can be found in supplementary Figure 2.8.

Eye Movement. Some of the brain regions, such as the frontal eye fields, the right dorsolateral prefrontal cortex, and in the left inferior parietal lobule/precuneus which showed increased activity with increasing inter-target interval were previously also found to be related to eye movements. Even though volunteers performed a central task (detection of changes in the fixation cross) it cannot be excluded that eye movements to motion distractors in the periphery may increase with increasing target interval. We therefore performed an additional analysis comparing effects of inter-target intervals during 'motion on' and 'motion off' phases. This analysis did not reveal any differential activations, arguing against a contribution of eye movements. Further, neural activity in these areas did not significantly contribute to the PLS prediction of area MT activation.

2.5.4 Impact of Vigilance-Related Networks on Processing Irrelevant Motion

Previously it was suggested that a reduction of neural activity in fronto-parietal areas reflects a shift from controlled to automatic processing. We therefore tested by means of a PLS regression approach whether neural activity in brain areas related to time on task effects can predict the processing of task irrelevant motion and found no evidence for such an association. No latent variable extracted by the PLS analysis could reliably explain covariance of the data between the time on task activations and the level of area MT activation.

In contrast, the increase in neural activity related to increasing inter-target intervals was able to reliably predict area MT activation. Furthermore, the PLS analysis revealed a separation of the network into areas that either contribute with positive or with negative weights to this prediction. Regions such as the ACC, pre-SMA and dopaminergic subcortical nuclei (ventral tegmental area and nucleus accumbens) predicted decreases in area MT activity while areas such as the basal forebrain, thalamus, orbitofrontal cortex, PCC and SMA predicted increases in area MT activity. Given the data by Rees et al. (1997) which suggests that processing irrelevant motion in area MT is decreased if the primary task engages full attention, we suggest that ACC, pre-SMA and dopaminergic subcortical nuclei may support directing and reallocating attention towards task relevant stimuli (e.g. Small et al., 2003; Weissman et al., 2005). In contrast, the second network may represent the action of cholinergic and noradrenergic neurotransmitter systems which have often been shown to increase signal-to-noise ratio in sensory processing regions (Hasselmo et al., 1997). The positive correlation of these regions to neural activity in area MT suggests a possible contribution to a compensating network that increases processing in sensory and motor areas.

Several areas within these two functionally segregated networks have previously been discussed in relation to the concept of attentional effort. According to Sarter et al. (2006) attentional effort is a construct at the interface of motivation, attention and arousal. Putative core components of the network mediating attentional effort are the ACC, prefrontal cortex, the ventral tegmental area, the nucleus accumbens and the cholinergic basal forebrain. While the ACC and dopaminergic subcortical structures which are reciprocally connected (Carr et al., 1999; Carr and Sesack, 2000) indicate performance decline, the cholinergic basal forebrain is suggested to trigger activity in the anterior attention system in medial prefrontal cortex and optimizes processing in sensory cortical regions. Cholinergic lesions in rats thus resulted in a decrease of overall responsiveness of medial prefrontal neurons during performance of a sustained attention task (Gill et al., 2000). Challenging attentional situations such as drug induced impairments of performance were shown to increase medial prefrontal cortical ACh release providing evidence for an involvement of ACh in situations that require attentional effort (Kozak et al., 2006). Put in the concept of attentional effort, the segregated networks revealed by our PLS analysis might reflect motivational and arousal components of a network, that is recruited when time between targets increases.

2.6 Conclusion

We here show that different brain regions and mechanisms underlie sustaining attention over minutes as opposed to seconds. The two processes thus represent different aspects of the intensity dimension of attention and should clearly be separated in future studies. Sustaining attention in between two targets involves increased neural activity in several brain regions previously discussed in relation to the concept of attentional effort. We suggest that these brain regions can be functionally segregated into two components. One may be involved in motivation, consisting of the anterior cingulate cortex, pre-SMA and nucleus accumbens. The other may represent an arousal-regulating component encompassing the basal forebrain, thalamus, orbitofrontal cortex, posterior parietal cortex and SMA.

2.7 Supplemental Material

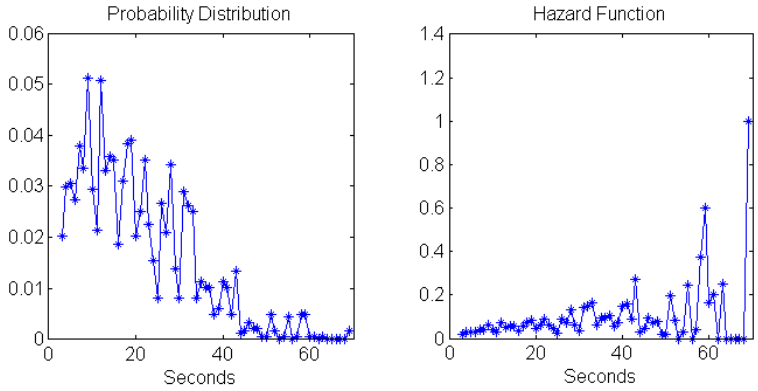

Figure 2.7: Probability Distribution and Hazard Function of target presentations during the vigilance task.

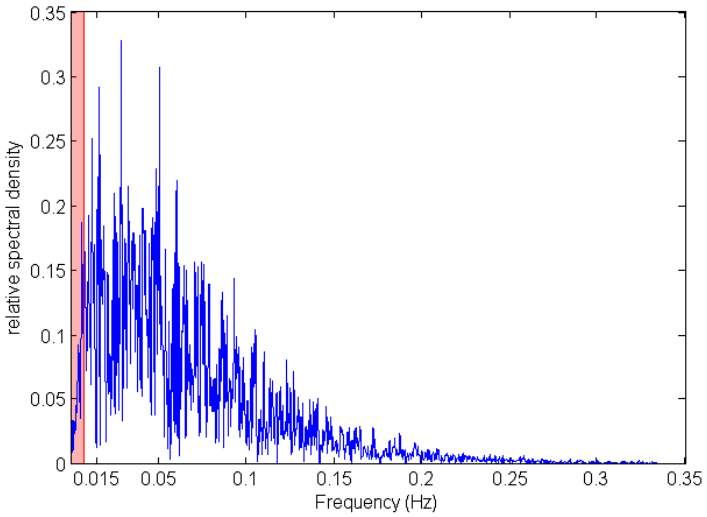

Figure 2.8: Frequency spectrum of parametric time modulation. High pass filter cut-off is highlighted in red (0.0078 Hz). Potential scanner drifts due to prolonged acquisition of fMRI-data are supposed to lie below 0.015 Hz (see Smith et al., 2002). Biggest part of the modulated frequencies from the used parametric weighting for the 'time on task' related activations in the current study lie above these frequencies.

2.8 References

Baayen,R.H. (2008). Analyzing Linguistic Data (New York: Cambridge University Press).

Baayen,R.H., Davidson,D.J., and Bates,D.M. (2008). Mixed-effects modeling with crossed random effects for subjects and items. Journal of Memory and Language 59, 390-412.

Boksem,M.A., Meijman,T.F., and Lorist,M.M. (2005). Effects of mental fatigue on attention: an ERP study. Brain Res Cogn Brain Res 25, 107-116.

Caplan,J.B., Luks,T.L., Simpson,G.V., Glaholt,M., and McIntosh,A.R. (2006). Parallel networks operating across attentional deployment and motion processing: a multi-seed partial least squares fMRI study. Neuroimage 29, 1192-1202.

Carr,D.B., O'Donnell,P., Card,J.P., and Sesack,S.R. (1999). Dopamine terminals in the rat prefrontal cortex synapse on pyramidal cells that project to the nucleus accumbens. Journal of Neuroscience 19, 11049-11060.

Carr,D.B., and Sesack,S.R. (2000). Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. Journal of Neuroscience 20, 3864-3873.

Cook,R.D., and Weisberg,S. (1982). Residuals and influences in regression (London: Chapman & Hall), p. 33.

Corbetta,M., and Shulman,G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. Nat. Rev. Neurosci. 3, 201-215.

Coull,J.T., Frackowiak,R.S.J., and Frith,C.D. (1998). Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task. Neuropsychologia 36, 1325-1334.

Coull,J.T., Frith,C.D., Dolan,R.J., Frackowiak,R.S., and Grasby,P.M. (1997). The neural correlates of the noradrenergic modulation of human attention, arousal and learning. Eur. J. Neurosci. 9, 589-598.

Coull,J.T., Frith,C.D., Frackowiak,R.S.J., and Grasby,P.M. (1996). A fronto-parietal network for rapid visual information processing: A PET study of sustained attention and working memory. Neuropsychologia 34, 1085-1095.

Coull,J.T., Middleton,H.C., Robbins,T.W., and Sahakian,B.J. (1995). Clonidine and Diazepam Have Differential-Effects on Tests of Attention and Learning. Psychopharmacology 120, 322-332. Dejong,S. (1993). Simpls - an Alternative Approach to Partial Least-Squares Regression. Chemometr Intell Lab Chemometr Intell Lab 18, 251-263.

Dinges,D.F., and Powell,J.W. (1985). Microcomputer Analyses of Performance on A Portable, Simple Visual Rt Task During Sustained Operations. Behavior Research Methods Instruments & Computers 17, 652-655.

Drummond,S.P., Bischoff-Grethe,A., Dinges,D.F., Ayalon,L., Mednick,S.C., and Meloy,M.J. (2005). The neural basis of the psychomotor vigilance task. Sleep 28, 1059-1068.

Genovese,C.R., Lazar,N.A., and Nichols,T.E. (2001). Threshold determination using the false discovery rate. Neuroimage 13, S124.

Giessing,C., Fink,G.R., Rosler,F., and Thiel,C.M. (2007). fMRI data predict individual differences of behavioral effects of nicotine: a partial least square analysis. J Cogn Neurosci 19, 658-670.

Gill,T.M., Sarter,M., and Givens,B. (2000). Sustained visual attention performance-associated prefrontal neuronal activity: Evidence for cholinergic modulation. Journal of Neuroscience 20, 4745-4757.

Gitelman,D.R., Nobre,A.C., Parrish,T.B., LaBar,K.S., Kim,Y.H., Meyer,J.R., and Mesulam,M. (1999). A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain 122 (Pt 6), 1093-1106.

Hasselmo,M.E., Linster,C., Patil,M., Ma,D., and Cekic,M. (1997). Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. Journal of Neurophysiology 77, 3326-3339.

Helton,W.S., Weil,L., Middlemiss,A., and Sawers,A. (2010). Global interference and spatial uncertainty in the Sustained Attention to Response Task (SART). Conscious. Cogn 19, 77-85.

Himmelheber,A.M., Sarter,M., and Bruno,J.P. (2001). The effects of manipulations of attentional demand

on cortical acetylcholine release. Brain Res Cogn Brain Res 12, 353-370.

Hopfinger,J.B., Buonocore,M.H., and Mangun,G.R. (2000). The neural mechanisms of top-down attentional control. Nature Neuroscience 3, 284-291.

Kim,Y.H., Gitelman,D.R., Nobre,A.C., Parrish,T.B., LaBar,K.S., and Mesulam,M.M. (1999). The large-scale neural network for spatial attention displays multifunctional overlap but differential asymmetry. Neuroimage 9, 269-277.

Kozak,R., Bruno,J.P., and Sarter,M. (2006). Augmented prefrontal acetylcholine release during challenged attentional performance. Cerebral Cortex 16, 9-17.

Krishnan,A., Williams,L.J., McIntosh,A.R., and Abdi,H. (2010). Partial Least Squares (PLS) methods for neuroimaging: A tutorial and review. Neuroimage.

Langner,R., Steinborn,M.B., Chatterjee,A., Sturm,W., and Willmes,K. (2010a). Mental fatigue and temporal preparation in simple reaction-time performance. Acta Psychol. (Amst) 133, 64-72.

Langner,R., Willmes,K., Chatterjee,A., Eickhoff,S.B., and Sturm,W. (2010b). Energetic effects of stimulus intensity on prolonged simple reaction-time performance. Psychol. Res. 74, 499-512.

Lim,J., Wu,W.C., Wang,J.J., Detre,J.A., Dinges,D.F., and Rao,H.Y. (2010). Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect. Neuroimage 49.

Mackworth,J.F. (1969). Vigilance and habituation: a neuropsychological approach (Baltimore: Penguin Books).

Mackworth,N.H. (1948). The Breakdown of Vigilance During Prolonged Visual Search. Quarterly Journal of Experimental Psychology 1, 6-21.

Malhotra,P., Coulthard,E.J., and Husain,M. (2009). Role of right posterior parietal cortex in maintaining attention to spatial locations over time. Brain 132, 645-660.

Mander,B.A., Reid,K.J., Davuluri,V.K., Small,D.M., Parrish,T.B., Mesulam,M.M., Zee,P.C., and Gitelman,D.R. (2008). Sleep deprivation alters functioning within the neural network underlying the covert orienting of attention. Brain Research 1217, 148-156.

McIntosh,A.R., Bookstein,F.L., Haxby,J.V., and Grady,C.L. (1996). Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 3, 143-157.

Mesulam,M.M., Nobre,A.C., Kim,Y.H., Parrish,T.B., and Gitelman,D.R. (2001). Heterogeneity of cingulate contributions to spatial attention. Neuroimage 13, 1065-1072.

Nobre,A.C., Sebestyen,G.N., Gitelman,D.R., Mesulam,M.M., Frackowiak,R.S., and Frith,C.D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. Brain 120 (Pt 3), 515-533.

Parasuraman,R., Warm,J.S., and See,J.E. (1998). The attentive brain. In Brain systems of vigilance, R. Parasuraman, ed. (Cambridge: MIT Press), pp. 221-256.

Passetti,F., Dalley,J.W., O'Connell,M.T., Everitt,B.J., and Robbins,T.W. (2000). Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attentional task. Eur. J Neurosci 12, 3051-3058.

Pattyn, N., Neyt, X., Henderickx, D., and Soetens, E., (2008). Psychophysiological investigation of vigilance decrement: Boredom or cognitive fatigue?. Physiology & Behavior 93, 369-378.

Paus,T., Zatorre,R.J., Hofle,N., Caramanos,Z., Gotman,J., Petrides,M., and Evans,A.C. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. Journal of Cognitive Neuroscience 9, 392-408.

Pinheiro,J.C., and Bates,D.M. (2000). Mixed-Effects Models in S and S-PLUS Springer). Portas,C.M., Rees,G., Howseman,A.M., Josephs,O., Turner,R., and Frith,C.D. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. Journal of Neuroscience 18, 8979-8989.

Posner,M.I., and Boies,S.J. (1971). Components of Attention. Psychological Review 78, 391-&.

Posner,M.I., and Petersen,S.E. (1990). The attention system of the human brain. Annu. Rev. Neurosci. 13, 25-42.

Rees,G., Frith,C.D., and Lavie,N. (1997). Modulating irrelevant motion perception by varying attentional

load in an unrelated task. Science 278, 1616-1619.

Rosipal,R., and Kramer,N. (2006). Overview and recent advances in partial least squares. Lect Notes Comput Sc Lect Notes Comput Sc 3940, 34-51.

Rueckert,L., and Levy,J. (1996). Further evidence that the callosum is involved in sustaining attention. Neuropsychologia 34, 927-935.

Sarter,M., Gehring,W.J., and Kozak,R. (2006). More attention must be paid: the neurobiology of attentional effort. Brain Res Rev 51, 145-160.

Small,D.M., Gitelman,D., Simmons,K., Bloise,S.M., Parrish,T., and Mesulam,M.M. (2005). Monetary incentives enhance processing in brain regions mediating top-down control of attention. Cerebral Cortex 15, 1855-1865.

Small,D.M., Gitelman,D.R., Gregory,M.D., Nobre,A.C., Parrish,T.B., and Mesulam,M.M. (2003). The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. Neuroimage 18, 633-641.

Smit,A.S., Eling,P.A.T.M., and Coenen,A.M.L. (2004). Mental effort causes vigilance decrease due to resource depletion. Acta Psychologica 115, 35-42.

Smith,A.M., Lewis,B.K., Ruttimann,U.E.,Ye,F.Q., Sinnwell,T.M.,Yang,Y.,Duyn,J.H., and Frank,J.A. (2002). Investigation of Low Frequency Drift in fMRI Signal. Neuroimage, 526-533.

Sturm,W., de Simone,A., Krause,B.J., Specht,K., Hesselmann,V., Radermacher,I., Herzog,H., Tellmann,L., Muller-Gartner,H.W., and Willmes,K. (1999). Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. Neuropsychologia 37, 797-805.

Sturm,W., Longoni,F., Fimm,B., Dietrich,T., Weis,S., Kemna,S., Herzog,H., and Willmes,K. (2004). Network for auditory intrinsic alertness: a PET study. Neuropsychologia 42, 563-568.

Thackray,R.I. (1981). The Stress of Boredom and Monotony - A Consideration of the Evidence. Psychosomatic Medicine 43, 165-176.

Tucker,A.M., Basner,R.C., Stern,Y., and Rakitin,B.C. (2009). The variable response-stimulus interval effect and sleep deprivation: an unexplored aspect of psychomotor vigilance task performance. Sleep 32, 1393-1395.

Vallesi,A., McIntosh,A.R., Shallice,T., and Stuss,D.T. (2009). When time shapes behavior: fMRI evidence of brain correlates of temporal monitoring. J. Cogn Neurosci. 21, 1116-1126.

van der Voet,H. (1994). Comparing the Predictive Accuracy of Models Using a Simple Randomization Test. Chemometr Intell Lab Chemometr Intell Lab 25, 313-323.

Weissman,D.H., Gopalakrishnan,A., Hazlett,C.J., and Woldorff,M.G. (2005). Dorsal anterior cingulate cortex resolves conflict from distracting stimuli by boosting attention toward relevant events. Cereb Cortex 15, 229-237.

Wold,S., Ruhe,A., Wold,H., and Dunn,W.J. (1984). The collinearity problem in linear regression. The partial least squares (PLS) approach to generalized inverses. SIAM Journal of Scientific and Statistical Computing 5, 735-743.

Zaborszky,L., Hoemke,L., Mohlberg,H., Schleicher,A., Amunts,K., and Zilles,K. (2008). Stereotaxic probabilistic maps of the magnocellular cell groups in human basal forebrain. Neuroimage 42, 1127-1141.

Study II

Long-Term Effects of Attentional Performance on Functional Brain Network Topology

Short title: Cognitive resilience and network topology

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Research highlights

- Prolonged task performance leads to less integrated functional brain networks.
- Changes in network integration persist for several minutes after task processing.
- Brain networks of cognitive resilient subjects recover faster from task performance.

Keywords: vigilance, sustained attention, complex networks, graph theory, resting state, recovery

3.1 Abstract

Individuals differ in their cognitive resilience. Less resilient people demonstrate a greater tendency to vigilance decrements during sustained attention. We hypothesized that a period of sustained attention would be followed by prolonged changes in organization of 'resting state' brain networks; and that individual differences in cognitive resilience could be related to differences in post-task network reorganization. For each of 20 healthy volunteers, we measured topological and spatial properties of brain networks derived from functional MRI data recorded for 6 Min 24 sec before, and for 12 Min 48 sec after performance of an attentional task lasting 32 Min. Cognitive resilience was quantified for each individual as the rate of increase in response latency as a linear function of the series of attentional trials. On average, functional networks measured immediately post-task demonstrated significant and prolonged changes in organization compared to pre-task networks with higher connectivity strength, more clustering, less efficiency, and shorter distance connections. Individual differences in cognitive resilience were significantly correlated with differences in the degree of recovery of some network parameters. Changes in network measures were still present in less resilient individuals in the second half of the post-task period (i.e. 6-12 Min after task completion) while resilient individuals already demonstrated significant reductions of functional connectivity and clustering towards pre-task levels. We conclude that sustained attentional task performance has prolonged, 'hang-over' effects on the organization of post-task resting-state brain networks; and that more cognitively resilient individuals demonstrate faster rates of network recovery following a period of attentional effort.

3.2 Introduction

Many daily activities require the maintenance of attention over periods of time. Prolonged attentional effort has been shown to cause deterioration of behavioural performance, demonstrating the limitations of the brain as an information processing system (Parasuraman et al., 1998; Helton & Warm, 2008; Warm et al., 2008). Performance decline comprises slowing of signal detection and information processing, behavioural changes often described as vigilance decrements (Parasuraman et al., 1998). In contrast, individuals whose performance declines less rapidly as a function of time on task can be described as cognitively resilient. In real life, humans recover from vigilance decrements during rest periods (e.g. between working shifts) with low cognitive demands. However, it remains an open question how the effects of sustained attention might be reflected in changes in organization of resting state networks measured immediately after task performance. It is also not known if individual differences in cognitive resilience are related to differences in post-task network reorganization.

There has been recent progress to describe the human brain as a complex network of interconnected processing nodes (Bullmore & Sporns, 2009; Sporns, 2011). Based on graph analytical approaches, previous studies documented that variations of functional network integration and the topological efficiency of information transfer are correlated with behavioural performance (Li et al., 2009; van den Heuvel et al., 2009). Studies investigating effects of ageing documented that older people show poorer attentional performance (Berardi et al., 2001; Gazzaley et al., 2005), and less integrated brain networks with higher clustering and network cliquishness (Gong et al., 2009; Wang et al., 2010). Similar results were shown for ADHD children (Wang et al., 2009) and patients with Alzheimer's disease (Sanz-Arigita et al., 2010).

Previous studies documented the flexibility of the brain network topology (Kitzbichler et al., 2011). It was shown that the integration of brain networks dynamically varied with different levels of task difficulty. However, there is also support for the principle that the flexibility of the brain is limited and that the processing of demanding tasks has long-lasting impact on neural activations and brain networks, possibly reducing the brain's capacity to adapt to new task demands. Duff et al. (2008) and Waites et al. (2005) compared resting state (RS) fMRI data before and after task performance and reported changes in functional connectivity directly following task performance. Further studies have shown that task induced learning can modulate subsequent RS activity in specific task relevant networks (Albert et al., 2009; Lewis et al., 2009; Stevens et al., 2010). Results of Barnes et al. (2009) revealed that endogenous neural oscillations in local brain regions change after a demanding task and need more than 400 sec to begin to recover. Thus, there are hints that task performance can modulate 'resting state' dynamics and networks in post-task fMRI data.

We acquired fMRI data during RS periods before and after a vigilance task and used a graph analytical approach to investigate long-lasting changes in functional brain topology induced by sustained attention. We assumed that (i) prolonged attentional performance leads to less integrated networks with more clustered brain regions and a change from long-distance to short-distance connections. Furthermore, we expected that (ii) altered network attributes would recover slowly after task processing and that (iii) there would be a relation between network recovery and individual task performance.

3.3 Material and Methods

3.3.1 Subjects

Twenty healthy, right-handed subjects (11 female, 9 male; mean age = 27.0 years, range = 24 to 39 years) participated in the experiment.

The study was approved by the ethics committee of the German Psychological Association (http://www.dgps.de/, PI: Christiane Thiel, registration number: CT05022008DGPS) and subjects signed written informed consent.

3.3.2 Experimental Design

Each scanning session was divided into different time periods in which either RS or task-related BOLD activations were measured (see Figure 3.1). There were two RS blocks with 256 and 512 scans before and after task performance, respectively. For data analysis, the second RS block was divided into two halves so that in total three RS periods were measured with 256 scans each (equivalent to 6 Min 24 sec). During RS data acquisition subjects were instructed to fixate a black fixation cross that was presented in the centre of a light grey background.

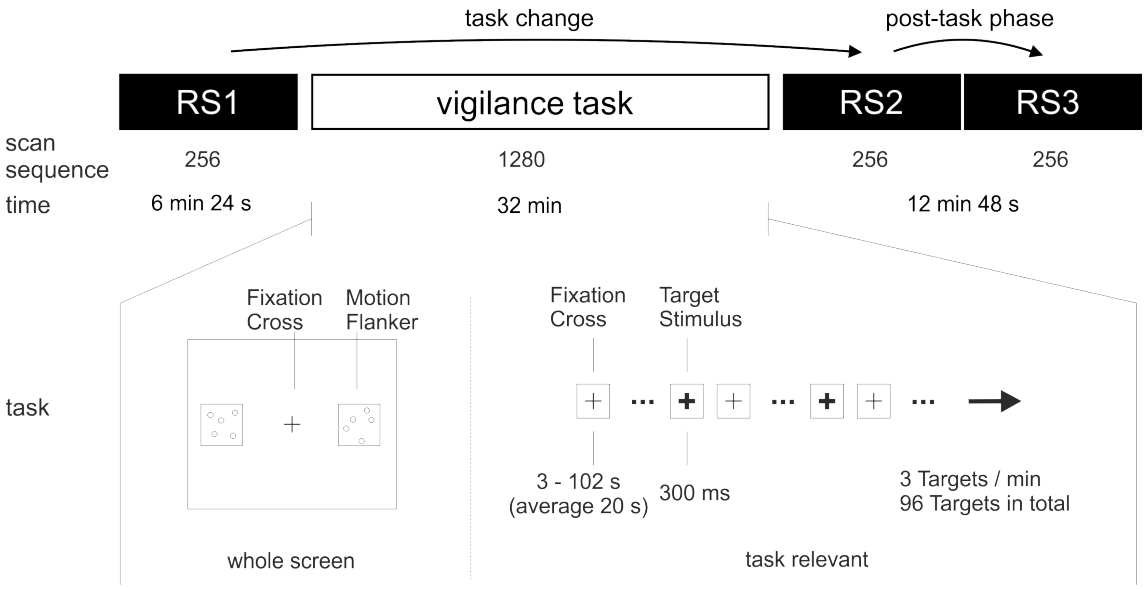

Figure 3.1: Experiment design. Top: Order of the resting state (RS) and task periods (with the number of acquired whole brain scans). **Bottom:** Scheme of the vigilance task during the task period. Participants were instructed to detect a red fixation cross (here depicted in bold).

3.3.3 Vigilance Task

During the task period, subjects performed a visual vigilance task in which a display with a central black fixation cross (the same as used during the RS condition) and two additional flanker windows were presented (Figure 3.1). Subjects were instructed to detect a colour change of the central fixation cross from black to red for 300 ms by pressing a response button as fast as possible. In total 96 targets were presented in 32 Min. The targets were equally distributed over the experiment by presenting three target stimuli per minute (with random inter-stimulus intervals within each minute). In the flanker windows, five dots randomly moved with low speed or were kept still. Both phases alternated every 24 s. Subjects were instructed to ignore the flanker windows. The fMRI data recorded during task processing were published previously (Breckel et al., 2011).

3.3.4 Analysis of the Behavioural Data

The individual vigilance decrement of each subject was estimated by the slope of a robust linear regression analysis with the individual response latencies or reaction times (RTs) as dependent variable and the series of attentional trial numbers as independent variable. In contrast to standard linear regression analysis in which each data point has equal influence on the least square curve fit, robust regression analysis uses a bisquare weighting function so that data points further apart from the expected line get reduced weight. Robust fits are less affected by outliers (Holland & Welsch, 1977).

The Stanford Sleepiness Scale (SSS; Hoddes et al., 1972) was administered before and after the fMRI experiment (outside the scanner) to measure subjective feelings of fatigue on a 10-point scale. Individual SSS scores were compared (before vs. after the fMRI experiment) using two-tailed paired t-tests.

3.3.5 FMRI Data Acquisition

Functional and structural images were acquired on a 1.5 Tesla MRI scanner (Siemens MAGNETOM Sonata, Siemens AG, Erlangen, Germany). Functional images were obtained using multislice T2*-weighted gradient echo planar imaging (EPI). Each volume consisted of 17 axial slices (voxel size of 3x3 mm, 4 mm in slice thickness, slice gap of 1.6 mm, field of view (FoV) = 200 x 200 mm^2, relaxation time (TR) = 1500 ms, echo time (TE) = 50 ms and 90° flip angle). EPI data were continuously measured with the same sequence in all RS and task periods. Structural T1-weighted images were obtained after the fMRI experiment, using magnetization frequency pulse and rapid gradient-echo (MP RAGE) sampling: 1 mm isotropic voxels, 176 slices, FoV = 256 x 256 mm^2, TR = 2130 ms, TE = 3.93 ms and 15° flip angle.

3.3.6 fMRI Data Processing and Time-Series Analysis

The time series of each voxel was corrected for head motion and slice timing offsets using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The functional images were spatially normalized to standard stereotaxic MNI space (Montreal Neurological Institute; http://www.mni.mcgill.ca/) and regionally parcellated using a template image comprising 442 cortical and subcortical brain regions to estimate the mean fMRI time series for each region for each participant during each RS period (Fornito et al., 2010; Zalesky et al., 2011). To reduce motion effects motion parameters of the spatial realignment were regressed out from the mean time series. Previous studies documented the behavioural relevance of graph metrics based on fMRI signal oscillations in the frequency range just below 0.1 Hz (Achard et al., 2006; Damoiseaux et al., 2006; van den Heuvel et al., 2009). Therefore, each regional time series was band-pass filtered (wavelet scale 3: 0.042 - 0.083 Hz) using the maximum overlap discrete wavelet transform (MODWT; Percival, 2006). For each pair of nodes the wavelet correlation was estimated, resulting in a 442 by 442 association matrix for each subject and RS period. The global strength of connectivity was computed as the mean of each association matrix.

3.3.7 Topological Metrics of Brain Graphs

Binary graphs of different connection densities were constructed based on the association matrix. A thresholding algorithm starting with the minimum spanning tree (MST) was used to ensure that each node was connected with at least one other node even at the sparsest connection density. Following the MST the algorithm adds the highest correlations of each node in an iterative way (see Alexander-Bloch et al., 2010 for further information). Graphs at 15 different costs levels were constructed for each subject and RS period in the range of 2.5% - 50%, with smaller sampling intervals in the lower cost range. The connection density defines the number of edges in a graph expressed as a ratio to the maximum possible number of edges (N*(N-1)/2 = 97,461). For the statistical analyses topological measures were calculated for each cost level separately and averaged over the entire cost range (see below).

Based on these adjacency matrices we calculated the central graph theoretical measures of global, nodal and local efficiency following the formulas of Latora and Marchiori (Latora & Marchiori, 2001; 2003). These metrics base on the minimum path lengths between connected nodes. The nodal efficiency of a particular node is inversely related to the mean minimum path length between this node and the rest of the network. In contrast, global efficiency is an estimate for the efficiency of an entire network, and is the mean over the nodal efficiencies. Thus networks with high global efficiency have highly integrated organization, characterized by short minimum path length between any pair of regional nodes.

Local efficiency is closely related to the clustering coefficient (Watts & Strogatz, 1998), and reflects the network's capacity for information transfer between the nearest neighbours of a particular node. This can be averaged to get an estimate of local efficiency for the graph as a whole. Thus networks that have a cliquish organization, characterized by many connections between the nearest neighbours of any given node, will have high local efficiency or clustering. To avoid terminological confusion with global and nodal efficiency, we will refer to this metric here as a measure of clustering.

3.3.8 Physical Distances

The physical distances were based on the Euclidean distances between the centers of coordinates (MNI-space) of all functionally connected brain seed regions. The averaged physical distances of all nodes built the measure of mean distances. Further, the number of connections/edges in each of several distance bins in the histogram of connection distances was counted (in bin intervals of 5 mm steps, starting with the minimal distance of 3 mm) at the cost level of 50%. Differences between the numbers of edges within each bin at different RS periods were tested with two-sided paired t-tests (Bonferroni corrected).

3.3.9 Statistical Analysis of Network Metrics

For each network metric a linear mixed-effects model (Pinheiro & Bates, 2000) was used to test for significant main effects of the RS period (three levels) and of behavioural performance (individual vigilance decrements as continuous factor, see analysis of behavioural data) and the interaction between both factors. The network metrics global efficiency, clustering, and mean distances were averaged over the a-priori-defined cost range in order to generalize the results across cost level. In contrast to the normal analyses of variance, linear mixed-effects models can handle data with unequal variances. Thus, before significance testing, variances of data between RS periods were compared and significant in-homogeneities of variances were explicitly modelled within the data analysis.

Pair-wise differences between RS periods were tested post-hoc by two-sided one-sample t-tests. Pearson's correlations were used to test whether participants with higher or lower vigilance decrements show differential changes in network metrics. To simplify this analysis, we also divided the participants into the two subgroups of 'attentionally impaired' (subjects with a significant vigilance decrement, n = 10) and 'attentionally resilient' subjects (subjects with no significant vigilance decrement, n = 10, see Results: behavioural data) and compared both groups with two-sample t-tests.

To control type 1 error in the context of the multiple comparisons entailed by analysis of nodal efficiency and clustering, we used $p \leq 0.0025$ (1/N) as the threshold for significance, so that less than one false positive test is expected for each whole brain analysis of nodal network properties.

In separate analyses we investigated whether our results were influenced by head motions. Therefore, we calculated the scan-to-scan displacement as suggested by van Dijk et al. (2012) and included them as further covariate in the linear mixed-effects models (see also Power et al., 2011).

3.4 Results

3.4.1 Behavioural Data

Subjects generally performed the task well and showed low rates of misses (mean = 1.95, STD = ± 0.94). Therefore the analysis of the behavioural data focused on reaction times (RT) only. Reaction times showed a significant vigilance decrement over all subjects (regression on median RTs; r = 0.48, p ≤ 0.001, Figure 3.2 A); median RT increased by 33.98 ms at the end of the experiment. A two tailed t-test over the individual regression slopes (robust fit prediction) as a measure of cognitive resilience of each subject confirmed this result (t(19)=4.41, p<0.001).

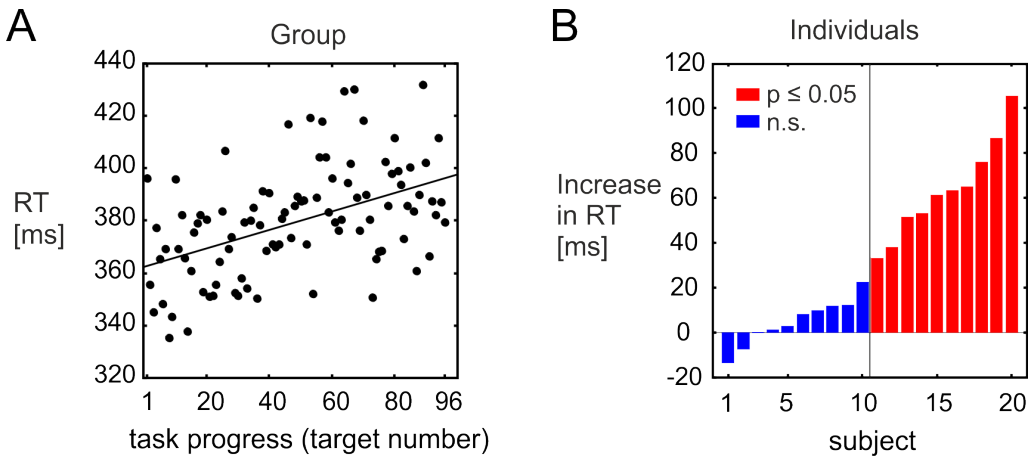

Figure 3.2: Vigilance decrements in attentional task. **(A)** Median reaction times of all 20 subjects for each of the 96 target presentations during the task are shown. Solid line = robust fit regression showed a significant RT increase/vigilance decrement. **(B)** On the individual level, participants showed a large variability in their change in RTs during task performance. For each subject, the individual robust fits for the RTs were used to estimate the RT change at the end of the task. For illustration we divided the participants into a group with significant RT increase (red, referred to as 'attentional impaired' subjects) and without a significant RT increase (blue, referred to as 'attentional resilient' subjects). However, to test the correlation between network parameters and behavioural performance without loss of information, the individual RTs increases were used and tested for a linear relationship.

However, response latency data also showed high between-subject variability. Ten participants demonstrated a significant vigilance decrement (prolongation of response time for target stimuli presented later in the series); whereas the other ten participants had no significant change in response time to targets over the course of the task (Figure 3.2 B). We refer to these sub-groups as the 'attentionally impaired' and 'attentionally resilient' groups, respectively.

The ratings in the Stanford Sleepiness Scale before and after the experiment showed that after task performance participants felt more fatigued ($t(19)=7.89$, $p \leq 0.001$, mean increase=2.23, STD=$\pm$1.25). There was no correlation between individual RT decrements and sleepiness ratings.

3.4.2 Network Metrics

Pre-Test: Variance Homogeneity

Since pre-tests showed that the variances of clustering and physical distances differed between RS periods ($p<0.01$, likelihood ratio tests comparing models with fixed vs. variable variances; see Pinheiro and Bates, 2000), we modelled unequal variances for both of these variables in the following data analysis. For connectivity strength and global efficiency we found no significant differences between variances.

Functional Connectivity Strength

Overall data analysis. For network connectivity strength the overall linear mixed-effects model revealed significant main effects for the factors RS period and performance (vigilance decrement) as well as a significant interaction between both factors (Table 3.1). In other words, connectivity strength significantly differed between RS periods and changes in network connectivity between RS periods were significantly correlated with the individual performance. These effects remained significant when controlled for linear effects of motion displacements ($p \leq 0.05$).

Table 3.1: Linear mixed-effects models

Response	Factor	Statistics	
Connectivity Strength	**Resting State (RS)**	**$F(2,36) = 5.80$,**	**$p \leq 0.01$**
	Performance	**$F(1,18) = 8.46$,**	**$p \leq 0.01$**
	Interaction RS*Performance	**$F(2,36) = 4.32$,**	**$p \leq 0.05$**
Global Efficiency	**RS**	**$F(2,36) = 15.8$,**	**$p < .0001$**
	Performance	$F(1,18) = 0.1$,	$p = 0.74$
	Interaction RS*Perf.	$F(2,36) = 1.6$,	$p = 0.22$
Clustering	**RS**	**$F(2,36) = 8.35$,**	**$p \leq 0.01$**
	Performance	$F(1,18) = 2.59$,	$p = 0.13$
	Interaction RS*Perf.	**$F(2,36) = 6.18$,**	**$p \leq 0.01$**
Physical Distances	**RS**	**$F(2,36) = 22.42$,**	**$p \leq 0.001$**
	Performance	$F(1,18) = 0.24$,	$p = 0.63$
	Interaction RS*Perf.	$F(2,36) = 1.82$,	$p = 0.17$

Mean Comparisons. Post-hoc analysis showed that connectivity strength increased significantly after task performance (RS1 vs. RS2; Table 3.2, Figure 3.3 A). There was no significant change in global connectivity strength within the post-task phase, i.e., between RS2 and RS3 (which were not separated by task performance), connectivity strength was still increased in RS3 in comparison to RS1. Note however the significant difference between resilient and impaired subjects in RS3.

Correlation with Behaviour. The individual vigilance decrements did not significantly correlate with the changes in connectivity strength following task performance (RS1 vs. RS2). However, we found a significant correlation between the individual decrements and changes in connectivity strength during the post-task phase (RS2 vs. RS3; Table 3.2 and Figure 3.4 A). Subjects with higher cognitive resilience showed larger decreases in global connectivity strength from RS2 to RS3 in the direction of pre-task values. If participants were divided into two sub-groups of cognitive resilient vs. cognitive impaired subjects the data analysis revealed similar results: Both subgroups revealed a significant difference in connectivity strength between RS2 and RS3 (Table 3.2, Figure 3.3 A): Thereby, attentionally resilient participants showed stronger decreases in global connectivity strength during the post-task phase (RS2 to RS3) than attentionally impaired subjects.

Efficiency and Clustering

Overall Data Analysis. For global efficiency and clustering the overall linear mixed-effects model revealed significant main effects for the factor RS period. For clustering there was also a significant interaction effect between the factors RS period and performance (Table 3.1). To put differently, global efficiency and clustering significantly differed between RS periods and changes in clustering between RS periods were correlated with the individual behavioural performance. Both, main effects of RS period for global efficiency and clustering and the interaction between RS period and performance for clustering remained stable (main effects $p \leq 0.05$, interaction $p \leq 0.08$) when controlled for linear effects of motion displacements.

Table 3.2: Post-hoc testing for resting state changes and relation to performance

Measure		Task (RS1-RS2)	Post-task (RS2-RS3)	RS1-RS3
Connectivity Strength	Change[a]	**T=-2.69, p<0.02**	T=-0.41, p=0.69	**T=-2.27, p<0.04**
	Correlation with performance[b]	R=-0.16, p=0.50	**R=-0.62, p<0.01**	**R=-0.47, p<0.05**
	(group difference[c])	(T=-0.16, p=0.87)	**(T=-3.12, p<0.01)**	(T=-1.66, p=0.12)
Global Efficiency	Change	**T=3.85, p<0.01**	T=1.28, p=0.22	**T=-5.09, p<0.01**
	Correlation with performance	R=0.18, p=0.44	R=0.24, p=0.32	R=0.39, p=0.09
	(group difference)	(T=0.82, p=0.43)	(T=0.05, p=0.96)	(T=0.89, p=0.38)
Clustering	Change	**T=-3.66, p<0.01**	T=-0.64, p=0.53	**T=-3.79, p<0.01**
	Correlation with performance	R=-0.08, p=0.75	**R=-0.63, p<0.01**	R=-0.38, p=0.10
	(group difference)	(T=-0.16, p=0.88)	**(T=-2.23, p<0.05)**	(T=-1.17, p=0.26)
Physical Distances	Change	**T=5.41, p<0.001**	T=0.74, p=0.46	**T=4.49, p<0.001**
	Correlation with performance	R=0.30, p=0.20	R=0.16, p=0. 49	R=0.36, p=0.12
	(group difference)	(T=0.18, p=0.86)	(T=0.05, p=0.96)	(T=0.18, p=0.86)

[a] Change between resting states, paired t-tests, df = 19.

[b] Differences between resting states correlated with individual vigilance decrements.

[c] Group comparison between attentionally impaired and resilient subjects, two-sample t-tests, df = 18.

Mean Comparisons. Post-hoc testing showed that both graph metrics changed significantly after task performance from RS1 to RS2: global efficiency decreased (Table 3.2, Figure 3.3 B) and clustering increased after task performance (Figure 3.3 C). In other words, performance of a sustained attention task led to less integrated networks with more clustered brain regions. An additional analysis, that investigated the data at each cost level separately, revealed that these effects were more pronounced in the low cost range (in the range from 2.5% to 20%; see supplemental Figures 3.8 A and 3.8 B). The differences during the post-task phase (between RS2 and RS3) were not significant for either of the topological metrics, but differences in network integration were still present in the last RS period from 6 to 12 minutes (RS3) compared to pre-task levels. Global efficiency was decreased and clustering was increased in RS3 in comparison to RS1.

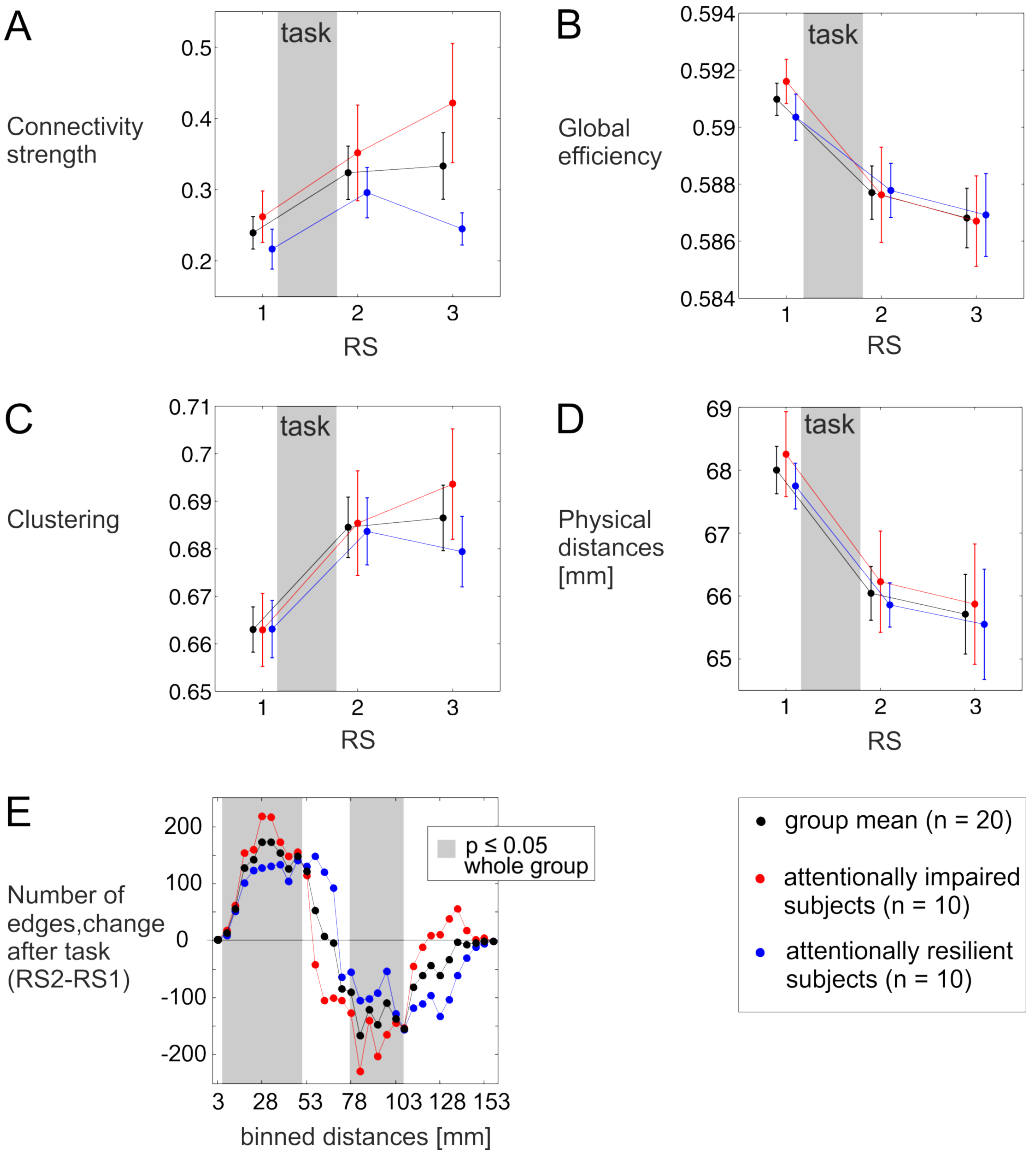

Figure 3.3: Changes in connectivity strength, topology and physical distances over resting state fMRI periods. **(A)** Global connectivity strength increased significantly after task performance (RS1 to RS2) and stayed increased during the post-task phase (RS2 to RS3) for the whole group (black, with SEM). Attentionally resilient subjects (blue) began to recover during the post-task phase, whereas attentionally impaired subjects (red) showed further increases in connectivity strength until the end of the experiment. **(B)** Global efficiency was significantly decreased after task performance. No significant changes were observed during the post-task phase. **(C)** Mean clustering significantly increased after task performance and was further increased during the post-task phase (black). Similar to the changes in connectivity strength, attentionally resilient subjects (blue) began to recover towards pre-task levels of clustering during the post-task phase, attentionally impaired subjects showed no changes towards the pre-task values. **(D)** Mean physical distances between connected nodes were significantly reduced after task performance. Changes during the post-task phase were not significant. **(E)** Distance distribution of edges before and after the task. Grey areas show distance ranges with significant changes after task performance averaged over the entire group. After task processing there were more short range connections and less long edges. Attentionally impaired subjects (red) showed a more pronounced shift in distance distribution than attentionally resilient subjects (blue).

Correlation with Behaviour. The correlation analysis revealed that changes in mean clustering during the post-task phase were significantly correlated with individual vigilance decrements (Figure 3.3 C and Figure 3.4 C; Table 3.2). An analysis with separated cost levels revealed that the correlations of individual vigilance decrements with the post-task clustering changes (RS2 to RS3) were significant at all cost-levels (supplemental Figure 3.8 B). More behaviourally resilient subjects showed decreases in clustering from RS2 to RS3 in the direction of the pre-task values. The two sub-groups showed significant differences in the change of clustering during the post-task phase. Attentionally resilient participants showed stronger decreases in clustering from RS2 to RS3 than attentionally impaired subjects.

We found no significant correlation between cognitive resilience and changes in global efficiency (Figure 3.4 B), or between resilience and changes in mean clustering between RS1 and RS2.

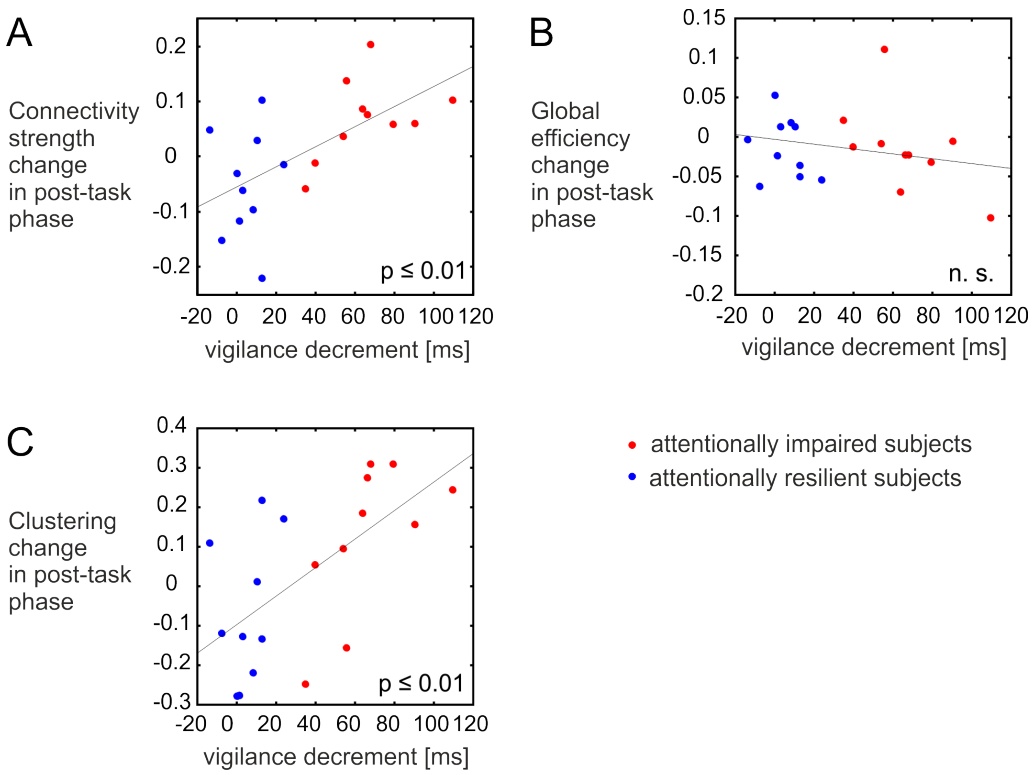

Figure 3.4: Correlations of functional network organization and cognitive resilience. (A) Changes in global connectivity strength during the post-task phase (RS3-RS2) significantly correlated with task performance. Subjects with smaller vigilance decrements began to recover and showed a decrease in connectivity strength whereas subjects with larger vigilance decrements showed increases in connectivity strength. **(B)** Global efficiency showed no relation to individual task performance in the post-task phase. **(C)** Changes in clustering during the post-task phase showed a significant correlation with individual performance. Subjects with larger vigilance decrements showed smaller recovery effects or even further increases in clustering.

Effects on Nodal Level. We also investigated the effects of rest period on topological metrics at the level of nodes or brain regions. As shown in Figure 3.5 we found major increases in clustering after task processing (from RS1 to RS2) in areas including the primary visual cortex the superior temporal gyri, the superior frontal gyri, the cuneus/medial parietal cortex, the left primary sensory cortex, the left lingual gyrus, the basal forebrain, and the anterior cingulate cortex.
Again, individual performance showed regional correlations with changes at nodal level only during the post-task phase (i.e. between RS2 and RS3). Regions that correlated with individual performance were localized in the left and right thalamus, right supramarginal gyrus, right precuneus, right amygdala, left insular cortex and right middle occipital cortex (see supplemental Figures 3.10 and 3.11 for an analysis of nodal effects as a function of cost level).

Physical Distances

Overall Data Analysis. The overall analysis of physical distances revealed neither a significant effect of performance and nor a significant interaction between performance and RS period. However, physical distances significantly changed with RS periods (Table 3.1) and this effect also remained significant when controlled for linear effects of motion displacements ($p \leq 0.05$).

Mean Comparisons. The mean physical distance of functional connections decreased significantly after task performance from RS1 to RS2 (Table 3.2 and Figure 3.3 D), but showed no significant change during the post-task period. Mean physical distance was still significantly reduced in the last RS period in comparison to RS1. An analysis with separated cost levels revealed that changes in mean distances following task processing were significant over the entire cost range (RS1 to RS2) (see supplemental Figure 3.8 C). At a cost level of 50% the distribution of physical distances between brain nodes significantly changed after task processing. After task processing, there were more nodes functionally connected in the short distance range from 8 to 53 mm and fewer nodes connected in the long distance range from 78 to 108 mm (Figure 3.3 E). An additional analysis revealed that this shift towards shorter distances after task processing was also significant at each of the investigated cost levels (see supplemental Figure 3.8). We found no significant changes in the distance distribution during the post-task phase following task processing (from RS2 to RS3).

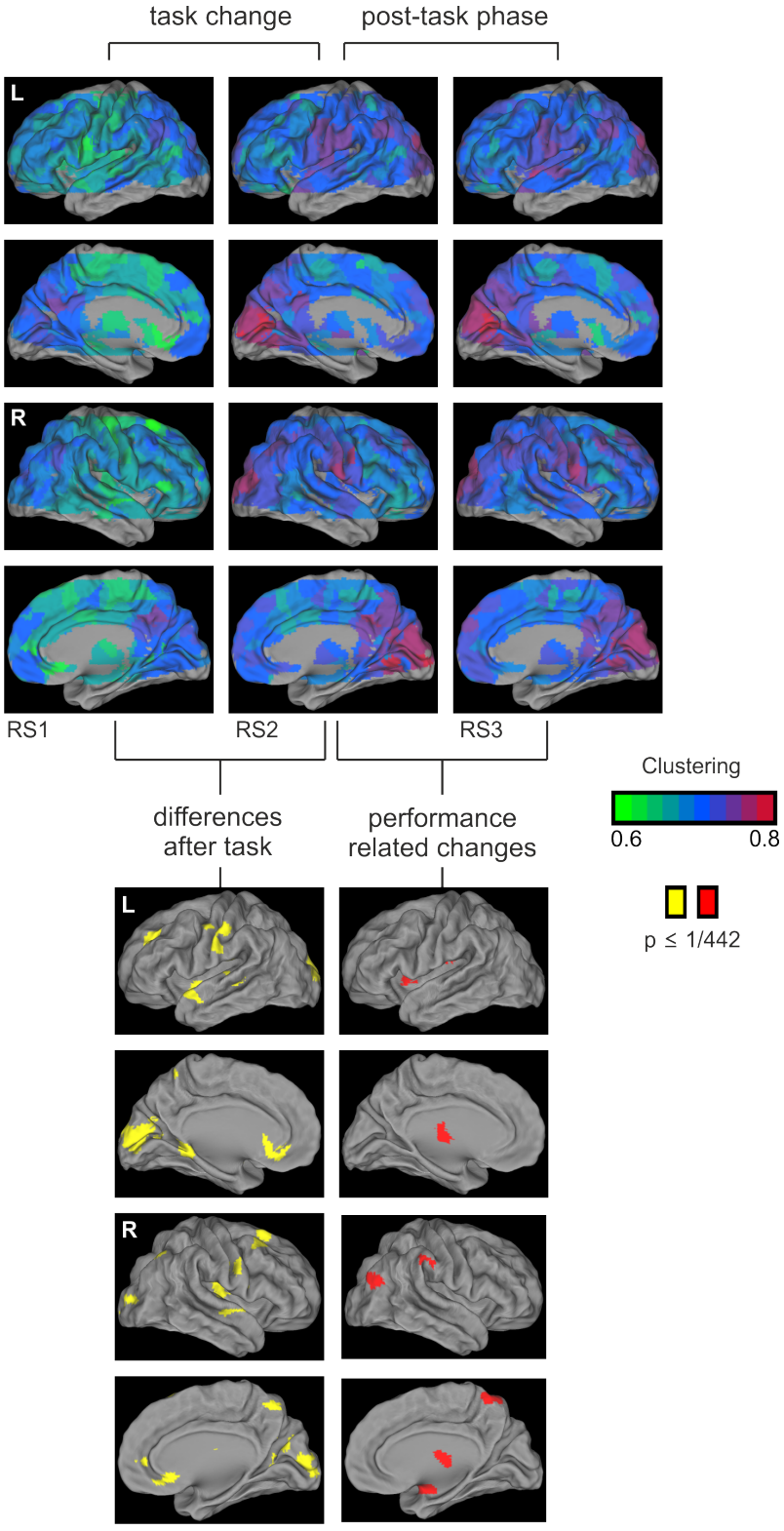

Figure 3.5: Changes in nodal network clustering over resting state fMRI periods. Top: Clustering changed over the three resting state fMRI periods. Following task performance all brain regions show higher clustering or cliquishness. **Bottom left:** Significantly different changes in clustering at nodal level (yellow) were evident among others in visual cortex and basal forebrain; brain areas involved in the processing of visual sustained attention tasks. **Bottom right:** Significant changes in clustering in the post-task phase that were related to vigilance decline were found among others in the thalamus (red).

3.5 Discussion

Our results revealed that an attentionally demanding task has strong impact on functional brain network topology even 12 minutes after task performance. Attentional task performance is followed by less efficient, more fragmented, and more clustered brain networks with less long-distance and more short-distance connections. As a second major finding, we could show that late changes in network topology (more than six minutes after the task) were correlated with individual differences in cognitive resilience during task performance. Attentionally resilient participants showed a larger reduction of network clustering and disintegration, i.e., a greater degree of recovery towards pre-task network topology during the post-task period.

3.5.1 Task Performance Affects Network Synchronization in the Low Frequency Range

Effects of changed RS connectivity in a lower frequency range (<0.1 Hz) subsequently to task performance were previously reported after motor (Duff et al. 2008) and language tasks (Waites et al. 2005). Furthermore, previous studies showed that motor learning (Albert et al., 2009) and perceptual learning (Lewis et al., 2009; Stevens et al., 2010) lead to long-lasting changes in functional connectivity and a modulation of region specific plasticity. Effects of task performance on functional brain network topology instead of simpler correlation measures have previously been described by Kitzbichler et al. (2011). They analysed high frequency magnetoencephalography data (MEG) and analysed functional networks during performance of a working memory task at various levels of difficulty. The more difficult versions of the task were associated with increased global efficiency and increased connection distance, reduced clustering and reduced modularity. The findings reported here confirm and extend these findings. Our data show that task performance has long-lasting effects on functional brain network topology that are based on oscillation in a much lower frequency range (∼0.1 Hz).

3.5.2 Task Performance Has Long-Lasting Effects on Network Topology

Long-lasting effects after task performance on RS oscillations have been infrequently reported in studies to date. One study by Barnes et al. (2009) could show that endogenous oscillations in different brain regions stay altered for more than 15 minutes after task performance. In contrast to Barnes et al. (2009), who investigated isolated time series, our study investigated the functional topology of the whole brain network and showed that effects on functional network topology persist over a long time period. The two RS periods after task processing covered a time window of more than 12 minutes and functional connectivity, global efficiency and clustering were still changed in RS3 (6-12 Min post-task).

On nodal level, effects of increased clustering were, among others, evident bilaterally in the visual cortices, the superior temporal cortices and the basal forebrain (Figure 3.5, bottom left). Many brain regions in which we found differences in clustering after task performance were also significantly activated during the task period, between RS1 and RS2 (compare Breckel et al., 2011; a list of overlapping regions is given in supplemental Table 3.3). Some of these regions including the visual and superior temporal cortices also showed increases in clustering after a visual attention task within a different data set (Giessing et al., unpublished data). These regions have been previously discussed in the context of visual processing and visual spatial attention (e.g. Corbetta & Shulman, 2002) and the observed changes in clustering in these regions probably reflect more general reconfiguration processes following visual attention tasks. More specific related to attentional effort, we found increased clustering after task processing within the basal forebrain. During task performance the activation within this brain region increased with higher cognitive demands due to prolonged time intervals between target stimuli (Breckel et al., 2011). The cholinergic basal forebrain is a crucial part of the attentional effort network as proposed by Sarter (2006) and is suggested to trigger activity in the anterior attention system in medial prefrontal cortex and to optimize processing in sensory cortical regions. Animal evidence indicates that attentional effort increases ACh release in medial prefrontal cortex (Kozak et al., 2006). In summary, our data suggest that task specific recruitment of brain regions can produce region-specific hang-over effects in brain topology after task performance.

3.5.3 Behavioural Performance and Functional Brain Networks

Our behavioural data support the claim that - averaged over all subjects - participants showed longer reaction times at the end of the vigilance task and that these behavioural effects were accompanied by reduced brain network integration. Previous studies support an association between brain topology and task performance. Subjects with higher scores in intelligence tests (based on performance in various tasks) showed shorter path lengths and higher global efficiency values in brain network topology (Li et al., 2009; van den Heuvel et al., 2009). Further, recent studies investigating ageing effects found age-related changes in network topology and showed that aged subjects have decreased global efficiency and increased clustering (Gong et al., 2009; Wang et al., 2010). From previous behavioural studies it is known that aged subjects show poorer performance in attentional tasks (Berardi et al., 2001; Gazzaley et al., 2005). A more direct piece of evidence for the correlation of network topology and attentional task performance is given by a study from Wang et al. (2009). Wang et al. (2009) compared the brain network topology of children with attention deficit hyperactivity disorder (ADHD) and healthy children. Children with the attentional deficit syndrome showed lowered global efficiency and significantly increased clustering in their brain topology. In summary, previous group and correlation

studies suggest that higher task performance is related to higher network integration. Our study revealed that this effect can also be manipulated experimentally by a challenging attentional task: task-induced decrements in vigilance were associated with less integrated brain networks.

3.5.4 Network Recovery and Task Performance: Behaviourally Impaired Subjects Recover Later

Behaviourally there was a large individual variability in the extent of performance decline during task performance. These behavioural individual differences did not predict task induced changes in network topology following the end of the task (i.e. RS1 vs. RS2), but were highly correlated with changes in topology in the post-task or recovery phase (RS2 and RS3).

Only few studies have investigated recovery effects after tasks on endogenous dynamics so far. Barnes et al. (2009) compared changes in endogenous oscillations on a longer time scale after a task with different workloads. They found workload dependent recovery effects in endogenous oscillations; a low load condition led to a faster and earlier recovery (about 400 s post-task) of the fractal properties of the BOLD time series. In our study we did not vary the workload, but the variability of performance between subjects indicated that the same task demand could introduce large differences in individual cognitive resilience. Brain networks in subjects with high vigilance decrements further continued to show increased global connectivity strength and mean clustering in the RS3 period. In contrast, brain networks in subjects with low or no vigilance decrement revealed a pattern of connectivity which resembled that prior to task performance. Although the acquired RS time window of 12 minutes post-task was not long enough for a full restoration of all network metrics our study is the first which shows demand-related recovery effects on functional network topology.

On nodal level, significant correlations or recovery effects in clustering were only observed in the post-task phase (RS2 to RS3) and among others evident in the thalamus, a key structure of the arousal system (Paus et al., 1997; Portas et al., 1998). Attentionally impaired subjects showed further increases of clustering in this region, whereas resilient subjects showed decreases of clustering. At a less conservative level of significance ($p<0.05$, uncorrected) our results also reveal an overlap between brain regions that show an effect of task processing (RS1 to RS2) and a performance-related change in the post-task phase (RS2 to RS3). This overlap was evident in visual cortices and superior temporal gyri.

However, the performance-related change of network topology in the thalamus was only evident in the post-task period. These differential effects might be related to the long- and short-lasting cognitive processes elicited by the sustained attention task (Breckel et al., 2011). During task processing participants had to detect an infrequent colour change of a simple visual stimulus during a time period of more than 30 minutes. Even though there are several factors that affect performance declines during periods of tonic alertness (Oken et al., 2006), previous studies support the idea that the attention system interacts with arousal level (Portas et al, 1998). All subjects might have 'used' the same brain networks for attentional processing, but subjects who performed the task in a less efficient way probably showed larger reductions of arousal following task performance. These differences in arousal between subjects may increase after a longer time period of resting state (resting state period 2 and 3) in which participants have to refrain from falling asleep. It is a common finding in psychology that inter-individual differences are more evident in 'weak' task conditions in which less cues provide behavioural psychological pressure and that are more ambiguously structured to engage a certain behavior (Mischel, 1973).

3.5.5 Biological Explanations for Long-Lasting Effects of Task Performance

Previous studies have shown that learning-induced plasticity can have a long-lasting impact on subsequent RS periods (Lewis 2009, Albert et al. 2009, Stevens et. al. 2010) and might therefore be responsible for the task-induced changes in functional connectivity and network topology observed after our sustained attention task. Animal data suggest that prolonged effort in attention tasks increases the release of acetylcholine (ACh) in prefrontal brain regions resulting in a top-down adjustment of sensory processes (Sarter et al. 2006). ACh induced plasticity can last several minutes even though ACh concentration has reached baseline level again (for a review see Rasmusson, 2000). Hence, changes in resting state connectivity after performance of a sustained attention task may be the consequence of prior task-induced ACh release.

On molecular level metabolic costs may account for long-lasting effects of task performance. Mental tasks are accompanied by an increased level of glycolysis in the brain (Fox et al., 1988; Blomqvist et al., 1994). Raised level of glycolysis can last up to 40 minutes after termination of task performance (Madsen et al., 1995) and prolonged aerobic glycolysis can cause imbalance in cell metabolism (e.g. proton and lactate accumulation; Newsholme et al., 1992). Our data revealed that the distribution of the physical distance between functionally connected nodes was shifted in favour of shorter distances after task performance. Neuronal transmission over shorter physical distances was earlier described as one strategy of the brain in order to preserve metabolic costs (Niven & Laughlin, 2008).

3.5.6 Methodological Considerations

Head Motion. There is evidence that head motion can influence measures of network topology and connection distances (Dijk et al., 2012; Power et al., 2012). Therefore, we used previously described measures to test for possible confounding effects (Power et al., 2012). We found that there were only few movement-related frame-wise displacements >0.5 mm in our data and 'scrubbing' the time series to eliminate frames of data that might be affected by head movement did not change the strength of functional connectivity between regions separated by short or long connection distances (see supplemental material 2).

Brain Parcellation. It has been demonstrated that the analysis of brain networks can be sensitive to the choice of parcellation template used to delineate nodes (Hayasaka & Laurienti, 2010; Zalesky et al., 2010; Wig et al., 2011). In this study, a relatively common parcellation template with minimal variation in nodal volume was used, thus minimizing the variation in signal-to-noise across nodes.

Corrections for Physiological Noise. There is an ongoing discussion whether BOLD signal time series should be corrected for signal changes in white matter and cerebrospinal fluid (Yarkoni et al., 2009; Jo et al., 2010; Iacovella & Hasson, 2011). However, additional analyses in which we corrected for possible physiological noise effects revealed the same or stronger effects of task performance on the functional connectivity strength and correlations with the individual vigilance decrements which suggest that our results are not biased by physiological noise (see supplemental material 4).

Eyes Open vs. Eyes Closed RS Conditions. Studies which compared RS periods with eyes open and eyes closed found differences in low frequency BOLD fluctuations and connectivity measures within visual brain areas (Raichle et al., 2001; Zou et al., 2009). In the current study we instructed subjects to keep their eyes open in order to have similar visual stimulation during the task and resting state conditions (see also Raichle et al. 2001, p. 680).

3.5.7 Implications of Long-Lasting Changes in Network Topology Following Tasks

In many studies investigating neural correlates of task-related processing (e.g., in fMRI, PET or ERP studies) spontaneous signal fluctuations were only considered as noise factor. Over the last years this perspective has changed, since previous studies have shown

that, for example, spontaneous blood oxygen level dependent (BOLD) signal fluctuations contribute to the prediction of variability in behavioural performance within and between subjects (Hampson et al., 2006; Fox & Raichle, 2007; Lim et al., 2010; Mennes et al., 2011). In computational neuroscience, previous results revealed that the complex network architecture of brains rapidly changes to meet the requirements of specific task demands (Bassett et al., 2009; Kitzbichler et al., 2011). As first study, our results show that task performance has also reflexive effects and leads to long-lasting changes in endogenous brain networks after task performance. Our data show that these long-lasting effects on brain network topology are correlated with behavioural measures of cognitive resilience in a prior sustained attentional task. Future studies, with several task and RS periods within one fMRI scanning session, might also show that individual differences in network recovery can be used to predict differences in behavioural performance within following task periods.

In real world, economical reasons often force researchers to present several tasks within one fMRI scanning or MEG session, neglecting or underestimating changes in functional brain networks resulting from a previous task. Our data indicate that 12 minutes of rest period between each task are not enough to fully recover functional brain networks from previous task processing. Our data strongly encourage to take into account 'hang-over' effects on the organization of post-task brain networks that possibly interact with the processing of new tasks. These 'hang-over' effects introduce a specific brain state, which will impact on subsequent neural processing and behavioural performance. In future, the individual capability of brain network recovery might be an additional measure to obtain cognitive resilience of patients and to detect early symptoms of potential neurological disorders. Our data support that the recovery of network topology is a biomarker of cognitive resilience that significantly contributes to the understanding of inter-subject differences in the recovery from cognitive demands.

3.6 Acknowledgements

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3.7 Supplemental Material

SUPPLEMENTAL MATERIAL 1

Region[1]	Center of gravity[2]		
BOLD Contrast 1: Target events > all (implicit baseline) (FDR corrected, $p \leq 10^{-5}$, $k \geq 40$)			
Seed regions in which a significant change in clustering after task processing (RS1/RS2)[3] overlapped with task activation			
R Superior Frontal Cortex / Premotor (BA6)	15	16	56
L Superior Frontal Cortex (BA9)	-24	30	34
R Rolandic Operculum (BA13)	43	-7	20
L Superior Temporal (BA 38)	-52	3	-11
L Superior Temporal / Insula	-40	-8	-9
L Postcentral / Sensorimotor Area	-54	-18	43
R Area 17 (Calcarine sulcus)	26	-64	5
L Area 17 (Calcarine sulcus)	-15	-76	11
L Area 18 (Lingual gyrus)	-13	-48	-6
R Cuneus	7	-73	22
R Middle Occipital gyrus	26	-87	5
R Thalamus	21	-15	16
Seed regions showing a significant correlation[3] of clustering change in the post-task period (RS2/RS3) with the vigilance decrement that overlapped with task activation			
R Supramarginal Sulcus (IPC)	60	-32	36
L Insula	-34	9	3
R Thalamus	2	-19	6
L Thalamus	-18	-22	14
BOLD Contrast 2: Target events weighted with time between targets (ISI) as measure of vigilance (FDR corrected, $p \leq 0.001$, $k \geq 40$)			
Seed regions in which a significant change in clustering after task processing (RS1/RS2)[3] overlapped with task activation			
Basal forebrain / ACC	0	26	-3
R Orbito frontal cortex (BA10)	18	44	2
L Postcentral / Sensorimotor Area	-54	-18	43
L Area 18 (Lingual gyrus)	-13	-48	-6
R Middle Occipital gyrus	26	-87	5

Table 3.3: Seed regions that overlap with task BOLD activity during the task. ([1]) Seed regions that overlap with at least with 20% of their volume with Task BOLD activity. ([2]) MNI-coordinate of the center of the seed regions. ([3]) Changes / Correlations that survived a corrected threshold of $p \leq 1/442$.

SUPPLEMENTAL MATERIAL 2: ANALYSES OF SUSPECT MOTION-CORRUPTED FRAMES

We have analyzed all datasets presented in this paper fully for motion-related effects. In accordance with Power et al.(2012) we have computed a number of metrics to identify suspect motion-corrupted frames of data and scrubbed these frames from our datasets to determine whether this confers any additional benefit. We have computed the following:

1. Frame-wise Displacement (FD, in mm) - this is the sum of the absolute derivatives of the six motion parameters (as described in Power et al., 2012). Rotational parameters were converted to displacements by computing the arc length displacement at the surface of a sphere of radius 50 mm.

2. The DVARS (in %x10) on the time series used for graph analysis. This was computed as the root mean square on the voxel-wise derivatives of percent signal change. This was expressed as %x10 as in Power et al. (2012).

3. The number of suspect frames that would be censored by the Power et al. (2012) 'scrubbing' methodology. Suspect frames were identified by having either FD>0.5 mm or DVARS>0.5%. These thresholds were identical to those used in Power et al. (2012).

4. A parallel set of times series for all datasets where the suspect frames in 3) were 'scrubbed' and temporally concatenated in accordance with Power et al. (2012). Frames were 'scrubbed' after confound regression and temporal wavelet filtering (Carp, 2011).

5. The relationship between ΔR caused by motion scrubbing (simply the 'scrubbed' correlation matrix minus the 'unscrubbed' correlation matrix) and the Euclidean distance between pairwise correlations of regional time series. We first computed this at a single-subject level, and subsequently averaged ΔR values across subjects for the group-level analysis, as described by Power et al. (2012).

6. The r^2 coefficient of determination for each group-level scatter plot between ΔR and Euclidean distance. This was computed using the following formula:

$$R^2 = 1 - \frac{\sum(y_i - f_i)^2}{(n-1)\cdot(y_i - \bar{y})^2}$$

   where f_i is the linear fit of the scatter plot and n is the total number of pairwise ΔR values.

First, we calculated the number of suspect frames of data that would be removed from the regional time series by 'scrubbing'. We found that only 23/60 (38%) of datasets would

need more than one frame 'scrubbed'. Of these datasets, 9/30 are in the 'Attentionally Resilient' condition, and 14/30 are in the 'Attentionally Impaired' condition. The total number of frames that would need to be removed from each dataset are shown in Table 3.4.

Next, we compared the percentage of suspect frames (as a percentage of the total number of frames in each dataset), as a measure of the amount of motion in our datasets, across the two conditions, and across the different resting state scans (Figure 3.6). There is no notable difference in motion between the two conditions ('Attentionally Resilient' and 'Attentionally Impaired'), and whilst there is a slight increase in head movement through the resting state scans (as one would expect), this is not restricted to one group. In addition, this slight increase in movement across resting state scans appears to have no distance-dependent impact on correlation between regional time series (Figure 3.7). To test this last point, we assessed whether there are any distance-dependent biases in correlation strength between regional time series in our data. For this, we scrubbed all datasets and computed the ΔR (which is the 'scrubbed' minus 'unscrubbed' correlation matrices). These values were plotted against the Euclidean distance between pairwise combinations of time series. We observed no differential effects of correlation strength at long versus short distances, which suggests that 'scrubbing' provides no additional benefit to our data (Figure 3.7). To complement this assertion, we computed the r^2 coefficient of determination for each group analysed in this way. The fraction of variance explained by linear fits for our data is negligible (see Figure 3.7) compared to values presented in Power et al., 2012 (r^2=0.18), confirming our conclusion that there is no relationship between movement-related changes in pairwise correlations between regional time series and distance in our data.

Table 3.4: Number of suspect frames per dataset that would need to be 'scrubbed' from the time series using the criteria outlined in Power et al. (2012) (FD>0.5 mm or DVARS>0.5 %). The total number of frames of data in each dataset is 256.

Attentionally Impaired				Attentionally Resilient			
SUBJECT	Rest 1	Rest 2	Rest 3	SUBJECT	Rest 1	Rest 2	Rest 3
1	1	5	9	3	0	0	0
2	0	0	0	4	1	1	0
5	1	0	1	6	1	4	1
8	1	4	1	7	50	24	44
9	0	2	7	11	0	0	0
10	3	21	29	15	2	3	0
12	1	15	12	16	0	0	0
13	7	56	55	17	0	0	0
14	0	0	0	18	2	7	15
20	0	0	5	19	0	0	0

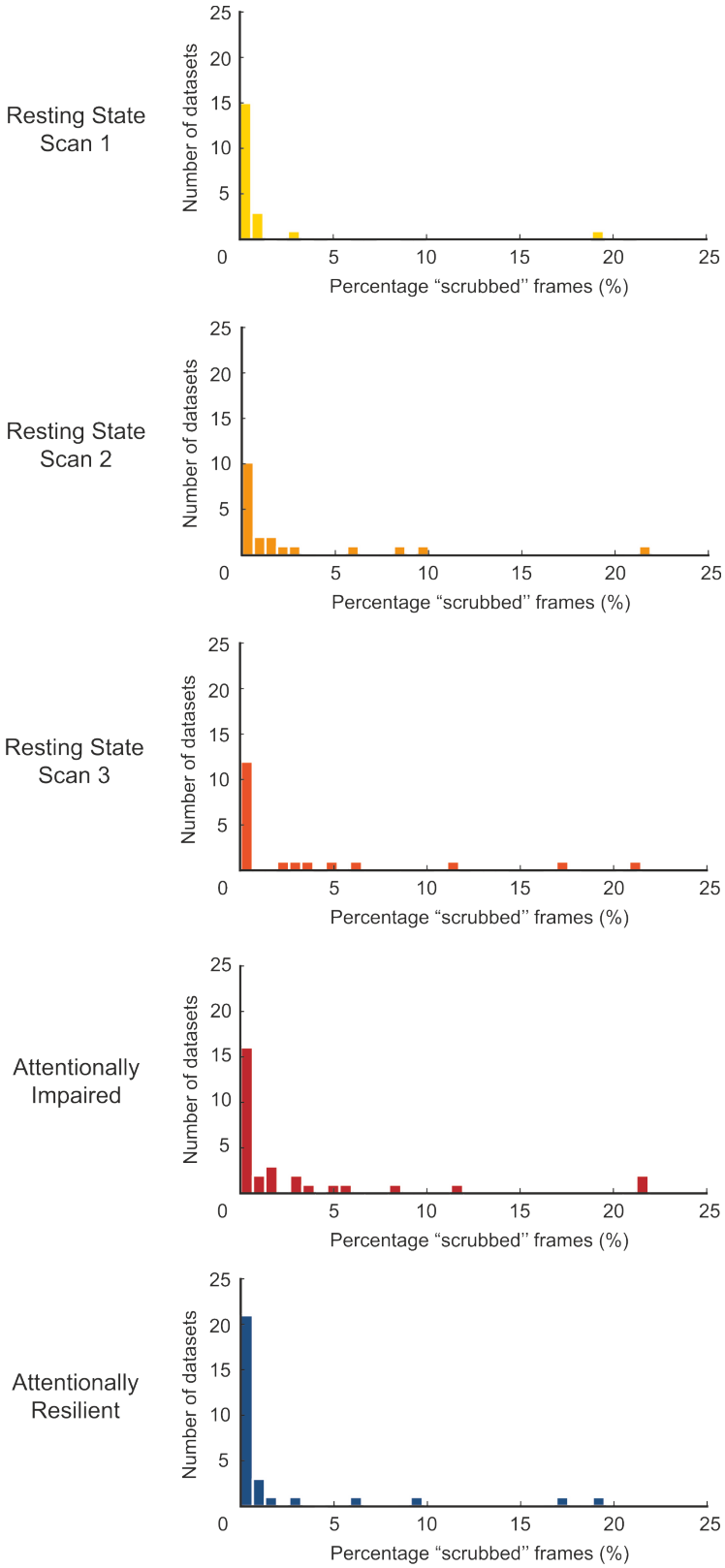


Figure 3.6: Histograms representing the percentage of motion-affected frames in each dataset. Frames are identified using thresholds defined in Power et al., 2012 (frames where FD>0.5 mm or DVARS>0.5%; see METHODS). The histograms labelled 'Resting state scan' combine datasets from both conditions ('Attentionally Resilient' and 'Attentionally Impaired'), and similarly, histograms for the two conditions combine datasets from all resting state scans undertaken by subjects in those conditions.

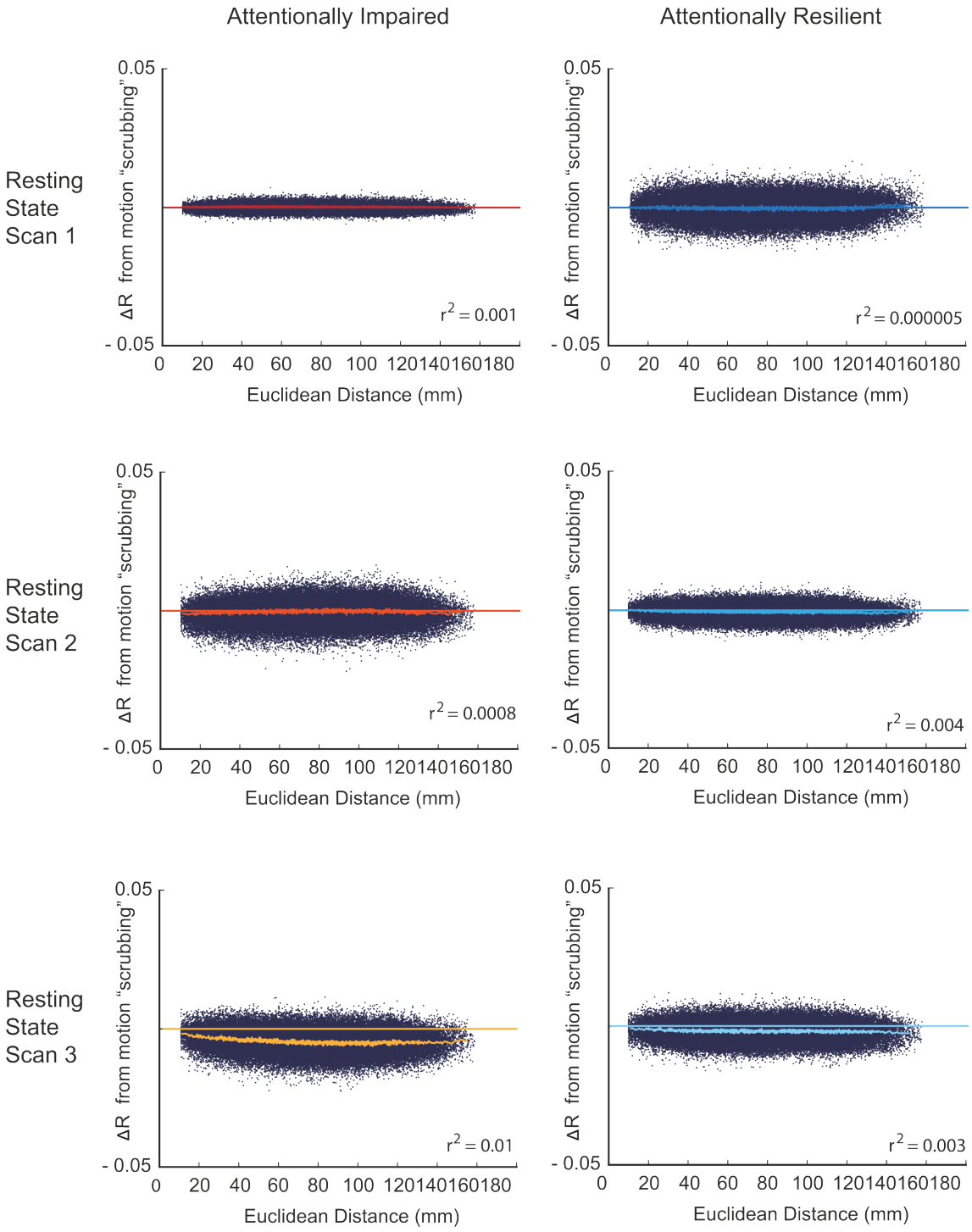
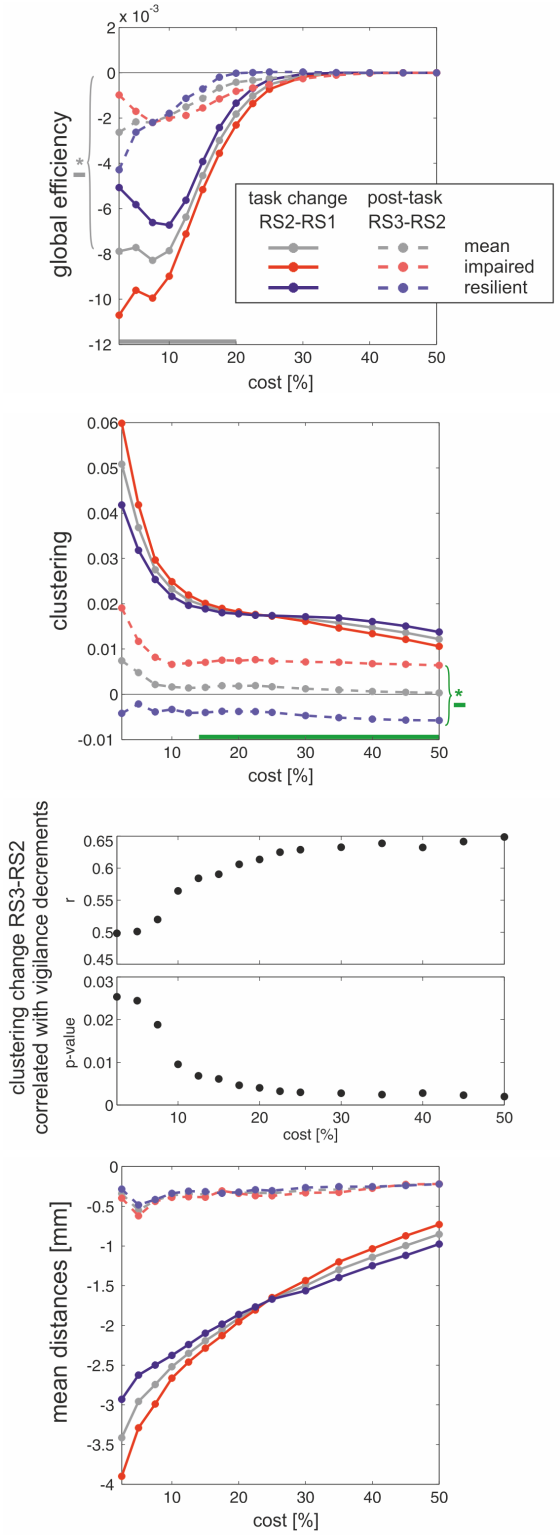


Figure 3.7: Scatter plots showing the impact of time frame 'scrubbing' on the relationship between Euclidean distance between regions and ΔR. ΔR is the difference in pairwise correlations before and after scrubbing, and is calculated by subtracting the 'unscrubbed' correlation matrix from the 'scrubbed' correlation matrix. Each scatter plot was fitted to a moving average line by binning every 100 points (sorted as a function of Euclidean distance) and calculating the average ΔR value for this set of distances. The r^2 values (coefficient of determination) for the relationship between Euclidean distance and ΔR were calculated for each scatter plot and noted alongside the plot (also see METHODS).

SUPPLEMENTAL MATERIAL 3:
GRAPH METRICS AS FUNCTION OF CONNECTION DENSITY



A. Global efficiency change over cost levels. Solid lines: Changes of global efficiency from RS1 to RS2 were more pronounced in lower cost ranges. The mean change of both groups (gray) was significant ($p<0.05$) in the range from 2.5% to 20%. At no cost level a significant group difference (between blue and red) was found. **Dashed lines:** Changes of global efficiency from RS2 tor RS3 were not significant at any cost level. Impaired vs. resilient subjects did not show significant differences.

B. Clustering change over cost levels. Solid lines: A significant change of clustering following task processing (RS1 to RS2) was found at all cost levels (more pronounced at lower cost levels). No group differences (blue vs. red) were found. **Dashed lines:** In the post-task phase (RS2 to RS3) no significant mean effect (gray) was found at any cost level. Significant differences between groups were found in a cost range from 15% to 50% ($p<0.05$, green range; see however below the correlation analysis).

C. Correlation of individual vigilance decrements with post-task change (RS3-RS2) in clustering. The correlations of individual vigilance decrements with post-task clustering changes (RS2 to RS3) were significant at all cost-levels. Significance level first decreased due to the higher number of edges within the graph and became stable at 20 percent of costs.

D. Mean physical distance changes over cost levels. Solid lines: Mean distance significantly changed over all cost levels following task processing (RS1 to RS2), but was more pronounced in lower cost levels. No difference between the groups was found to be significant.**Dashed lines.** In the post-task phase (RS2 to RS3) no significant change or difference between groups was found at any cost level.

Figure 3.8: Graph metrics over cost levels.

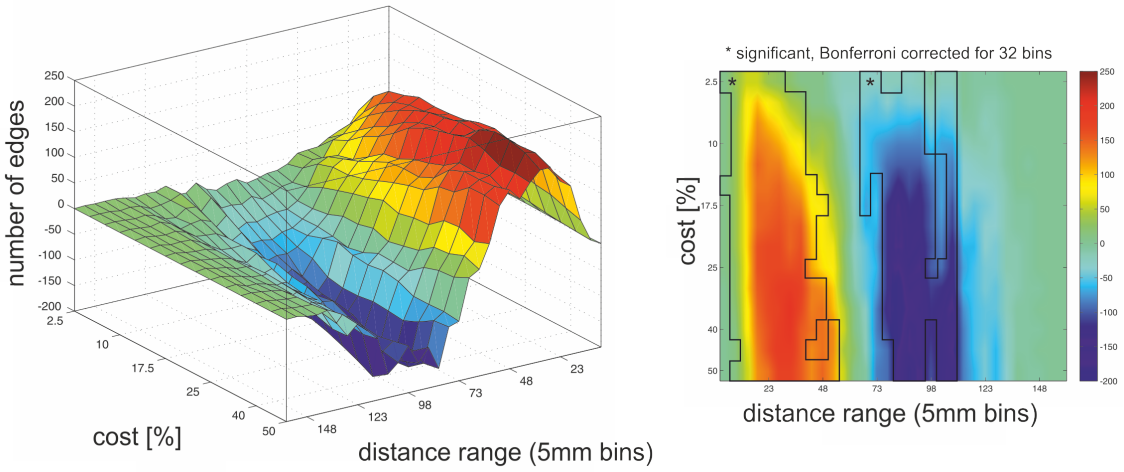


Figure 3.9: Physical distance distribution changes over task (binned number of edges RS2-RS1). Differences in the distribution of physical distances were numerically higher in the high cost range since within the high cost range more connections were compared between conditions (left panel). However, the shift towards shorter distances after task processing was prominent at all cost levels. After task processing the number of short distances significantly increased and longer distances significantly decreased independent from the investigated cost range (right panel, significant bins with p≤0.01).

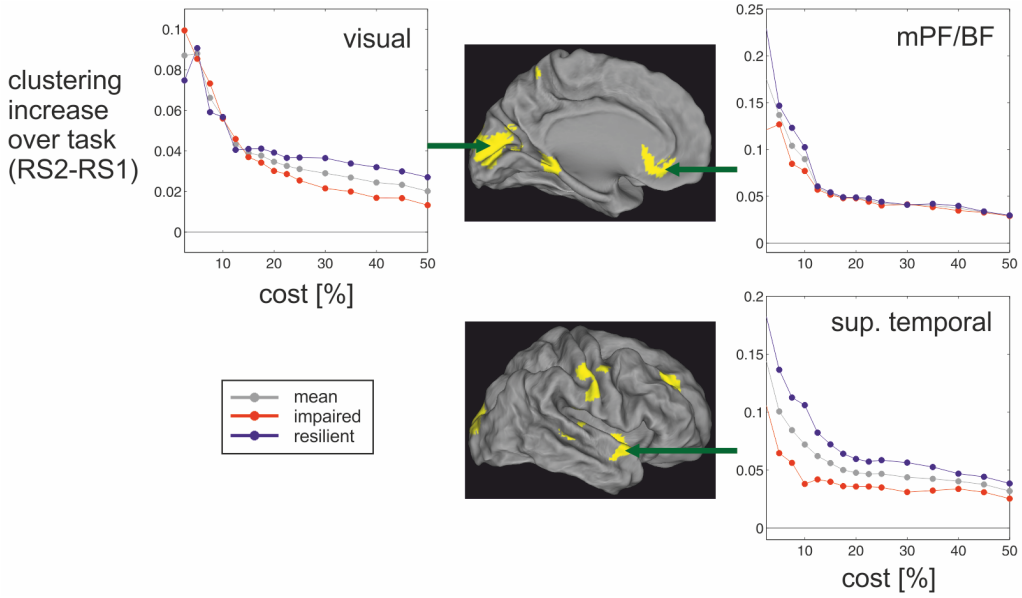


Figure 3.10: Changes in nodal clustering following task processing (RS1 vs. RS2) separated for cost levels. Effects of task processing on clustering were analyzed as a function of cost level. Within those brain regions discussed within the main text (visual areas, medial prefrontal region/basal forebrain (mPF/BF), and superior temporal gyrus) effects on nodal clustering were mainly driven by differences between graphs within the low-cost-range with lower connection densities. Graphs within the low cost range have on average higher correlations values and are less influenced by noisy connections.

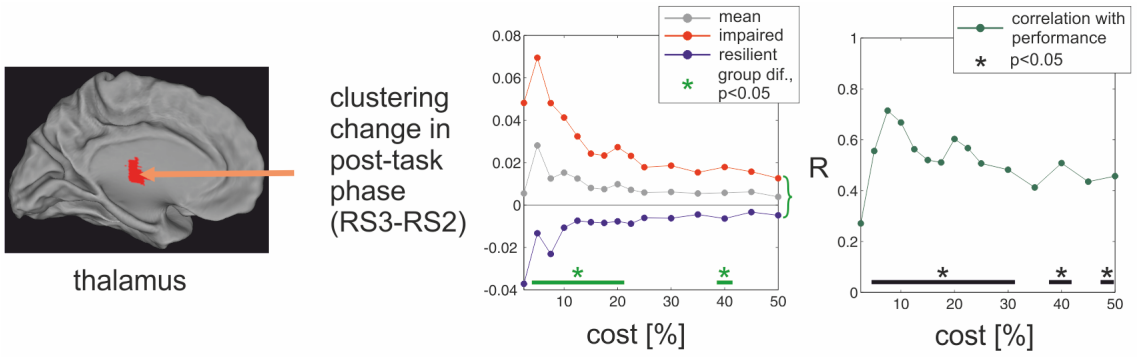


Figure 3.11: Changes in nodal clustering in the post-task phase (RS2 vs. RS3) plotted over costs and its correlation with performance. Over all subjects, the thalamus (left panel) did not show any significant changes in clustering during the post-task phase. However, changes in clustering were opposite for resilient and impaired subjects with stronger differences in the low cost range (middle panel). This result was also supported by correlation analysis: the individual vigilance decrements and the change in clustering in the post-task period correlated over a wide cost range and correlation values tended to be higher for the low cost range (right panel). Graphs within the low cost range have on average higher correlations values and are less influenced by noisy connections.

SUPPLEMENTAL MATERIAL 4: ANALYSES RELATED TO ADDITIONAL CSF/WM REGRESSION OF BOLD TIME SERIES

Two methods for BOLD time series pre-processing were compared and analysed with regard to potential confounds for the comparisons between the three RS periods and the two performance groups. Connectivity matrices were calculated on the basis of two sets of low-frequency wavelet filtered BOLD time series:

For the first set the mean BOLD time series were corrected for motion by regressing out the six motion parameters as derived from the spatial realignment step during BOLD image pre-processing (the approach as used in the manuscript). Following this correction the time series were wavelet filtered.

For the second set the mean BOLD time series were also corrected by signal changes in the cerebro spinal fluid (CSF) and in the white matter (WM). CSF and WM signal changes were extracted and averaged from voxel time courses of spherical ROIs with 7 voxels each. We averaged over three ROIs in the CSF (anterior medial and posterior left and right in the ventricles; MNI = [4 11 9; -24 -45 9; 27 -44 9]) and four regions in the WM (anterior and posterior part in the corpus callosum and left and right lateral white matter areas; MNI = [-2 -36 13; 1 24 1; 26 -34 31; -25 -34 30]).

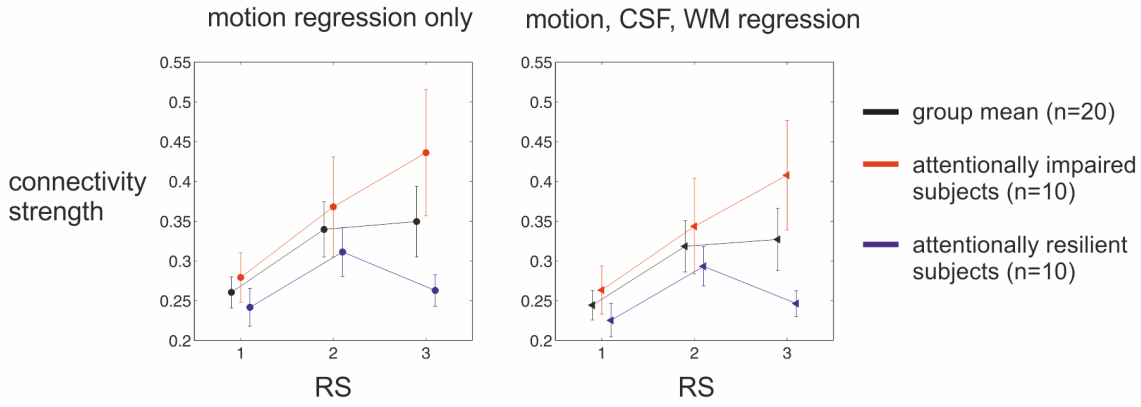


Figure 3.12: Global connectivity strength averaged over whole group and separated for both performance groups. If time series are corrected for CSF- and WM- signal changes global connectivity strengths decreased (right panel) in comparison to the global connectivity strengths with motion correction only (left panel). However, the pattern of results revealed the same in both analyses and the CSF- and WM-signal corrected data showed slightly increased statistical effects (see table 3.5. below).

Table 3.5: Linear mixed-effects models

Response	Factor	Statistics
Connectivity Strength (motion corrected)	**Resting State (RS)**	**$F(2,36) = 5.80$, $p \leq 0.01$**
	Performance	**$F(1,18) = 8.46$, $p \leq 0.01$**
	Interaction RS*Performance	**$F(2,36) = 4.32$, $p \leq 0.05$**
Connectivity Strength (motion/CSF/WM signal corrected)	**Resting State (RS)**	**$F(2,36) = 6,95$, $p \leq 0.01$**
	Performance	**$F(1,18) = 9.55$, $p \leq 0.01$**
	Interaction RS*Performance	**$F(2,36) = 4,69$, $p \leq 0.05$**

Table 3.6: Post-hoc testing for connectivity strength changes and relation to performance

Measure		Task (RS1-RS2)	Post-task (RS2-RS3)	RS1-RS3
Connectivity Strength (motion corrected)	Change[1]	**T=-2.69, p<0.02**	T=-0.41, p=0.69	**T=-2.27, p<0.04**
	Correlation with performance[2]	R=-0.16, p=0.50	**R=-0.62, p<0.01**	**R=-0.47, p<0.05**
	(group difference[3])	(T=-0.16, p=0.87)	**(T=-3.12, p<0.01)**	(T=-1.66, p=0.12)
Connectivity Strength (motion /CSF/WM corrected)	Change	**T=-2.93, p<0.01**	T=-0.48, p=0.64	**T=-2.42, p<0.03**
	Correlation with performance	R=-0.22, p=0.35	**R=-0.62, p<0.01**	**R=-0.49, p<0.03**
	(group difference)	(T=-0.24, p=0.82)	**(T=-4,11, p<0.001)**	(T=-1.92, p=0.07)

[1] Change between resting states, paired t-tests, df = 19.

[2] Differences between resting states correlated with individual vigilance decrements.

[3] comparison between attentionally impaired and resilient subjects, two-sample t-tests, df = 18.

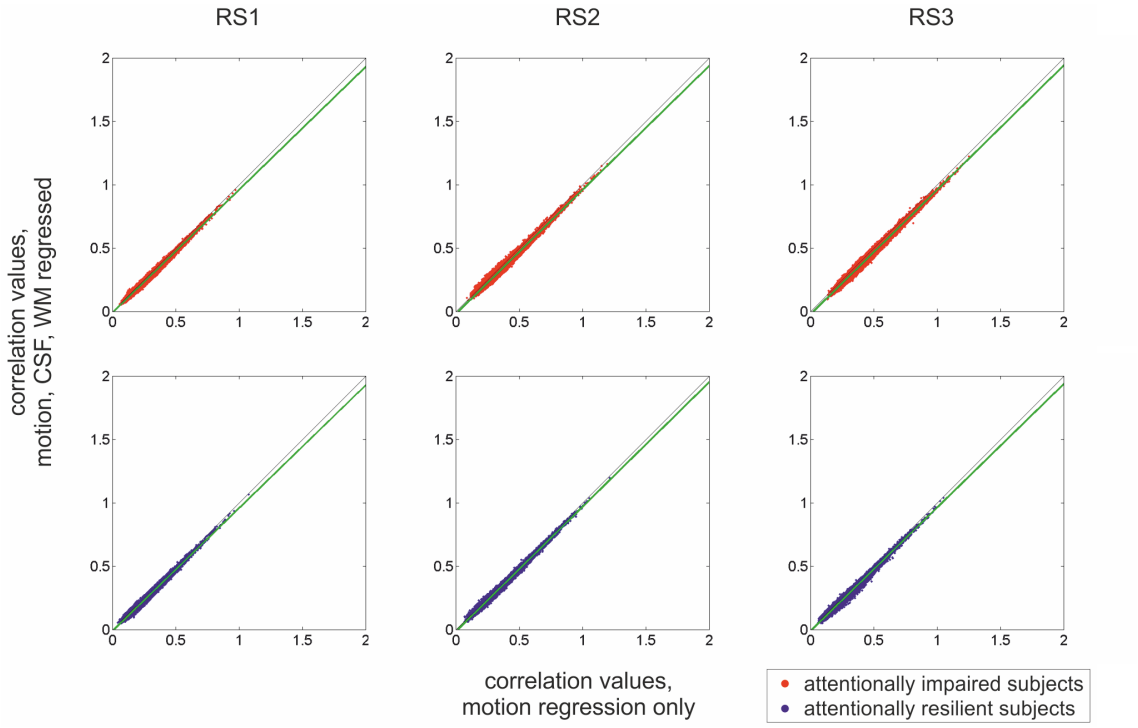


Figure 3.13: Similarity of the correlation values (Fisher's z-transformed) derived with both correction methods. Values based on time series with motion regression only (x-axes) versus values based on time series with motion, CSF and WM regression (y-axes). The fitted regression lines (green) show a small shift to higher correlation values when only motion regression was used in time series preprocessing. This change is very homogeneous across the three RS periods and also across the two performance groups. However, except for this offset the distribution of correlation values did not change systematically.

3.8 References

Achard, S., Salvador, R., Whitcher, B., Suckling, J. & Bullmore, E. (2006) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. The Journal of neuroscience : the official journal of the Society for Neuroscience, 26, 63-72.

Albert, N.B., Robertson, E.M. & Miall, R.C. (2009) The resting human brain and motor learning. Curr Biol, 19, 1023-1027.

Barnes, A., Bullmore, E.T. & Suckling, J. (2009) Endogenous Human Brain Dynamics Recover Slowly Following Cognitive Effort. PloS one, 4.

Bassett, D.S., Bullmore, E.T., Meyer-Lindenberg, A., Apud, J.A., Weinberger, D.R. & Coppola, R. (2009) Cognitive fitness of cost-efficient brain functional networks. P Natl Acad Sci USA, 106, 11747-11752.

Berardi, A., Parasuraman, R. & Haxby, J.V. (2001) Overall vigilance and sustained attention decrements in healthy aging. Experimental aging research, 27, 19-39.

Blomqvist, G., Seitz, R.J., Sjogren, I., Halldin, C., Stone-Elander, S., Widen, L., Solin, O. & Haaparanta, M. (1994) Regional cerebral oxidative and total glucose consumption during rest and activation studied with positron emission tomography. Acta physiologica Scandinavica, 151, 29-43.

Breckel, T.P., Giessing, C. & Thiel, C.M. (2011) Impact of brain networks involved in vigilance on processing irrelevant visual motion. NeuroImage, 55, 1754-1762.

Bullmore, E. & Sporns, O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience, 10, 186-198.

Carp, J. (2011) Optimizing the order of operations for movement scrubbing: Comment on Power et al. NeuroImage.

Corbetta, M. & Shulman, G.L. (2002) Control of goal-directed and stimulus-driven attention in the brain. Nature reviews. Neuroscience, 3, 201-215.

Damoiseaux, J.S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M. & Beckmann, C.F. (2006) Consistent resting-state networks across healthy subjects. P Natl Acad Sci USA, 103, 13848-13853.

Duff, E.P., Johnston, L.A., Xiong, J., Fox, P.T., Mareels, I. Egan, G.F. (2008) The power of spectral density analysis for mapping endogenous BOLD signal fluctuations. Human brain mapping, 29, 778-790.

Fornito, A., Zalesky, A. & Bullmore, E.T. (2010) Network scaling effects in graph analytic studies of human resting-state FMRI data. Frontiers in Systems Neuroscience, 4, 22.

Fox, M.D. & Raichle, M.E. (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci, 8, 700-711.

Fox, P.T., Raichle, M.E., Mintun, M.A. & Dence, C. (1988) Nonoxidative glucose consumption during focal physiologic neural activity. Science, 241, 462-464.

Gazzaley, A., Cooney, J.W., Rissman, J. & D'Esposito, M. (2005) Top-down suppression deficit underlies working memory impairment in normal aging. Nature Neuroscience, 8, 1298-1300.

Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z.J., He, Y. & Evans, A.C. (2009) Age- and gender-related differences in the cortical anatomical network. The Journal of neuroscience : the official journal of the Society for Neuroscience, 29, 15684-15693.

Hampson, M., Driesen, N.R., Skudlarski, P., Gore, J.C. & Constable, R.T. (2006) Brain connectivity related to working memory performance. J Neurosci, 26, 13338-13343.

Helton, W.S. & Warm, J.S. (2008) Signal salience and the mindlessness theory of vigilance. Acta Psychol (Amst), 129, 18-25.

Hoddes, E., Zarcone, V. & Dement, W. (1972) Development and Use of Stanford Sleepiness Scale (Sss). Psychophysiology, 9, 150-&.

Iacovella, V. & Hasson, U. (2011) The relationship between BOLD signal and autonomic nervous system functions: implications for processing of 'physiological noise'. Magnetic resonance imaging, 29, 1338-1345.

Jo, H.J., Saad, Z.S., Simmons, W.K., Milbury, L.A. & Cox, R.W. (2010) Mapping sources of correlation in resting state FMRI, with artifact detection and removal. NeuroImage, 52, 571-582.

Kitzbichler, M.G., Henson, R.N., Smith, M.L., Nathan, P.J. & Bullmore, E.T. (2011) Cognitive effort drives workspace configuration of human brain functional networks. The Journal of neuroscience : the official journal of the Society for Neuroscience, 31, 8259-8270.

Kozak, R., Bruno, J.P. & Sarter, M. (2006) Augmented prefrontal acetylcholine release during challenged attentional performance. Cerebral cortex, 16, 9-17.

Latora, V. & Marchiori, M. (2001) Efficient behavior of small-world networks. Phys Rev Lett, 87, 198701.

Latora, V. & Marchiori, M. (2003) Economic small-world behavior in weighted networks. European Physical Journal B, 32, 249-263.

Lewis, C.M., Baldassarre, A., Committeri, G., Romani, G.L. & Corbetta, M. (2009) Learning sculpts the spontaneous activity of the resting human brain. Proc Natl Acad Sci U S A, 106, 17558-17563.

Li, Y.H., Liu, Y., Li, J., Qin, W., Li, K.C., Yu, C.S. & Jiang, T.Z. (2009) Brain Anatomical Network and Intelligence. Plos Computational Biology, 5.

Lim, J., Wu, W.C., Wang, J.J., Detre, J.A., Dinges, D.F. & Rao, H.Y. (2010) Imaging brain fatigue from sustained mental workload: An ASL perfusion study of the time-on-task effect. NeuroImage, 49, 3426-3435.

Madsen, P.L., Hasselbalch, S.G., Hagemann, L.P., Olsen, K.S., Bulow, J., Holm, S., Wildschiodtz, G., Paulson, O.B. & Lassen, N.A. (1995) Persistent resetting of the cerebral oxygen/glucose uptake ratio by brain activation: evidence obtained with the Kety-Schmidt technique. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism, 15, 485-491.

Mennes, M., Zuo, X.N., Kelly, C., Di Martino, A., Zang, Y.F., Biswal, B., Castellanos, F.X. & Milham, M.P. (2011) Linking inter-individual differences in neural activation and behavior to intrinsic brain dynamics. NeuroImage, 54, 2950-2959.

Mischel, W. (1973) Toward a cognitive social learning reconceptualization of personality. Psychological review, 80, 252-283.

Newsholme, E.A., Blomstrand, E. & Ekblom, B. (1992) Physical and mental fatigue: metabolic mechanisms and importance of plasma amino acids. British medical bulletin, 48, 477-495.

Niven, J.E. & Laughlin, S.B. (2008) Energy limitation as a selective pressure on the evolution of sensory systems. The Journal of experimental biology, 211, 1792-1804.

Oken, B.S., Salinsky, M.C. & Elsas, S.M. (2006) Vigilance, alertness, or sustained attention: physiological basis and measurement. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 117, 1885-1901.

Parasuraman, R., Warm, J.S. & See, J.E. (1998) The attentive brain. In Parasuraman, R. (ed) Brain systems of vigilance. MIT Press, Cambridge, pp. 221-256.

Paus, T., Zatorre, R.J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M. & Evans, A.C. (1997) Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. Journal of Cognitive Neuroscience, 9, 392-408.

Percival, D.B.W., A. T. (2006) Wavelet Methods for Time Series Analysis. Cambridge University Press, Cambridge.

Pinheiro, J.C. & Bates, D.M. (2000) Mixed-Effects Models in S and S-PLUS. Springer.

Portas, C.M., Rees, G., Howseman, A.M., Josephs, O., Turner, R. & Frith, C.D. (1998) A specific role for the thalamus in mediating the interaction of attention and arousal in humans. J Neurosci, 18, 8979-8989.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L. & Petersen, S.E. (2011) Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A. & Shulman, G.L. (2001) A default mode of brain function. P Natl Acad Sci USA, 98, 676-682.

Rasmusson, D.D. (2000) The role of acetylcholine in cortical synaptic plasticity. Behavioural brain re-

search, 115, 205-218.

Sanz-Arigita, E.J., Schoonheim, M.M., Damoiseaux, J.S., Rombouts, S.A., Maris, E., Barkhof, F., Scheltens, P. & Stam, C.J. (2010) Loss of 'small-world' networks in Alzheimer's disease: graph analysis of FMRI resting-state functional connectivity. PloS one, 5, e13788.

Sarter, M., Gehring, W.J. & Kozak, R. (2006) More attention must be paid: the neurobiology of attentional effort. Brain Res Rev, 51, 145-160.

Sporns, O. (2011) The human connectome: a complex network. Annals of the New York Academy of Sciences, 1224, 109-125.

Stevens, W.D., Buckner, R.L. & Schacter, D.L. (2010) Correlated low-frequency BOLD fluctuations in the resting human brain are modulated by recent experience in category-preferential visual regions. Cereb Cortex, 20, 1997-2006.

van den Heuvel, M.P., Stam, C.J., Kahn, R.S. & Pol, H.E.H. (2009) Efficiency of Functional Brain Networks and Intellectual Performance. J Neurosci, 29, 7619-7624.

Van Dijk, K.R., Sabuncu, M.R. & Buckner, R.L. (2012) The influence of head motion on intrinsic functional connectivity MRI. NeuroImage, 59, 431-438.

Waites, A.B., Stanislavsky, A., Abbott, D.F. & Jackson, G.D. (2005) Effect of prior cognitive state on resting state networks measured with functional connectivity. Human brain mapping, 24, 59-68.

Wang, L., Li, Y., Metzak, P., He, Y. & Woodward, T.S. (2010) Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. NeuroImage, 50, 862-872.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., Zhong, Q. & Wang, Y. (2009) Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Human brain mapping, 30, 638-649.

Warm, J.S., Parasuraman, R. & Matthews, G. (2008) Vigilance requires hard mental work and is stressful. Hum Factors, 50, 433-441.

Watts, D.J. & Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. Nature, 393, 440-442.

Yarkoni, T., Barch, D.M., Gray, J.R., Conturo, T.E. & Braver, T.S. (2009) BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. PloS one, 4, e4257.

Zalesky, A., Fornito, A., Seal, M.L., Cocchi, L., Westin, C.F., Bullmore, E.T., Egan, G.F. & Pantelis, C. (2011) Disrupted axonal fiber connectivity in schizophrenia. Biological psychiatry, 69, 80-89.

Zou, Q., Long, X., Zuo, X., Yan, C., Zhu, C., Yang, Y., Liu, D., He, Y. & Zang, Y. (2009) Functional connectivity between the thalamus and visual cortex under eyes closed and eyes open conditions: a resting-state fMRI study. Human brain mapping, 30, 3066-3078.

Study III

The Efficiency of Functional Brain Networks Does Not Differ Between Smokers and Non-Smokers

Short title: Resting-state topology in smokers and non-smokers

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4.1 Abstract

Recently there has been a growing interest to investigate changes in functional brain network connectivity and topology in psychiatric disease such as schizophrenia and ADHD. In both patient groups smoking rates are high and there are currently no investigations on how smoking status changes brain network topology. Previous results suggest that *acute* nicotine consumptions change the integration of functional brain networks (Giessing et al., under review). To investigate *long-lasting* effects of nicotine consumption the functional brain network topology of 18 minimally deprived healthy smokers and 17 healthy non-smokers were compared during a resting state condition. Graph theoretical metrics (global efficiency and mean clustering) which has been shown to be affected by acute nicotine administration were compared between groups. Our results showed that smoking status did not show a significant change in functional network integration. Additional mathematical methods were used to statistically test the non-inferiority of functional brain network topologies of smokers. These analyses confirmed the similarity of overall brain networks topology and of global efficiency in regions which have previously been associated with craving behaviour and nicotine addiction such as the anterior cingulate cortex, the posterior cingulate cortex, left prefrontal cortex, and insula. We concluded that the integration of functional brain networks is not altered in minimally deprived smokers.

4.2 Introduction

Graph theoretical analysis of functional connectivity MRI data is a versatile tool to describe the complex organization of brain networks (Bullmore & Sporns, 2009). The metrics derived from graph theory can be used to quantify the efficiency of information processing in the human brain. Efficiency measures have been shown to vary interindividually in the healthy population as a function of age (Hagmann et al., 2010) or intelligence (Li et al., 2009; van den Heuvel et al., 2009). In the field of clinical research, progress has been made in describing pathological brain networks by comparing healthy subjects with patient groups (for a review see Guye et al., 2010). Neuropsychiatric disorders such as schizophrenia and ADHD, which have been related to dysfunctional connectivity (Fornito et al., 2010; Konrad & Eickhoff, 2010), have been investigated with graph analytical approaches in several studies. These studies provide evidence for changes in brain network topology reflecting a reduction in the efficiency of information transfer (Bassett et al., 2008; Wang et al., 2009; Lynall et al., 2010). One confounding factor when comparing patients with schizophrenia and ADHD with healthy control subjects is however the high prevalence of smokers in both patient groups (Milberger et al., 1997; de Leon & Diaz, 2005). There are currently no studies addressing the issue whether chronic cigarette smoking affects brain network topology.

Prior studies suggest that chronic smoking is associated with prefrontal grey matter damage (Brody et al., 2004; Gallinat et al., 2006; Zhang et al., 2011b) and reduced white matter integrity (Gons et al., 2011; Zhang et al., 2011a) which may impact on measures of functional connectivity. Only few studies compared differences in functional connectivity between smokers and non-smokers. These studies used seed based connectivity approaches and focussed on few brain regions, such as the frontal cortex and insula which are associated with craving or neural activity related to smoking cues (e.g. see Zhang et al 2011, Wang et al. 2007). The data by Zhang et al. (2011) supports the view that functional connectivity between these brain regions in the resting state is related to phasic increases in neural activity to smoking cues. Whether chronic cigarette smoking impacts on connectivity in the whole network or reduces the efficiency of information transfer could not be answered with these analyses. The current study compared neural activity in smokers and non-smokers in the resting state by means of graph analysis to investigate whether chronic cigarette smoking impacts on brain network topology and should be accounted for when comparing network topology in groups of subjects that differ in terms of smoking prevalence.

As graph analytical measures we analysed the network's 'efficiency' and 'clustering'. The networks' efficiency tends to be large in highly integrated networks with high capacity for parallel information transfer; in contrast clustering reflects the cliquishness or modularity of brain networks. Previous results (Giessing et al., submitted) showed that in minimally deprived smokers both measures of network topology directly changed following nicotine administration. Therefore it is reasonable to assume that network efficiency and clustering would also be sensitive towards possible effects of long-lasting nicotine consumption like in cigarette smokers.

Our data showed non-significant differences between network topologies of smokers and non-smokers. To further corroborate this finding we compared the effect sizes of both groups and statistically tested the derived graph metrics for non-inferiority. Effect size analyses and non-inferiority testing are so far rarely used in the field of neuroscience, but can be used to explicitly test the equivalence of two distributions or treatments instead of just keeping the null hypothesis of no significant differences. In our case we used these methods to demonstrate that smokers show no deterioration of network parameters.

4.3 Methods

4.3.1 Subjects

Eighteen smokers (7 females; mean age = 27.6 years, range = 19 to 38 years) and 17 never smokers (9 females; mean age = 25.6 years, range = 24 to 30 years) participated in the experiment. Exclusion criteria were age below 18 or above 40 years, left handedness, psychiatric or neurological disease and intake of any medication apart from contraceptives. Inclusion criteria for smokers were a history of smoking for at least 2 years with a minimum of 5 cigarettes per day. All non smokers were never smokers. Smokers smoked on average 16.3 ± 2.02 cigarettes per day and had an average of 9.17 ± 2.4 pack years. The Fagerström questionnaire indicated a mild degree of nicotine dependence (3.47 ± 0.55). Subjects were allowed to smoke their last cigarette 2 hrs before the start of the experiment. The study was approved by the ethics committee of the German Psychological Association and subjects signed written informed consent.

4.3.2 Resting State fMRI Data Acquisition

Images were acquired on a 1.5 Tesla MRI scanner (Siemens MAGNETOM Sonata, Siemens AG, Erlangen, Germany). Functional images were obtained using multislice T2*-weighted gradient echo planar imaging (EPI). Each volume consisted of 17 axial slices (voxel size of 3x3 mm, 4 mm in slice thickness, slice gap of 1.6 mm, field of view (FoV) = 200 x 200 mm^2, relaxation time (TR) = 1500 ms, echo time (TE) = 50 ms and 90° flip angle). 256 volumes were acquired (total duration 6 min 24 s) and subjects were instructed to keep the eye open and fixate on a black fixation cross presented on a light grey background. A structural T1-weighted image was obtained after the fMRI experiment, using magnetization frequency pulse and rapid gradient-echo (MP RAGE) sampling: 1 mm isotropic voxels, 176 slices, FoV = 256 x 256 mm^2, TR = 2130 ms, TE = 3.93 ms and 15° flip angle.

4.3.3 fMRI Data Processing and Time-Series Analysis

Functional images were spatially realigned according to head motion and spatially normalized to standard stereotaxic MNI space (Montreal Neurological Institute; http://www.mni.mcgill.ca/) by using the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm/). A regionally parcellated MNI template comprising 456 cortical and subcortical brain regions was used to estimate the mean fMRI time series for each region for each participant (Fornito et al., 2010; Zalesky et al., 2010). In order to minimize motion related signal changes the mean time series were motion detrended with a multiple regression approach by using the estimated motion parameters from the spatial realignment. Previous studies documented the behavioural relevance of graph metrics based on fMRI signal oscillations in the frequency range below 0.1 Hz (Achard et al., 2006; Damoiseaux et al., 2006).

Therefore, each regional time series was band-pass filtered by using the maximum overlap discrete wavelet transform (MODWT; Percival, 2006). Two wavelet scales (respectively two frequency ranges, 0.083 0.167 Hz and 0.042 0.083 Hz) were further analysed. For each pair of regions (nodes) the wavelet correlation was estimated, resulting in a 456 by 456 association matrix for each subject and scale. Resulting association matrices were used to derive graph metrics for smokers and non-smokers.

4.3.4 Topological Metrics of Brain Graphs

Binary graphs of arbitrary connection densities were constructed for both frequency ranges by thresholding the association matrices to create adjacency matrices. A thresholding algorithm based on the minimum spanning tree was used to ensure that each node was connected with at least one other node even at the sparsest connection density (Alexander-Bloch et al., 2010). Graphs at 15 different connection densities (i.e. topological costs) were constructed for each subject and RS period in the range of 2.5% - 50%, with smaller sampling intervals in the lower cost range. The connection density defines the number of edges in a graph expressed as a ratio to the maximum possible number of edges (N*(N-1)/2 = 103,740). Based on these adjacency matrices we calculated the central graph theoretical measures of efficiency and clustering following the formulas of Watts & Strogatz (1998) and Latora & Marchiory (Wellek & Michaelis, 1991; 2003; Hentschke & Stuttgen, 2011). Both metrics are bases on path lengths between connected nodes. Nodal efficiency is inversely related to the mean path lengths between a particular node and all other nodes of the network. In other words, mean nodal efficiency estimates the capacity of a network for parallel information transfer. In contrast, local efficiency or clustering, measures the capacity for parallel information transfer in the immediate neighbourhood of each node. The measure is inversely related to the mean path lengths between *in the nearest-neighbour graph of a certain node*, the sub-graph which build by the directly connected nodes to the particular node. Thus networks that have a cliquish organization, characterized by many connections between the nearest neighbours of any given node, will have high local efficiency or clustering. Further, we investigated the mean physical distance between connected brain regions, which based on the averaged Euclidean distances in mm of all edges in a graph.

4.3.5 Statistical Testing, Differential Effect Sizes and Non-Inferiority Testing

In a first step, measures of connectivity strength, graph metrics and physical distances of smokers and non-smokers were compared by use of common null hypothesis significance testing (NHST) using two-sample t-tests. Measures of connectivity strength were compared between smokers and non smokers: i) mean connectivity strength (based on the averaged association matrices) and ii) connectivity strengths for different distance bins (correlation strengths between brain regions with different physical distances in 5 mm steps). An investigation of correlation strengths as function of regional distances was done in order to screen if the overall level of correlation strengths is homogeneous in both groups across regional distances. Distance specific changes are often correlated with changes in topological metrics like clustering and efficiency and could be a first hint for changes in network topology (Alexander-Bloch et al., 2012). The three graph metrical measures which were compared between smokers and non-smokers were nodal efficiency, clustering and physical distance. The measures were tested when averaged over the whole investigated cost range (2.5-50%) and separately for each of the 15 different cost levels.

Since one cannot establish the absence of an effect with classical statistical inference we used in a second step a non-inferiority testing approach to test the hypothesis that network topology is not less efficient in our group of smokers as compared to our non-smokers. In short, non-inferiority testing in our study tests the null hypothesis whether the 'true' inferiority of smokers is located within a tolerance range so that both groups differ not more than by a neglectable small amount. For this purpose the magnitude of the difference between groups is expressed in terms of a measure of effect size and their confidence intervals are estimated (see e.g. Wellek & Michaelis, 1991; Hentschke & Stuttgen, 2011).

We estimated the effect sizes of nodal efficiency and clustering of each node (brain region) in smokers and non-smokers. Hedges' g (Hedges, 1981) was used to express the difference in effect sizes between the two populations in standard deviations (STD). For all differential effect sizes, the approximate confidence intervals of 95% for one sided hypothesis testing were calculated for providing the margins of the expected errors for our sample size (formulas see e.g. Nakagawa & Cuthill, 2007).

As necessary in testing for non-inferiority, a tolerance threshold for the differential effect sizes was defined. This tolerance threshold defines how large the difference in effect size between two samples (as smokers and non-smokers in the current study) has to be in order to reject the equivalence assumption. The tolerance threshold for the metrics of nodal efficiency and clustering was set to ± 0.5 STD. The hypotheses, we regionally (nodally) tested for, were i) that smokers showed no lower efficiency and ii) no higher clustering as compared to non-smokers.

4.4 Results

4.4.1 Connectivity Strength

Differences in connectivity strength between the group of smokers and the group of non-smokers were statistically not significant. This was the case at both investigated frequency ranges and both, for the global mean of connectivity strength as averaged over all connections and for the mean connectivity strength within each physical distance bin. Value distributions of smokers and non-smokers were very similar, as shown in the descriptive Figure 4.1.

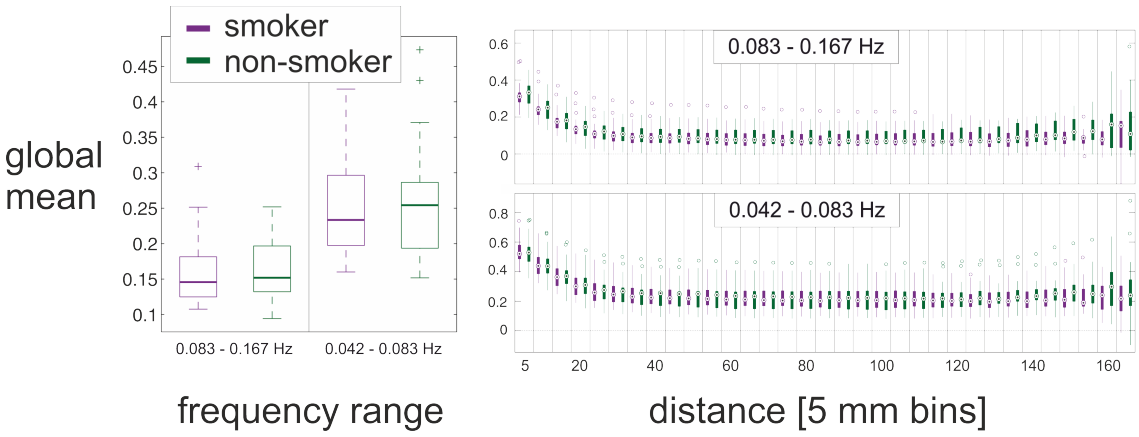

Figure 4.1: Distribution of connectivity strengths. Smokers and non-smokers showed no differences of connectivity strength with respect to global correlation values (left) and as a function of physical distances between the nodes (right). Connectivity strengths got lower when connections had a longer physical (Euclidean) distance (right), which was homogeneously the case for both, smokers and non-smokers (boxplots with a center mark for the median, box edges at the 25^{th} and 75^{th} percentiles, whiskers at 5^{th} and 95^{th} percentiles and marks above and below as 'outliers' of the distribution.)

4.4.2 Graph Metrics

No statistical differences were found for the investigated graph metrics of clustering, efficiency and physical distances for both frequency ranges. This was the case for the averaged values over the whole cost range as well as for the metrics derived from the graphs at the 15 different cost levels (graph densities). The distributions of these metrics were similar between smokers and non-smokers (see descriptive Figure 4.2).

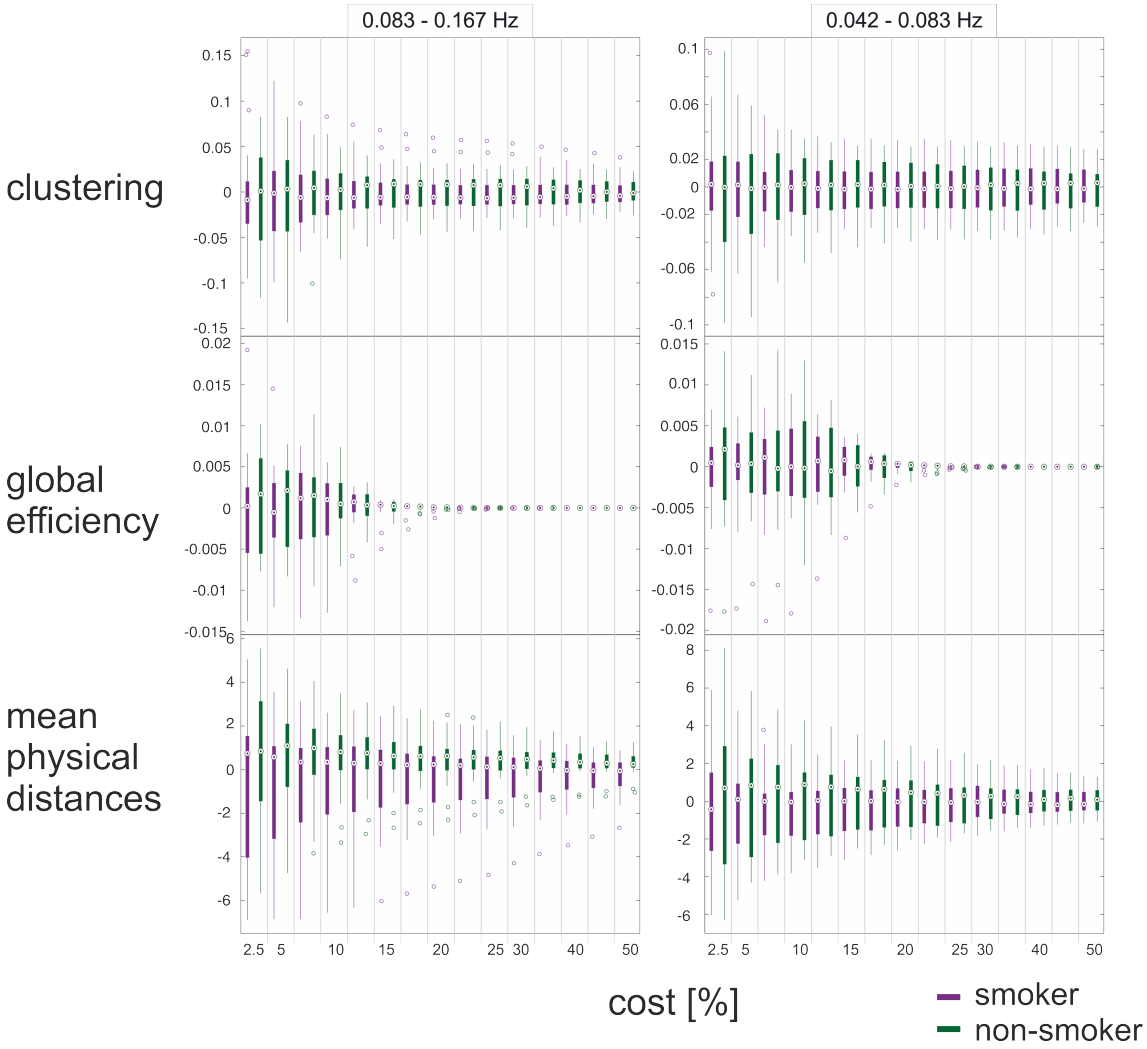

Figure 4.2: Distributions of graph metrics over different cost levels. Smokers showed similar distributions in the investigated graph metrics as compared to non-smokers for graphs at all 15 cost levels (graph densities). For each cost level mean centred values are shown as boxplots with a center mark for the median, box edges at the 25^{th} and 75^{th} percentiles, whiskers at 5^{th} and 95^{th} percentiles and marks above and below indicating 'outliers' of the distribution.

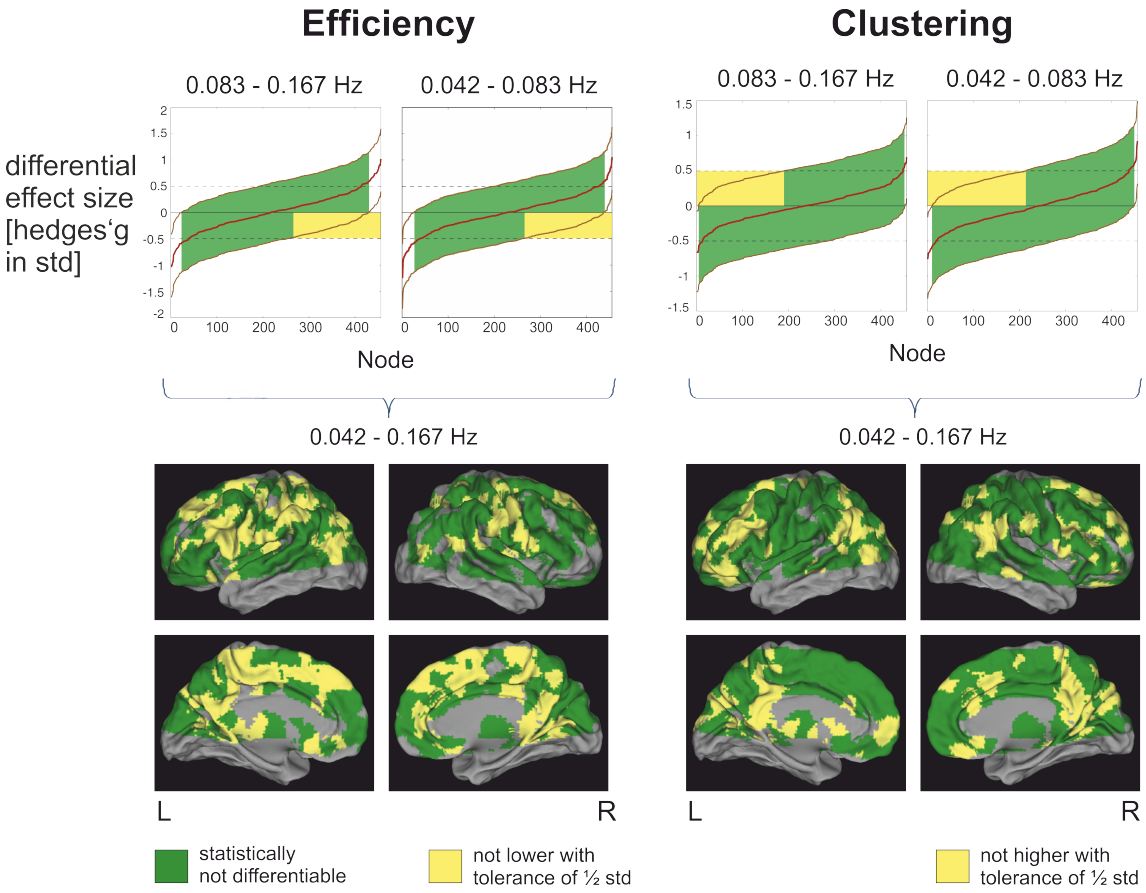

Figure 4.3: Differential effect sizes and non-inferiority test results. **Top:** Hedgesg differential effect sizes of smokers and non-smokers ([smokers] [non-smokers]) for all nodes with confidence intervals (sorted according to the effect sizes; network metrics averaged over costs). Nodes with a confidence interval that comprised zero were statistically not different ($p>0.05$, green area). Non-inferiority testing with a tolerance threshold of 0.5 standard deviation proved that in many brain regions the functional network integration of smokers were not decreased by long-lasting nicotine consumption. Yellow nodes showed the significant null effect of no reduced efficiency (left) or no higher clustering (right) in smokers in comparison to non-smokers. **Bottom:** Measures of efficiency and clustering in smoker brains were not different from non-smoker brains over wide cortical and subcortical regions (regions that were statistically non-differentiable in both frequency ranges are coloured in green; regions that showed non-inferiority in both frequency ranges are coloured in yellow). A significant null effect that nicotine consumption did not reduce efficiency (left, yellow) was e.g. present in prefrontal regions. Further, a significant null effect showed that clustering (right, yellow) was not higher in regions as the cingulate and frontal cortex and medial temporal gyrus. All of these regions were earlier described to show significant differences in these network parameters in schizophrenia patients (Bassett et al., 2008).

In a second step we compared the network efficiency and clustering of smokers and non-smokers within each brain region or node (Figure 4.3, top). These analyses revealed that within many brain regions the network efficiency and clustering of smokers and non-smokers was statistically not differentiable (see Figure 4.3, green areas).

In a third step we used the more conservative approach of non-inferiority testing. This approach showed for a number of brain regions that smokers as compared to non-smokers had no deterioration of network integration (e.g. no reduction in efficiency or no increase in clustering; see Figure 3, top, yellow areas). In other words, these are the brain areas showing a significant 'null effect'. For generalization across both low frequency ranges, only regions that showed non-inferiority in both frequency ranges are further described (Figure 4.3, bottom, yellow areas). Brain regions showing no reduced efficiency in smokers were widespread over the brain; comprising medial frontal and occipital regions, parietal cortices and lateral prefrontal regions with a slight dominance of the left hemisphere and thalamic regions. Brain regions showing no higher clustering in smokers as compared to non-smokers were extended in lateral and medial frontal regions (also with a subliminal left lateralization), medial occipital cortices, lateral parietal cortices and left thalamic regions.

4.5 Discussion

In summary, our study shows that resting state topology in our group of smokers is statistically not differentiable from non-smokers in network parameters which have been previously shown to be sensitive for acute nicotine administration. Smokers show a similar functional network efficiency and clustering, two central measures of functional network integration, even in brain regions that were previously associated with structural changes or differences in task-related neural activity in smokers (Brody et al., 2002; Lee et al., 2005; Van Rensburg et al., 2009).

Earlier studies which described differences in network topology in schizophrenia patients as compared to healthy subjects reported less efficiently wired and abnormally clustered network attributes in schizophrenia patients (Bassett et al., 2008, Lynall et al., 2009). Common findings were regionally reduced efficiency and network integration in prefrontal and temporal regions (see also van den Heuvel et al., 2010). Further, graph theoretical findings revealed reduced global efficiency (prolonged path lengths between functionally connected brain nodes) in ADHD patients as compared to healthy control groups and an increased clustering (Wang et al. 2009, Konrad & Eickhoff 2012).

Even though the prevalence of smoking differs significantly between these patient populations and healthy controls (Lohr & Flynn, 1992; Pomerleau et al., 1995; Milberger et al., 1997; de Leon & Diaz, 2005), the role of smoking status has not been addressed in these studies. Standard approaches of null hypothesis testing revealed no significant differences in network metrics between smokers and non-smokers in our study. To corroborate these findings, we performed to additional analyses. The analyses of differential effect sizes confirmed the absence of differences in network efficiency and clustering in widespread brain areas in smoker brains as compared to non-smoker brains. Testing for non-inferiority revealed that in smoker's brains nodal efficiency is not lowered in brain regions such as medial frontal and lateral prefrontal areas as well as that clustering is not higher in e.g. the anterior cingulate cortex, dorsolateral prefrontal cortices, tempo-parietal junction and medial occipital regions. Based on our findings, the reported topological differences in these regions in schizophrenia or ADHD patients as compared to healthy subjects (see above) seem to be unbiased by the trait of smoking.

Comparisons of effect sizes and testing for non-inferiority are often used techniques in medical research in order to e.g. test if new treatments for patients yielded an improvement for negative symptoms. In neuroscience these approaches benefit from growing interest but are still rarely in use to date, as most study designs focus on revealing differences between subject groups or task conditions (see e.g. Hentschke & Stttgen 2011). We here demonstrate its use for analysis of similarity of brain networks in different subject groups.

In summary, our study provides evidence that, at least in healthy controls, smoking status is not related to changes in network topology. We therefore suggest that differences in smoking status are unlikely to contribute to changes in network topology observed in schizophrenic patients and patients with ADHD. Note however, that our sample group of smokers consisted of relatively weak smokers as compared to observed cigarette consumption behaviour in schizophrenia and ADHD patients (see e.g. Pormleau et al., 2002, Fagerström score in ADHD patients = 6.7; or see de Leon, 1997, number of cigarettes per day in schizophrenia patients = 26).

4.6 References

Achard, S., Salvador, R., Whitcher, B., Suckling, J. & Bullmore, E. (2006) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. The Journal of neuroscience : the official journal of the Society for Neuroscience, 26, 63-72.

Alexander-Bloch, A.F., Gogtay, N., Meunier, D., Birn, R., Clasen, L., Lalonde, F., Lenroot, R., Giedd, J. & Bullmore, E.T. (2010) Disrupted modularity and local connectivity of brain functional networks in childhood-onset schizophrenia. Frontiers in systems neuroscience, 4, 147.

Alexander-Bloch, A.F., Vertes, P.E., Stidd, R., Lalonde, F., Clasen, L., Rapoport, J., Giedd, J., Bullmore, E.T. & Gogtay, N. (2012) The Anatomical Distance of Functional Connections Predicts Brain Network Topology in Health and Schizophrenia. Cereb Cortex.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R. & Meyer-Lindenberg, A. (2008) Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci, 28, 9239-9248.

Brody, A.L., Mandelkern, M.A., Jarvik, M.E., Lee, G.S., Smith, E.C., Huang, J.C., Bota, R.G., Bartzokis, G. & London, E.D. (2004) Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiat, 55, 77-84.

Brody, A.L., Mandelkern, M.A., London, E.D., Childress, A.R., Lee, G.S., Bota, R.G., Ho, M.L., Saxena, S., Baxter, L.R., Jr., Madsen, D. & Jarvik, M.E. (2002) Brain metabolic changes during cigarette craving. Archives of general psychiatry, 59, 1162-1172.

Bullmore, E. & Sporns, O. (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience, 10, 186-198.

Damoiseaux, J.S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M. & Beckmann, C.F. (2006) Consistent resting-state networks across healthy subjects. P Natl Acad Sci USA, 103, 13848-13853.

de Leon, J. & Diaz, F.J. (2005) A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res, 76, 135-157.

Fornito, A., Zalesky, A. & Bullmore, E.T. (2010) Network scaling effects in graph analytic studies of human resting-state FMRI data. Frontiers in Systems Neuroscience, 4, 22.

Gallinat, J., Meisenzahl, E., Jacobsen, L.K., Kalus, P., Bierbrauer, J., Kienast, T., Witthaus, H., Leopold, K., Seifert, F., Schubert, F. & Staedtgen, M. (2006) Smoking and structural brain deficits: a volumetric MR investigation. Eur J Neurosci, 24, 1744-1750.

Gons, R.A., van Norden, A.G., de Laat, K.F., van Oudheusden, L.J., van Uden, I.W., Zwiers, M.P., Norris, D.G. & de Leeuw, F.E. (2011) Cigarette smoking is associated with reduced microstructural integrity of cerebral white matter. Brain : a journal of neurology, 134, 2116-2124.

Guye, M., Bettus, G., Bartolomei, F. & Cozzone, P.J. (2010) Graph theoretical analysis of structural and functional connectivity MRI in normal and pathological brain networks. MAGMA, 23, 409-421.

Hagmann, P., Sporns, O., Madan, N., Cammoun, L., Pienaar, R., Wedeen, V.J., Meuli, R., Thiran, J.P. & Grant, P.E. (2010) White matter maturation reshapes structural connectivity in the late developing human brain. Proc Natl Acad Sci U S A, 107, 19067-19072.

Hedges, L.V. (1981) Distribution theory for Glass's estimator of effect size and related estimators. Journal of Educational Statistics, 6, 107-128.

Hentschke, H. & Stuttgen, M.C. (2011) Computation of measures of effect size for neuroscience data sets. Eur J Neurosci, 34, 1887-1894.

Konrad, K. & Eickhoff, S.B. (2010) Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. Human brain mapping, 31, 904-916.

Latora, V. & Marchiori, M. (2003) Economic small-world behavior in weighted networks. European Physical Journal B, 32, 249-263.

Lee, J.H., Lim, Y., Wiederhold, B.K. & Graham, S.J. (2005) A functional magnetic resonance imaging (FMRI) study of cue-induced smoking craving in virtual environments. Applied psychophysiology and biofeedback, 30, 195-204.

Li, Y.H., Liu, Y., Li, J., Qin, W., Li, K.C., Yu, C.S. & Jiang, T.Z. (2009) Brain Anatomical Network and Intelligence. Plos Computational Biology, 5.

Lohr, J.B. & Flynn, K. (1992) Smoking and schizophrenia. Schizophr Res, 8, 93-102.

Lynall, M.E., Bassett, D.S., Kerwin, R., McKenna, P.J., Kitzbichler, M., Muller, U. & Bullmore, E. (2010) Functional connectivity and brain networks in schizophrenia. The Journal of neuroscience : the official journal of the Society for Neuroscience, 30, 9477-9487.

Milberger, S., Biederman, J., Faraone, S.V., Chen, L. & Jones, J. (1997) ADHD is associated with early initiation of cigarette smoking in children and adolescents. J Am Acad Child Psy, 36, 37-44.

Nakagawa, S. & Cuthill, I.C. (2007) Effect size, confidence interval and statistical significance: a practical guide for biologists. Biological reviews of the Cambridge Philosophical Society, 82, 591-605.

Percival, D.B.W., A. T. (2006) Wavelet Methods for Time Series Analysis. Cambridge University Press, Cambridge.

Pomerleau, O.F., Downey, K.K., Stelson, F.W. & Pomerleau, C.S. (1995) Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. Journal of substance abuse, 7, 373-378.

van den Heuvel, M.P., Mandl, R.C., Stam, C.J., Kahn, R.S. & Hulshoff Pol, H.E. (2010) Aberrant frontal and temporal complex network structure in schizophrenia: a graph theoretical analysis. J Neurosci, 30, 15915-15926.

van den Heuvel, M.P., Stam, C.J., Kahn, R.S. & Pol, H.E.H. (2009) Efficiency of Functional Brain Networks and Intellectual Performance. J Neurosci, 29, 7619-7624.

Van Rensburg, K.J., Taylor, A. & Hodgson, T. (2009) The effects of acute exercise on attentional bias towards smoking-related stimuli during temporary abstinence from smoking. Addiction, 104, 1910-1917.

Wang, L., Zhu, C., He, Y., Zang, Y., Cao, Q., Zhang, H., Zhong, Q. & Wang, Y. (2009) Altered small-world brain functional networks in children with attention-deficit/hyperactivity disorder. Human brain mapping, 30, 638-649.

Watts, D.J. & Strogatz, S.H. (1998) Collective dynamics of 'small-world' networks. Nature, 393, 440-442.

Wellek, S. & Michaelis, J. (1991) Elements of significance testing with equivalence problems. Methods of information in medicine, 30, 194-198.

Zalesky, A., Fornito, A., Harding, I.H., Cocchi, L., Yucel, M., Pantelis, C. & Bullmore, E.T. (2010) Whole-brain anatomical networks: does the choice of nodes matter? NeuroImage, 50, 970-983.

Zhang, X., Salmeron, B.J., Ross, T.J., Geng, X., Yang, Y. & Stein, E.A. (2011a) Factors underlying prefrontal and insula structural alterations in smokers. NeuroImage, 54, 42-48.

Zhang, X., Salmeron, B.J., Ross, T.J., Gu, H., Geng, X., Yang, Y. & Stein, E.A. (2011b) Anatomical differences and network characteristics underlying smoking cue reactivity. NeuroImage, 54, 131-141.

Erklärung

Darlegung der Anteile aller Autoren an den wissenschaftlichen Einzelarbeiten der kumulativen Dissertation
Gemäß §8 Abs. 3 der Promotionsordnung.

Als Erstautor der in dieser Dissertation aufgeführten Manuskripte war ich hauptsächlich oder zu großen Teilen für das Studiendesign, die Datenerhebung, deren Auswertung und die Verfassung der Manuskripte verantwortlich. Als Betreuerin war Prof. Dr. Christiane Thiel bei allen Aspekten beteiligt und lenkte die Ausrichtung der Studien. Zur methodischen Unterstützung der Datenauswertung trug Dr. Carsten Giessing wesentlich zu der Erarbeitung der PLS Methode und des Graph-theoretischen Ansatzes bei.

Einzelbeiträge der Autoren der Studien: **Studie I:** *Christiane Thiel.* Inhaltliche Ausrichtung der Studie und Rahmen des Designs, inhaltliche Konzepte, Mitarbeit an Einleitung und Diskussion des Manuskripts und inhaltliche und sprachliche Feinschliffe der finalen, publikationsreifen Version. *Carsten Giessing.* Unterstützung bei der statistischen Auswertung und wesentlicher Beitrag bei der Erarbeitung des multivariaten PLS Ansatzes. Mitarbeit im Methodenteil des Manuskriptes. *Thomas Breckel.* Studiendesign und inhaltliche Konzepte, Erstellung des Paradigmas, Erhebung der Daten, Auswertung der Daten, Umsetzung des multivariaten PLS Ansatzes, Verfassen des Manuskripts mit Hilfe der Co-Autoren mit Hauptanteil an geschriebenem Text. **Studie II:** *Christiane Thiel.* Inhaltliche Ausrichtung der Studie und Rahmen des Designs, Mitarbeit am Manuskript und inhaltliche und sprachliche Feinschliffe der finalen, publikationsreifen Version. *Edward Bullmore.* Beitrag zu Festlegung der methodischen und inhaltlichen Schwerpunkte bei Verwendung des Graph analytischen Ansatzes für fMRT Daten. *Andrew Zalesky.* Matlab-basierte Routinen für die Erstellung der Gehirn-Schablone für die Extraktion der Zeitreihen. *Ameera Patel.* Ergänzende Auswertung der Resting State Daten im Hinblick auf Bewegungsartefakte. *Carsten Giessing.* Festlegung der inhaltlichen Schwerpunkte, wesentlicher Beitrag bei der Erarbeitung des Graph analytischen Ansatzes, Mitarbeit an Methoden- und Diskussionsteil des Manuskripts. *Thomas Breckel.* Studiendesign, Erstellung des Paradigmas und Datenerhebung, Statistische Auswertung der Daten und Umsetzung und Elaborierung des Graph analytischen Ansatzes, Verfassen des Manuskripts mit Hilfe der Co-Autoren mit Hauptanteil an geschriebenem Text. **Studie III:** *Christiane Thiel.* Design und inhaltliche Ausrichtung der Studie, Mitarbeit am Manuskript und inhaltliche und sprachliche Feinschliffe der finalen, publikationsreifen Version. *Carsten Giessing.* Beitrag für inhaltliche Konzepte, Datenerhebung der Raucher-Daten, methodischer Beitrag für den Graph analytischen Ansatz und das Äquivalenz-Test-Verfahren, Mitarbeit am Manuskript. *Thomas Breckel.* Datenerhebung der Nicht-Raucher Daten, Statistische und Graph analytische Datenauswertung, Verfassen des Manuskripts mit Hilfe der Co-Autoren mit Hauptanteil an geschriebenem Text.

Erklärung zur selbständigen Verfassung der Arbeit und der verwendeten Hilfsmittel
Gemäß §10 Abs. 2b der Promotionsordnung.

Hiermit versichere ich, dass ich die vorliegende Dissertation selbstständig verfasst und nur die angegebenen Quellen verwendet habe. An den aufgeführten Manuskripten trug ich, wie oben ausgeführt, den Hauptanteil bei.

Thomas Breckel

Danksagung

Im Laufe dieser Arbeit durfte ich Teil eines wirklich ***großartigen Teams*** *werden. Ein Team, das ich immer an meiner Seite fühlte und in dem ich Unterstützung, Zusammenhalt und fachliche Kompetenz erfahren durfte.*
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Curriculum Vitae

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ABSTRACTS

Breckel, T.P.K., Mutschler, I., Ball, T. (2007) Scale-space variability of visuomotor fMRI responses, 51st Annual Meeting of the German Society of Neurophysiology and Functional Imaging, Munich.

Breckel, T.P.K., Giessing, C., Thiel, C. (2009) Infrequent Stimuli Increase Demands on Alertness network, 15th Annual Meeting of the Organisation of Human Brain Mapping, San Francisco.

Breckel, T.P.K., Thiel, C., Bullmore, E., Giessing, C. (2011) Effects of prolonged attentional performance on resting state topology, 17th Annual Meeting of the Organisation of Human Brain Mapping, Quebec.

Breckel, T.P.K., Thiel, C., Giessing, C. (2012) Smokers show no differences in functional resting state network configuration as compared to non-smokers, Society for Neuroscience 2012, New Orleans.

PAPERS

Ball, T., Breckel, T.P.K., Mutschler, I., Aertsen, A., Schulze-Bonhage, A., Hennig, J., Speck, O. (2011) Variability of fMRI-Response Patterns at Different Spatial Observation Scales. Human Brain Mapping.

Breckel, T.P.K., Giessing, C., Thiel, C. (2011) Impact of Brain Networks Involved in Vigilance on Processing Irrelevant Visual Motion. NeuroImage.

Hildebrandt, H., Fink, F., Eling, P., Stuke, H., Lentschig, M., Kastrup, A., Thiel, C., Breckel, T.P.K. (2012) Neural Correlates of Stimulus Response and Stimulus Outcome Shifting in Healthy Participants and MS Patients. Brain and Cognition.

Breckel, T.P.K., Thiel, C., Bullmore, E., Zaleski, A., Patel, A., Giessing, C. (submitted). Long-Term Effects of Attentional Performance on Functional Brain Network Topology.

Breckel, T.P.K., Thiel, C., Giessing, C. (submitted). The Efficiency of Functional Brain Networks Does Not Differ Between Smokers and Non-Smokers.

SPECIAL SKILLS AND COMPETENCIES

Languages	German (native language), English (fluent; spoken and written), French (basic knowledge), Latin (basic knowledge).
Computer skills	Excellent knowledge in MS-Office (Word, Excel, Powerpoint), programming languages Matlab and R, SPM, image processing (esp. Corel Draw and Corel Photo Paint), LaTeX.
Teaching skills	Supervisor and teacher of a Matlab Course (Introduction into Matlab), Teaching of fMRI data processing, Tutor in SPM-courses (Preprocessing and Statistics of fMRI data), supervisor of bachelor and master students, introduction and education of technical assistants to fMRI data acquisition and use of a MR-scanner.
Special skills	Seven years experience in operation of a MR-scanner and acquisition and analysis of fMRI-data.

Thomas Breckel
Oldenburg, 5th of December 2012