Multimodal characterization of neural correlates of executive functioning

Inaugural dissertation

for the attainment of the title of doctor
in the Faculty of Mathematics and Natural Sciences
at the Heinrich Heine University Düsseldorf

presented by

Julia Ann Camilleri
from Pieta', Malta

Düsseldorf, December 2018

from the institute of Neuroscience and Medicine (INM-7)
at the Forschungszentrum Jülich

Published by permission of the
Faculty of Mathematics and Natural Sciences at
Heinrich Heine University Düsseldorf

Supervisor: Prof. Dr. Simon B. Eickhoff
Co-supervisor: Prof. Dr. Tobias Kalenscher

Date of the oral examination: 03/12/2018

Declaration of Authorship:

I hereby certify that this thesis has been composed by me and is based on my own work, unless stated otherwise. No other person’s work has been used without due acknowledgment. All references have been quoted and all sources of information have been specifically acknowledged.

Date: Signature:

Table of Contents

1. Abstract

Executive functioning (EF) is central to goal-directed behavior and is thus crucial for leading an independent and productive life. Its importance and pervasiveness have instigated a consequent effort towards understanding the construct and the brain regions involved. However, due to multiple reasons, the conceptualization of EF is still rather elusive. The two studies present in this dissertation are aimed at improving the understanding of the concept of EF in the broader sense through the use of multi-modal neuroimaging analysis. In both studies this was done by using different approaches to investigate functional (and structural) connectivity patterns of seed regions using magnetic resonance imaging (MRI) data.

The primary aim of the first study was to investigate the regions and associated networks related to performance on a specific sub-test of the Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT), a commonly used test to measure EF. The sub-test of choice, the D-KEFS TMT-MS, is designed to measure motor speed and findings revealed that performance on the test is specifically related to the local brain volume of a small region in the lower bank of the left inferior frontal sulcus (IFS). That is, better performance was associated with higher gray matter volume (GMV) in this cluster, across subjects. Since the IFS is usually associated to EF rather than motor functions results of the current study suggest that performance on this particular sub-test may primarily depend on EF thus insinuating that motor speed in a more naturalistic setting may be more strongly associated with executive rather than primary motor function.

The aim of the second study was to provide a robust definition of an extended multiple demand network (eMDN) based on task-dependent and task-independent functional connectivity analyses seeded from regions previously shown to be convergently recruited across neuroimaging studies probing working memory, attention and inhibition, i.e., the proposed key components of executive functioning. The resulting eMDN, which is here proposed to be the most likely neurobiological substrate for EF, was characterized into three cliques by means of hierarchical clustering, including a subcortical group mainly related to sensorimotor processing, a

core of potential “organizer” regions, and a more heterogeneous set of “worker” regions dynamically recruited based on task demands.

Additionally, the region that was found to be associated with TMT-MS performance, together with the regions that were found to be part of the associated core network in Study 1 converge with the regions of the core eMDN defined in Study 2, suggesting that the region in the IFS that was found to be associated with the TMT-MS dynamically interacts with regions that are also associated with EF and thus further emphasizing the involvement of EF in the successful completion of the TMT-MS.

Furthermore, both studies verified that common networks could be revealed across highly divergent connectivity approaches. Together, these studies thus stress the importance of multi-modal analysis when attempting to reveal underlying brain networks. Additionally, taken collectively, these studies confirm the complexity of the concept of EF while verifying the need for further studies investigating the neural correlates of commonly used pen-and-paper tests.

2. Zusammenfassung

Exekutive Funktionen (EF) sind unabdingbar für zielgerichtetes Verhalten und somit entscheidend für ein unabhängiges und produktives Leben. Ihre Bedeutung und Allgegenwart haben zu konsequenten Bemühungen geführt, das Konstrukt und die beteiligten Hirnregionen zu verstehen. Aus verschiedenen Gründen ist die Konzeptualisierung von EF jedoch immer noch schwer fassbar. Die zwei Studien, die in dieser Dissertation vorgestellt werden, zielen darauf ab, das Verständnis des EF-Konzepts im weiteren Sinne durch den Einsatz multimodaler Bildgebungs-Analysen zu verbessern. In beiden Studien wurde dies mithilfe verschiedener Ansätze zur Untersuchung funktioneller (und struktureller) Konnektivitätsmuster von Kernregionen unter Verwendung von Magnetresonanz-Bildgebungsdaten (MRI) durchgeführt.

Das primäre Ziel der ersten Studie war die Untersuchung der einzelnen Hirnregionen und der damit verbundenen Netzwerke in Bezug auf die Leistung in einem spezifischen Sub-Test des Delis-Kaplan Executive Function System (D-KEFS TMT), einem häufig verwendeten Test zur Messung von EF. Der verwendete Sub-Test, der D-KEFS TMT-MS, wurde entwickelt, um die Motorische Geschwindigkeit zu messen. Die Ergebnisse zeigten, dass die Leistung des Tests spezifisch mit dem lokalen Hirnvolumen einer kleinen Region im linken unteren Anteil des inferioren frontalen Sulcus (IFS) korreliert. Das heißt, eine bessere Leistung wurde bei allen Testpersonen mit einem höheren GMV in diesem Cluster assoziiert. Da der IFS in der Regel eher mit EF als mit motorischen Funktionen assoziiert wird, deuten die Ergebnisse der aktuellen Studie darauf hin, dass die Leistung bei diesem speziellen Sub-Test primär von EF abhängt. Daher ist zu vermuten dass die motorische Geschwindigkeit in einer eher naturalistischen Umgebung stärker mit der Exekutive Funktionnern erbunden sein könnte, als mit primären motorischen Funktionen.

Das Ziel der zweiten Studie war es, eine aussagekräftige Definition eines erweiterten Multiple Demand Networks (eMDN) basierend auf aufgabenabhängigen und aufgabenunabhängigen funktionellen Konnektivitätsanalysen. Dafür wurden Regionen werwendet, bei denen zuvor aufgezeigt wurde, dass sie konvergierend in Bildgebungs-Studien über das Gedächtnis, die Aufmerksamkeit und Hemmungen, d. h. die vorgeschlagenen Schlüsselkomponenten des exekutiven Funktionierens,

rekrutiert werden. Das resultierende eMDN, das hier als das wahrscheinlichste neurobiologische Substrat für EF vorgeschlagen wird, wurde durch hierarchische Clusterbildung in drei Gruppen eingeteilt, einschließlich einer subkortikalen Gruppe, die hauptsächlich mit der sensomotorischen Verarbeitung in Zusammenhang steht, einem Kern potentieller "Organisator" -Regionen und eine Gruppe von heterogenerer "Arbeiter -Regionen“, die basierend auf den Aufgabenanforderungen dynamisch rekrutiert werden.

Darüber hinaus konvergiert die Region, die mit TMT-MS-Leistung in Verbindung gebracht wurde, zusammen mit den Regionen, die in Studie 1 Teil des zugehörigen Kernnetzwerks waren, mit den in Studie 2 definierten Regionen des Kern-eMDNs. Eine Region in der IFS, die mit der TMT-MS assoziiert ist, interagiert dynamisch mit Regionen, die ebenfalls mit EF assoziiert sind, und betont somit die Beteiligung von EF bei der erfolgreichen Beendigung der TMT-MS.

Darüber hinaus haben beide Studien bestätigt, dass sich gemeinsame Netzwerke in stark divergierenden Konnektivitätsansätzen offenbaren. Zusammen betonen diese Studien daher die Bedeutung der multimodalen Analyse, wenn man versucht, zugrundeliegende Gehirnnetzwerke zu offenbaren. Des Weiteren bestätigen diese Studien zusammenfassend die Komplexität des EF-Konzepts, während sie gleichzeitig die Notwendigkeit weiterer Studien, die zur Untersuchung der neuronalen Korrelate häufig die Stift-und-Papier-Tests verwenden, bestätigen.

3. General Introduction

Over the years, research studies, together with clinical observations, have shown that executive functioning (EF) is crucial for an independent, and socially productive life and its impairment is now thought to play a major role in a wide range of different psychiatric and neurological disorders (Zelazo & Müller, 2002). As a result of its importance and its pervasive nature, various fields of study have attempted to investigate the construct of EF, often focusing on a specific aspect and thus resulting in a number of diverse definitions and labels that attempt to explain the same construct. A number of such labels include cognitive control, executive processes, executive control, executive attention and frontal lobe functions.

3.1 Conceptualizations of EF

The concept of executive functioning (EF) was first introduced by Luria, Karpov, & Yarbuss, (1966), who concluded that problem-solving abilities required a number of essential skills. Later, Baddely and Hitch (1974) conceptualized this construct as a Central Executive System that coordinates information provided by two slave systems, the phonological loop and the visuo-spatial sketch pad. However, the term "executive functioning" was coined later in 1982 by Lezak, who formally defined EF as those mental capacities that are necessary for formulating goals, planning how to achieve these goals and carrying out the plans effectively (Muriel D. Lezak, 1982). Later, this construct was also described as a set of general-purpose control mechanisms that regulate the dynamics of human cognition and action (Miyake & Friedman, 2012). In other words, they can be considered to be a collection of top-down control processes used in cases where it would be ill-advised, insufficient or impossible to rely on instinct or intuition if a specific goal needs to be achieved (Damasio, 1995; Stuss et al., 2005).

Since EF is not a single process but rather a "macro-construct" encompassing various aspects of mental functioning (Zelazo, Carter, Reznick, & Frye, 1997), many studies have focused on conceptualizing this construct, with some trying to break it down into components. This has resulted in a number of different conceptualizations all attempting to explain the same construct. Table 1 lists some of the studies that have suggested components for EF (adapted from review by Jurado & Rosselli, 2007).

Table 1:

Authors	**Conceptualization of executive functions**
Luria et al., (1966)	Anticipation, planning, execution, self-monitoring
Norman & Shallice, (1986)	Supervisory attentional system
Lezak, (1995)	Volition, planning, purposive action, effective performance
Lafleche & Albert, (1995)	Concurrent manipulation of information: cognitive flexibility, concept formation, cue-directed behavior
Borkowski & Burke, (1996)	Task-analysis, strategy control, strategy monitoring
Miyake et al., (2000)	Shifting, updating, inhibition
Sohlberg & Mateer, (2001)	Initiation and drive, response inhibition, task persistence, organization, generative thinking, awareness
Anderson, (2001)	Attentional control, cognitive flexibility, goal setting
Delis, Kaplan, & Kramer, (2001)	Flexibility of thinking, inhibition, problem-solving, planning, impulse control, concept formation, abstract thinking, creativity
Hobson & Leeds, (2001)	Planning, initiation, preservation and alteration of goal-directed behavior
Keil & Kaszniak, (2002)	Planning, generation, shifting & suppression, concept formation & abstract reasoning
Piguet et al., (2002)	Concept formation, reasoning, cognitive flexibility
Elliott, (2003)	Solving novel problems, modifying behaviour in light of new information, generating strategies, sequencing complex actions

As can be seen from the above table, EF has been conceptualized in many different ways throughout the years resulting in a myriad of definitions and subcomponents thought to make up EF. However, similarities and convergences do exist between the different concepts, especially when it comes to the complexity and importance of EF to human behavior (Jurado & Rosselli, 2007). Nevertheless, although the importance and pervasive nature of EF is rather well known and EF has thus been studied profusely by different fields of study, the concept remains rather elusive since there is still no one definition that unifies all the different conceptualizations that have been proposed.

3.2 Measurement of EF

Further understanding of this concept inherently relies on the ability to measure EF in a standardized manner. In fact, a number of neuropsychological tests have been designed throughout the years, with the primary purpose of capturing different executive abilities. Some commonly used examples of such tests include the Stroop Task (Stroop, 1935), the Wisconsin Card Sorting Test (Berg, 1948), and the Tower of London Test (Shallice, 1982). However, the measurement of EF poses a number of challenges (Jurado & Rosselli, 2007; Lezak, 1982; Miyake et al., 2000; Miyake & Friedman, 2012).

3.2.1 Challenges in measuring EF

Besides the problem of no clear definition and different conceptualisations of EF, another reason for this measurement difficulty is known as the task-impurity problem (Burgess, 1997). This refers to the fact that EF requires other cognitive processes to operate on and thus any score derived from an EF task will unavoidably include systematic variance that can be attributed to non-EF processes associated with that specific task context (Miyake et al., 2000; Miyake & Friedman, 2012). This systematic variance can be rather substantial, and thus making it difficult to measure the variance of interest that is specifically attributed to EF. An attempt to overcome this problem uses the latent-variable approach (Miyake & Friedman, 2012). This approach makes use of multiple tasks that capture the same EF ability but are different enough to share as little systematic non-EF variance as possible. The commonalities across these tasks can then be statistically extracted using multivariate statistical techniques and the resulting latent variable is considered to be the measure of EF.

Additionally, complex tasks that attempt to measure EF have been found to suffer from relatively low internal and/or test-retest reliability (P. Burgess, 1997; Lowe & Rabbitt, 1998). Reasons for this may be the possibility of people adopting different strategies on different occasions (Miyake et al., 2000), and the probability that EF strategies are more strongly involved when the task is novel (Rabbit, 1997; Chan, 2008). The latter reason thus suggests that repeated measure using the same task may reduce the effectiveness of the test.

Furthermore, an other reason for the measurement difficulty associated with EF is that tests used as indicators of EF (or dysfunction) are sometimes very different than most real-life situations and sometimes there is little equivalence between the cognitive resources that are being tapped in the testing condition, and those being tapped in the real world (Burgess, 1997; Burgess et al., 1998). This suggests that some EF tests may suffer from low ecological validity. In line with this, studies have also suggested that although many of the tests developed to probe EF are considered to be acceptable measures, their construct validities are not completely established (Reitan & Wolfson, 1994).

3.2.2 The Delis-Kaplan Executive Function System

The difficulty in measurement of EF has consequently instigated a number of studies specifically aimed at designing valid and reliable assessment tools and batteries that can measure EF in both healthy and clinical populations. One such battery of tests is the Delis-Kaplan Executive Function System (D-KEFS) which was one of the first normed set of tests developed specifically to assess EF (Delis et al., 2001). The D-KEFS consists of nine tests that cover a wide spectrum of verbal and non-verbal executive functions, all designed to be stand-alone instruments that can be administered individually or together with other D-KEFS tests. In addition to having been thoroughly examined for its internal consistincy, test-retest reliability and validity (Delis et al., 2001; Swanson, 2005), the main novelty of the D-KEFS includes the ability to isolate non-EF cognitive processes by providing rigorous measures of the different fundamental skills that are involved in the successful performance of the specific test, and thus tackling the task-impurity problem.

The D-KEFS Trail Making Test (TMT), which is a modification of the classic Trail Making Test (Brown & Partington, 1942), is an example of a test specifically designed for extracting the fundamental cognitive components that might affect performance on the EF task. The classic version of the test is aimed at measuring visual attention and cognitive flexibility by using number and letter sequencing and is composed of two parts, Part A and Part B. Part B is the core of the test and measures the cognitive flexibility on a visual-motor sequencing task, while Part A is a baseline measure that assesses number sequencing without switching. The latter serves to extract number sequencing from Part B since this could have an effect on performance on the cognitive flexibility part of the test. The D-KEFS TMT was modified in such a way that other significant component processes that also contribute to performance on the core part of the test can also be extracted. These processes are namely, letter sequencing, visual scanning, and motor speed in addition to number sequencing. The D-KEFS TMT is thus composed of five sub-tests, four of which serve as baseline measures for the number-letter switching sub-test. This ensures that the specific EF process (in this case cognitive flexibility) can be properly investigated and thus overcoming certain challenges that are involved in the measurment of EF. However, to our knowledge, although a lot has been done to make sure that each of the tests provide standardized, reliable, and ecologically valid measures of the individual level of functioning (Delis et al., 2004), rather little is yet known about the neurobiological underpinnings of the specific tests and sub-tests.

These observations motivated the first study reported here. Study 1 used scores from one of the sub-tests of the D-KEFS TMT to investigate the relationship between brain morphology, specifically gray matter volume (GMV), and performance on this particular test. The sub-test of choice was the motor speed subtest (TMT-MS) since it is not only used as a baseline for other TMT sub-tests, but also provides information of drawing speed *per se*, and thus can be used by clinicians as an assessment of motor function (Delis et al., 2001). The TMT-MS require participants to trace over a dotted line as quickly as possible while making sure that the line drawn touches every circle along the path. The participant is asked to focus on speed rather than neatness while still making sure that the line drawn touches all the circles. The scoring measure is the time (in seconds) that the participant needs to complete the task. Simple neuropsychological pen-and-paper tests such as the TMT-MS are often chosen to evaluate motor functions of patients to guide further therapy. Thus, the twofold purpose of this test, namely being a stand alone test that measures motor function while also acting as a baseline for a commonly used EF test, made the TMT-MS a good candidate for our study to further investigate its neurobiological underpinnings. This was achieved by performing a whole-brain voxel-based morphometery (VBM) analysis using the anatomical T1-weighted images of 109 subjects from the Enhanced Nathan Klein Institute Rockland Sample (Nooner et al., 2012;

http://fcon_1000.projects.nitrc.org/indi/enhanced) together with the inidividual TMT-MS performance scores of each of the participants, to investigate any potential correlation between gray matter volume and performance. Further details regarding the method used can be found in the Methods section of Study 1.

3.3 Brain regions associated with EF

3.3.1 EF and the frontal cortex

Studies investigating the neural correlates associated with EF were originally motivated by observations of patients with frontal lobe lesions. In fact, research on the concept of EF itself has historical roots in neuropsychological studies of patients with frontal lobe damage (Miyake et al., 2000). One well-known example that demonstrated the relationship between frontal lobe damage and severe difficulties in self-control and behavior regulation was Phineas Gage who suffered an injury that resulted in extensive left frontal lobe damage. Comparably, soldiers who had suffered frontal lobe damage in wars also demonstrated changes in behavior as well as problems with engaging in appropriate actions to complete a specific goal (Stuss & Benson, 1986). These observations led to the emergence of a number of controlled studies conducted in a laboratory setting aimed at investigating the relationship between the frontal lobes and EF. Such studies commonly tested the performance of patients with frontal lobe lesions on traditional neuropsychological EF tests involving functions such as set-shifting (Milner, 1963) and planning (Shallice, 1982) and reporting impairment in behavior. Due to these reports executive functions were commonly referred to as frontal lobe functions and later, the group of behavioral and cognitive irregularities found in frontal patients were coined as the “dysexecutive syndrome” (Baddeley & Wilson, 1988). Conversely, anatomical studies have suggested a cortico-striatal system that links different brain regions including the frontal cortex to striatal structures via the thalamus and the pallidum (G. Alexander, 1986; Alvarez & Emory, 2006). This view has been supported by tracer studies in experimental animals revealing dense connections between prefrontal and subcortical structures (Alexander & Crutcher, 1990; Joel & Weiner, 1994; Markowitsch et al., 1985; Middleton & Strick, 1997; Tanaka, 1976). Additionally, patients with basal ganglia pathology, e.g., those suffering from Huntington's and Parkinson's disease, have well documented deficits in executive functioning (Elliott, 2003), highlighting the critical role of cortico-striatal-thalamic circuits for EF. Such studies have suggested that EF might depend on more brain regions than the pre-frontal cortex alone, appropriately prompting further investigation. Later, advances in functional neuroimaging provided the tools necessary to assess prefrontal mediation of EF and the recruitment of other brain regions in further detail (Elliott, 2003).

3.3.2 Neuroimaging of EF

A large number of studies using different neuroimaging techniques including positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalagraphy (MEG) and functional magnetic resonance imaging (fMRI) have attempted to investigate the different brain regions involved when engaging in specific EF tasks (for a list of selected results see Jurado & Rosselli, 2007). Such studies have corroborated the involvement of the frontal lobe in EF that was previously suggested by neuropsychological studies (Jurado & Rosselli, 2007). However, such studies have discredited the earlier suggestions that the frontal lobe is involved in EF as a homogenous entity and pointed more towards the idea of different areas of the frontal cortex being associated with specific aspects of EF (Stuss & Alexander, 2000; Stuss & Levine, 2002) as part of a network of regions including parietal areas, subcortical structures and thalamic pathways (Jurado & Rosselli, 2007; Lewis et al., 2004; Monchi et al., 2007). The large number of neuroimaging studies have resulted in a large body of work, aimed at investigating brain regions associated with different aspects of EF. These results however are at times heterogenous, possibly due to the difficulty associated with defining EF. Subsequently, meta-analyses benefitted from the wealth of results that was brought about by the advancement of neuroimaging techniques, by attempting to synthesise the large number of results in an unbiased fashion (Müller et al., 2018). Such meta-analyses have attempted to summarise and integrate neuroimaging findings across specific tasks to answer specific research questions associated with the various facets of EF.

One such example by Rottschy et al., (2012), was aimed at examining the brain regions that are commonly and differently active during various working memory tasks by performing a co-ordinate based meta-analysis over 189 fMRI experiments on healthy subjects. This study revealed a consistent bilateral activation of a fronto-parietal network including regions such as frontal areas BA44/45, the anterior insula, posterior superior frontal gyrus (dorsal premotor cortex — dPMC) and inferior frontal gyrus (ventral premotor cortex — vPMC; extending into area 44). Additionally, bilateral activation was also found in the medial (pre-) supplementary motor area (SMA), as well as the intraparietal sulcus (IPS), and the superior parietal lobule (SPL). Furthermore, the lateral prefrontal cortex (LPFC) showed bilateral activation in caudal and rostral parts. Bilateral activation was also found in ventral visual cortex as well as in lobule VI of the cerebellum. Subcortical activation was found in bilateral regions of the thalamus and mainly the left basal ganglia (Rottschy et al., 2012). A similar fronto-parietal network of regions was reported when performing a meta-analysis focused on inhibitory control (Cieslik et al., 2015). This activation network included the anterior insula and adjacent inferior frontal gyrus (IFG) dorsolateral prefrontal cortex (DLPFC), dPMC, as well as bilateral IPS extending into the SPL. Additionally, convergent activity was found in the right temporoparietal junction (TPJ) and in the left inferior occipital gyrus as well as in the (pre)SMA extending into the anterior midcingulate cortex (aMCC). Subcortical activity was observed in the right thalamus and the right caudate nucleus (Cieslik et al., 2015). An other meta-analysis which focused on brain activation associated with vigilant attention revealed a bilateral (albeit right-dominant) network of regions that include the anterior insula, the pre-SMA and midcingulate cortex, extending to more anterior medial pre-frontal cortex (PFC); bilateral inferior PFC (inferior frontal junction [IFJ] and dorsal area 44), extending to the vPMC in the right hemisphere (Langner & Eickhoff, 2013). Additionally in the right hemisphere activations in the adjacent frontal operculum; bilateral thalamus; right midlateral PFC; TPJ; right inferior parietal lobule and IPS; right middle occipital gyrus, reaching medially to area 17; left dPMC; left temporo-occipital junction extending to fusiform gyrus; and cerebellar vermis were also found (Langner & Eickhoff, 2013).

3.3.3 Functional integration and distributed networks associated with EF

The brief overview of neuroimaging literature above clearly suggests that EF processes are not necessarily tied to a specific brain region but are rather mediated by networks that include multiple cooperating cortical regions that overlap in functions (Elliott, 2003; Mesulam, 1998). This coincides with the proposed integrative nature of the brain (K. Friston, 2002), which suggests that multiple brain regions are flexibly communicating with each other and mental capacities, including EF, depend on a dynamic interaction and exchange of information between the different regions (Eickhoff & Grefkes, 2011; Genon et al., 2018). It is important to note that this integrative view of the brain does not contradict the view of segregation that suggests that the brain can be subdivided into distinct modules based on functional and microstructural properties (reviewed in Eickhoff & Grefkes, 2011). Rather, it suggests that the brain is topographically organized into distinct areas that are integrated into networks. This view represents a major conceptual shift, and significantly increased the challenge in functional imaging requiring research to be aimed at investigating how multiple brain regions dynamically interact with each other, instead of focusing on the one-to-one mapping of structures to function (Elliott, 2003).

This suggested view has resulted in a subsequent effort directed towards investigating brain networks associated with EF. Consequently, different studies using different perspectives and operationalizations have resulted in a rather diverse co-existence of brain networks all associated with EF. One such network is the multiple-demand system as defined by convergent activation across multiple cognitive tasks in fMRI (Duncan, 2010) which was instigated by the suggestion that "executive networks" seem to sustain a wide range of cognitive functions (Cabeza & Nyberg, 2000; Fedorenko, et al., 2013). Other similar networks include the cognitive control network (Cole & Schneider, 2007), the fronto-parietal control system (Vincent et al., 2008); the superordinate cognitive control network (Niendam et al., 2012), and the extrinsic mode network (Hugdahl et al., 2015). Examining these networks, it can be clearly seen that a number of similarities exist across all networks such as the posterior-medial frontal cortex [pre-SMA and adjacent middle cingulate cortex (MCC)], the bilateral anterior insula (aINS), the IPS, and posterior IFS.

Interestingly these regions emerged from a recent integration (Müller et al., 2015) of the three large-scale meta-analyses mentioned above, on working memory (Rottschy et al., 2012), vigilant attention (Langner & Eickhoff, 2013), and inhibitory control (Cieslik et al., 2015). However, due to the conservative nature of the conjunction analysis used, this network failed to report a number of regions that are well known to contribute to executive processes. Such regions include the basal ganglia and the thalamus, the more anterior IFS/dorsolateral prefrontal cortex, and the dorsal premotor cortex. Additionally, this network is based on the (most robust) convergence of activation data and does not directly consider the perspective of a distributed neural network. As a result, the main aim of the second study reported here was to define a broad network of regions associated with EF based on functional connectivity analyses rather than activations alone. This was done by using the regions of the meta-analytic Multiple Demand Network (MDN) that was defined by Müller et al, (2015), as seed-regions. Furthermore, due to the integrative nature of the brain and the fact that the understanding of how a brain region subserves a specific task requires information regarding its interaction with other brain regions (Eickhoff & Grefkes, 2011), Study 1 additionally aimed to investigate the networks associated with the regions that were found to be related to TMT-MS performance.

3.4 Multimodal connectivity analyses

A number of different approaches can be employed to investigate brain network interactions. The section below outlines the different MRI connectivity analyses that were performed in the two studies reported here.

3.4.1 Task-Independent Functional Connectivity

Resting-state functional connectivity (RS-FC) is a commonly used method of analysis to investigate functionally connected brain regions and is based on the fact that the brain remains functionally active during resting conditions (M D Fox & Greicius, 2010). This activity can be measured using functional magnetic resonance imaging (fMRI) by observing the spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal. RS-FC can then be used to measure functional connectivity between brain regions by identifying temporal correlation patterns in these spontaneous fluctuations (Biswal et al., 1995; van den Heuvel & Pol, 2010).

This RS-FC has been shown to correspond to structural connections (Greicius et al., 2009).

Whole-brain connectivity patterns can be examined by using model-free methods such as independent component analysis (Beckmann et al., 2005) and principal component analysis (Friston et al., 1993), which are designed to look for general connectivity patterns across the whole brain and thus enable the exploration of connectivity patterns without necessitating an *a priori* defined seed region (cf. van den Heuvel & Pol, 2010). Alternatively, seed-based RS-FC approaches examine the temporal correlations of an *a priori* defined seed region with spatially distinct brain regions (Fox & Raichle, 2007; Smith et al., 2013).

Seed-based RS-FC was used in both studies reported here. In Study 1 a seed-based RS-FC analysis was used to investigate the task-independent functional connectivity of the regions that were found to be related to TMT-MS performance. In Study 2 a seed-based RS analysis was used to investigate the task-independent functional connectivity of each original MDN region. Additionally, once the final network (the extended MDN - eMDN) was defined, a network-based RS-FC analysis was performed to compute the FC of all the regions within the eMDN. The computed functional connectivities that resulted from this network-based analysis were then used to cluster all the seed regions of the network based on their similarities in RS-FC. Details on the methods used can be found in the Methods section of Study 1 and Study 2.

3.4.2 Task-Dependent Functional Connectivity

Meta-analytic connectivity modeling (MACM) (Eickhoff et al., 2011; Fox et al., 2014; Laird et al., 2013) investigates co-activation patterns between a seed region and the rest of the brain, by calculation of meta-analyses across many task-based fMRI experiments and paradigms. MACM thus investigates which brain regions are concurrently activated with a specific region across a wide range of different tasks and thus benefits from the fact that a large number of such studies are now available in a highly standardized format in databases such as the BrainMap database (Laird et al., 2009; Laird et al., 2011). Co-activation patterns that result from using this approach reflect functional connectivity between the given regions.

In both Study 1 and Study 2 MACM was used to characterize whole-brain connectivity of seed regions during the execution of experimental tasks through the identification of significant co-activations with the seed across many individual experiments (Laird et al., 2013). In Study 1, MACM was used to investigate the task-dependent whole-brain connectivity of the region that was found to be related to TMT-MS performance. Similarly, in Study 2 MACM was used to characterize the whole-brain connectivity of each MDN seed region. Co-activation patterns of the resulting eMDN were also used in a hierarchical clustering analysis to investigate clusters of regions that are similar based on the MACM co-activation patterns.

Additionally, the use of a large-scale neuroimaging database such as BrainMap can also be used to functionally characterize resulting regions based on meta-data (Laird et al., 2009, 2011; Fox & Lancaster, 2002). This was done in Study 1 to functionally characterize the regions that were found to be associated with TMT-MS performance and resulting regions of the network analyses. In Study 2 the regions of the final eMDN network were functionally characterized. Additionally, the functional labels associated with each of the resulting regions were also used in a hierarchical clustering analysis to cluster the different eMDN regions based on their function.

Detailed information regarding the methods used can be found in the Methods section of Study 1 and Study 2.

3.4.3 Structural Covariance

Structural covariance (SC) is based on the correlation patterns across a population of gray-matter characteristics such as volume or thickness (Albaugh et al., 2013; Lerch et al., 2006) that are thought to reflect shared mutational, genetic, and functional interaction effects of the regions involved (Alexander-Bloch et al., 2013; Evans, 2013). In Study 1 this approach was used to investigate the pattern of cortical gray-matter morphology across the whole brain by measuring the correlations of GMV, obtained through VBM, between the seed region (the regions found to be associated with TMT-MS performance) and the rest of the brain.

Detailed information regarding the methods used can be found in the Methods section of Study 1.

3.4.4 Probabilistic Tractography

Albeit having major conceptual differences, the three modalities described above all share the goal of delineating regions that interact functionally with a particular seed region. By contrast, probabilistic tractography (PT) focuses on white-matter anatomical connectivity obtained from diffusion-weighted images (DWI) by producing a measure of how likely it is that the two specific regions are structurally connected (Behrens et al., 2003; Parker et al., 2003). PT was used in Study 1 to investigate white-matter anatomical connectivity from the regions that were found to be associated to TMT-MS performance to the rest of the brain.

Detailed information regarding the methods used can be found in the Methods section of Study 1.

3.4.5 Convergences and differences across modalities

All of the modalities described above have been substantially used in the literature to investigate brain connectivity. However, as outlined above the different approaches are conceptually different with the main dividing line amongst them being between structural connectivity and functional connectivity (Eickhoff & Müller, 2015). Structural connectivity is a prerequisite for any connection to occur as without physical structural connections information transfer is not possible. On the other hand, functional connectivity also reveals indirect relationships due to the fact that it is based on correlational analyses. Due to this elusive relationship between structure and function a number of studies have focused on using these modalities concurrently to characterize convergences and divergence across the modalities. Previous studies have reported convergence between RS and MACM (Cauda et al., 2011; Hoffstaedter et al., 2014; Jakobs et al., 2012), between RS and SC (He et al., 2007; Seeley et al., 2009), RS and tractography methods (Damoiseaux & Greicius, 2009; Greicius et al., 2009; Koch et al., 2002; van den Heuvel et al., 2009), and between RS, MACM, and SC (Clos et al., 2014; Reid et al., 2015). However, prominent differences among the different connectivity approaches have also been found (Damoiseaux & Greicius, 2009; Clos et al., 2014).

Similarly, study 1 investigates convergences and differences among all the different connectivity used. This was done by overlapping all the four thresholded connectivity maps (RS, MACM, SC, and PT) and computing a minimum statistic conjunction (Nichols et al., 2005), in order to identify common connectivity with the seed across the different modalities. An additional minimal conjunction analysis was also performed across the three modalities used to investigate gray-matter regions, namely, RS, MACM, and SC. Furthermore, we looked at *specifically present connectivity* for each of the modalities i.e. regions that were connected with the seed in one modality but *not* in the other three, and *specifically absent connectivity* i.e. regions that were specifically absent in one modality but present in the other three.

In Study 2 the key aim was to identify an extended multiple demand system by detecting the brain regions that are functionally connected to multiple of the original MDN regions as defined by Müller et al., (2015). In order to make sure that the network does not reflect a specific brain state we performed a conjunction analysis across the RS and MACM functional connectivity maps for each seed using the minimum statistic (Nichols et al., 2005). This resulted in eight consensus functional connectivity maps, showing the areas consistently interacting with each seed across different brain states (cf. Clos et al., 2014; Hardwick et al., 2015). The extended multiple-demand network was then delineated by identifying all regions that were significantly connected with multiple seeds, i.e., regions in which the consensus connectivity maps of at least half of the seeds overlapped.

Detailed information regarding the methods used can be found in the Methods sections of Study 1 and Study 2.

3.5 Aim of studies

The two studies reported here have used multimodal neuroimaging analysis in the attempt to better understand the concept of EF in the broader sense. In both studies this was done by investigating functional (and structural) connectivity patterns of seed regions using multi-modal analyses.

Specifically, Study 1 was aimed at better understanding the underpinnings of a specific sub-test of the D-KEFS TMT, a commonly used test to measure EF. This was done by investigating the relationship between brain morphology, GMV, and performance on this particular test through a VBM analysis. Due to the fact that the brain is composed of distinct spatial regions that interact with each other in the form of networks Study 1 also aimed at using multi-modal MRI approaches to investigate regions that are functionally and structurally connected to the region that was found to be associated with perfomance on the test. Additionally, both the divergence and convergence of the different approaches used were characterized.

In Study 2 the core aim of the study was to map and characterize a robust network associated with EF. In more detail, this entailed the computation of robust connectivity maps for each original MDN region by combining task-free and task-based functional connectivity analyses. The eMDN was then identified by convergence across multiple of these robust connectivity maps for the seed regions. Furthermore, potential cliques of regions within the extended MDN were investigated based on similarities in connectional and functional profiles.

References

Albaugh, M. D., Ducharme, S., Collins, D. L., Botteron, K. N., Althoff, R. R., Evans, A. C., … Hudziak, J. J. (2013). Evidence for a cerebral cortical thickness network anti-correlated with amygdalar volume in healthy youths: Implications for the neural substrates of emotion regulation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2012.12.071

Alexander-Bloch, A., Raznahan, A., Bullmore, E., & Giedd, J. (2013). The Convergence of Maturational Change and Structural Covariance in Human Cortical Networks. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3554-12.2013

Alexander, G. (1986). Parallel Organization of Functionally Segregated Circuits Linking Basal Ganglia and Cortex. *Annual Review of Neuroscience*, *9*(1), 357–381. https://doi.org/10.1146/annurev.neuro.9.1.357

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences*. https://doi.org/10.1016/0166-2236(90)90107-L

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*. https://doi.org/10.1007/s11065-006-9002-x

Amft, M., Bzdok, D., Laird, A. R., Fox, P. T., Schilbach, L., & Eickhoff, S. B. (2015). Definition and characterization of an extended social-affective default network. *Brain Structure and Function*. https://doi.org/10.1007/s00429-013-0698-0

Anderson, V. (2001). *Developmental neuropsychology : a clinical approach*. *Brain damage, behaviour, and cognition*.

Baddeley, A. D., & Wilson, B. (1988). Comprehension and working memory: A single case neuropsychological study. Year of Publication 1988. *Journal of Memory and Language*, *27*(5), 479–498. https://doi.org/http://dx.doi.org/10.1016/0749-596X%2888%2990021-6

Baddeley, A., & Hitch, G. (1974). Working memory. *Psychology of Learning and Motivation*, *8*, 47–89. https://doi.org/10.1016/S0079-7421(08)60452-1

Beckmann, C. F., Deluca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into Resting-state Connectivity using Independent Component Analysis. *Philos Trans R Soc Lond B Biol Sci*, *360*(May), 1001–1013. https://doi.org/10.1098/rstb.2005.1634

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., Smith, S. M., Wheeler-Kingshott, C. A. M., Boulby, P. A., … Matthews, P. M. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience*. https://doi.org/10.1038/nn1075

Benson, S. &, D., F., & T, D. (1986). The frontal lobes. *Quarterly Review of Biology*.

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking.

Journal of General Psychology, *39*(1), 15–22. https://doi.org/10.1080/00221309.1948.9918159

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo???planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Borkowski, J. G., & Burke, J. E. (1996). Theories, models, and measurements of executive functioning: An information processing perspective. In *Attention, memory, and executive function* (pp. 235–261).

Brown, R. R., & Partington, J. E. (1942). The intelligence of the narcotic drug addict. *Journal of General Psychology*, *26*(1), 175–179. https://doi.org/10.1080/00221309.1942.10544722

Burgess, P. (1997). Theory and methodology in executive function research. In *Methodology of frontal and executive function* (pp. 81–116). https://doi.org/10.1024//1016-264X.10.2.123

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. A. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, *4*(6), 547–558. https://doi.org/10.1017/S1355617798466037

Cabeza, R., & Nyberg, L. (2000). Imaging Cognition II: An Empirical Review of 275 PET and fMRI Studies. *Journal of Cognitive Neuroscience*, *12*(1), 1–47. https://doi.org/10.1162/08989290051137585

Cauda, F., Cavanna, A. E., D'agata, F., Sacco, K., Duca, S., & Geminiani, G. C. (2011). Functional Connectivity and Coactivation of the Nucleus Accumbens: A Combined Functional Connectivity and Structure-Based Meta-analysis. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2011.21624

Chan, R. C. K., Shum, D., Toulopoulou, T., & Chen, E. Y. H. (2008). Assessment of executive functions: Review of instruments and identification of critical issues. *Archives of Clinical Neuropsychology*. https://doi.org/10.1016/j.acn.2007.08.010

Cieslik, E. C., Mueller, V. I., Eickhoff, C. R., Langner, R., & Eickhoff, S. B. (2015). Three key regions for supervisory attentional control: Evidence from neuroimaging meta-analyses. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2014.11.003

Clos, M., Rottschy, C., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2014). Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.05.030

Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, *37*(1), 343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Damasio, A. R. (1995). On Some Functions of the Human Prefrontal Cortex. *Annals* *of the New York Academy of Sciences*, *769*(1), 241–252. https://doi.org/10.1111/j.1749-6632.1995.tb38142.x

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function*, *213*(6), 525–533. https://doi.org/10.1007/s00429-009-0208-6

Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: An update. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S1355617704102191

Delis, D., Kaplan, E., & Kramer, J. (2001). Delis-Kaplan executive function system (D-KEFS). *Canadian Journal of School Psychology*, *20*(1–2), 117–128. https://doi.org/10.1177/0829573506295469

Diamond, A. (2000). Close Interrelation of Motor Development and Cognitive Development and of the Cerebellum and Prefrontal Cortex. *Child Development*. https://doi.org/10.1111/1467-8624.00117

Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.01.004

Eickhoff, S. B., Bzdok, D., Laird, A. R., Roski, C., Caspers, S., Zilles, K., & Fox, P. T. (2011). Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2011.05.021

Eickhoff, S. B., & Grefkes, C. (2011). Approaches for the Integrated Analysis of Structure, Function and Connectivity of the Human Brain. *Clinical EEG and Neuroscience*, *42*(2), 107–121. https://doi.org/10.1177/155005941104200211

Eickhoff, S. B., & Müller, V. I. (2015). Functional Connectivity. In *Brain Mapping*. https://doi.org/10.1016/B978-0-12-397025-1.00212-8

Elliott, R. (2003). Executive functions and their disorders. *British Medical Bulletin*. https://doi.org/10.1093/bmb/65.1.49

Evans, A. C. (2013). Networks of anatomical covariance. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.05.054

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, *110*(41), 16616–16621. https://doi.org/10.1073/pnas.1315235110

Fox, M. D., & Greicius, M. (2010). Clinical applications of resting state functional connectivity. *Frontiers in Systems Neuroscience*, *4*(June), 19. https://doi.org/10.3389/fnsys.2010.00019

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn2201

Fox, P. T., & Lancaster, J. L. (2002). Mapping context and content: The BrainMap model. *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn789

Fox, P. T., Lancaster, J. L., Laird, A. R., & Eickhoff, S. B. (2014). Meta-Analysis in Human Neuroimaging: Computational Modeling of Large-Scale Databases. *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-062012-170320

Friston, K. (2002). Functional integration and inference in the brain. *Progress in Neurobiology*. https://doi.org/10.1016/S0301-0082(02)00076-X

Friston, K. J., Frith, C. D., & Frackowiak, R. S. (1993). Principal component analysis learning algorithms: a neurobiological analysis. *Proceedings. Biological Sciences / The Royal Society*, *254*(1339), 47–54. https://doi.org/10.1098/rspb.1993.0125

Genon, S., Reid, A., Langner, R., Amunts, K., & Eickhoff, S. B. (2018). How to Characterize the Function of a Brain Region. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2018.01.010

Grefkes, C., Nowak, D. A., Eickhoff, S. B., Dafotakis, M., Küst, J., Karbe, H., & Fink, G. R. (2008). Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Annals of Neurology*. https://doi.org/10.1002/ana.21228

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cerebral Cortex*, *19*(1), 72–78. https://doi.org/10.1093/cercor/bhn059

Hardwick, R. M., Lesage, E., Eickhoff, C. R., Clos, M., Fox, P., & Eickhoff, S. B. (2015). Multimodal connectivity of motor learning-related dorsal premotor cortex. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2015.08.024

He, Y., Chen, Z. J., & Evans, A. C. (2007). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhl149

Hobson, P., & Leeds, L. (2001). Executive functioning in older people. *Reviews in Clinical Gerontology*. https://doi.org/10.1017/S0959259801011479

Hoffstaedter, F., Grefkes, C., Caspers, S., Roski, C., Palomero-Gallagher, N., Laird, A. R., … Eickhoff, S. B. (2014). The role of anterior midcingulate cortex in cognitive motor control. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22363

Hugdahl, K., Raichle, M. E., Mitra, A., & Specht, K. (2015). On the existence of a generalized non-specific task-dependent network. *Frontiers in Human Neuroscience*, *9*. https://doi.org/10.3389/fnhum.2015.00430

Jakobs, O., Langner, R., Caspers, S., Roski, C., Cieslik, E. C., Zilles, K., … Eickhoff, S. B. (2012). Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus-context integration. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2012.02.037

Joel, D., & Weiner, I. (1994). The organization of the basal ganglia-thalamocortical circuits: Open interconnected rather than closed segregated. *Neuroscience*, *63*(2), 363–379. https://doi.org/10.1016/0306-4522(94)90536-3

Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*. https://doi.org/10.1007/s11065-007-9040-z

Keil, K., & Kaszniak, A. W. (2002). Examining executive function in individuals with brain injury: A review. *Aphasiology*. https://doi.org/10.1080/02687030143000654

Koch, M. A., Norris, D. G., & Hund-Georgiadis, M. (2002). An investigation of functional and anatomical connectivity using magnetic resonance imaging. *NeuroImage*. https://doi.org/10.1006/nimg.2001.1052

Lafleche, G., & Albert, M. S. (1995). Executive function deficits in mild Alzheimer's disease. *Neuropsychology*, *9*(3), 313–320. https://doi.org/10.1037/0894-4105.9.3.313

Laird, A. R., Eickhoff, S. B., Fox, P. M., Uecker, A. M., Ray, K. L., Saenz, J. J., … Fox, P. T. (2011). The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Research Notes*. https://doi.org/10.1186/1756-0500-4-349

Laird, A. R., Eickhoff, S. B., Li, K., Robin, D. A., Glahn, D. C., & Fox, P. T. (2009). Investigating the Functional Heterogeneity of the Default Mode Network Using Coordinate-Based Meta-Analytic Modeling. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.4004-09.2009

Laird, A. R., Eickhoff, S. B., Rottschy, C., Bzdok, D., Ray, K. L., & Fox, P. T. (2013). Networks of task co-activations. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.04.073

Langner, R., & Eickhoff, S. B. (2013). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*, *139*(4), 870–900. https://doi.org/10.1037/a0030694

Lerch, J. P., Worsley, K., Shaw, W. P., Greenstein, D. K., Lenroot, R. K., Giedd, J., & Evans, A. C. (2006). Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2006.01.042

Lewis, G. N., Polych, M. A., & Byblow, W. D. (2004). Proposed cortical and sub-cortical contributions to the long-latency stretch reflex in the forearm. *Experimental Brain Research*, *156*(1), 72–79. https://doi.org/10.1007/s00221-003-1767-z

Lezak, M. D. (1982). THE PROBLEM OF ASSESSING EXECUTIVE FUNCTIONS. *International Journal of Psychology*, *17*(1–4), 281–297. https://doi.org/10.1080/00207598208247445

Lezak, M. D. (1995). *Neuropsychological assessment (3rd ed.)*. *Neuropsychological* *assessment (3rd ed.).*

Lowe, C., & Rabbitt, P. (1998). Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. *Neuropsychologia*, *36*(9), 915–923. https://doi.org/10.1016/S0028-3932(98)00036-0

Luria, A. R., Karpov, B. A., & Yarbuss, A. L. (1966). Disturbances of Active Visual Perception with Lesions of the Frontal Lobes. *Cortex*, *2*(2), 202–212. https://doi.org/10.1016/S0010-9452(66)80003-5

Markowitsch, H. J., Emmans, D., Irle, E., Streicher, M., & Preilowski, B. (1985). Cortical and Subcortical Afferent Connections of the Primates Temporal Pole - a Study of Rhesus-Monkeys, Squirrel-Monkeys, and Marmosets. *Journal of Comparative Neurology*, *242*, 425–458. https://doi.org/10.1002/cne.902420310

Mesulam, M. M. (1998). From sensation to cognition. *Brain*. https://doi.org/10.1093/brain/121.6.1013

Middleton, F. A., & Strick, P. L. (1997). Cerebellar output channels. *International Review of Neurobiology*, *41*, 61–82. https://doi.org/10.1016/S0074-7742(08)60347-5

Milner, B. (1963). Effects of Different Brain Lesions on Card Sorting. *Archives of Neurology*, *9*(1), 90–100. https://doi.org/10.1001/archneur.1963.00460070100010

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences inMiyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. Current Directions in Psychological Science, 21(1), 8–14. *Current Directions in Psychological Science*, *21*(1), 8–14. https://doi.org/10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The Unity and Diversity of Executive Functions and Their Contributions to Complex “Frontal Lobe” Tasks: A Latent Variable Analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Monchi, O., Petrides, M., Mejia-Constain, B., & Strafella, A. P. (2007). Cortical activity in Parkinson’s disease during executive processing depends on striatal involvement. *Brain*, *130*(1), 233–244. https://doi.org/10.1093/brain/awl326

Moore Sohlberg, M., & Mateer, C. A. (2001). Improving attention and managing attentional problems: Adapting rehabilitation techniques to adults with ADD. *Wasserstein, Jeanette [Ed]; Wolf, Lorraine E [Ed]; LeFever, F Frank [Ed] (2001) Adult Attention Deficit Disorder: Brain Mechanisms and Life Outcomes (Pp 359-375) x, 409 Pp New York, NY, US: New York Academy of Sciences; US*, 359–375. Retrieved from http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=psyc3&AN=2001-01484-021%5Cnhttp://lib.exeter.ac.uk:4556/resserv?sid=OVID:psycdb&id=pmid:&id=doi:&issn=&isbn=157331255X&volume=&issue=&spage=359&pages=359-375&date=2001&title=Adult+attent

Müller, V. I., Cieslik, E. C., Laird, A. R., Fox, P. T., Radua, J., Mataix-Cols, D., … Eickhoff, S. B. (2018). Ten simple rules for neuroimaging meta-analysis. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2017.11.012

Müller, V. I., Langner, R., Cieslik, E. C., Rottschy, C., & Eickhoff, S. B. (2015). Interindividual differences in cognitive flexibility: influence of gray matter volume, functional connectivity and trait impulsivity. *Brain Structure and Function*, *220*(4), 2401–2414. https://doi.org/10.1007/s00429-014-0797-6

Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2004.12.005

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective and Behavioral Neuroscience*, *12*(2), 241–268. https://doi.org/10.3758/s13415-011-0083-5

Nooner, K. B., Colcombe, S. J., Tobe, R. H., Mennes, M., Benedict, M. M., Moreno, A. L., … Milham, M. P. (2012). The NKI-Rockland sample: A model for accelerating the pace of discovery science in psychiatry. *Frontiers in Neuroscience*. https://doi.org/10.3389/fnins.2012.00152

Norman, D., & Shallice, T. (1986). Attention to action. In *Consciousness and Self-Regulation: Advances in Research and Theory*.

Parker, G. J. M., Haroon, H. A., & Wheeler-Kingshott, C. A. M. (2003). A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. In *Journal of Magnetic Resonance Imaging*. https://doi.org/10.1002/jmri.10350

Piguet, O., Grayson, D. A., Broe, G. A., Tate, R. L., Bennett, H. P., Lye, T. C., … Ridley, L. (2002). Normal aging and executive functions in “old-old” community dwellers: Poor performance is not an inevitable outcome. *International Psychogeriatrics*, *14*(2), 139–159. https://doi.org/10.1017/S1041610202008359

Rabbit, P. (1997). Introduction: Methodologies and models in the study of executive function. In *Methodology Of Frontal And Executive Function*.

Reid, A. T., Bzdok, D., Langner, R., Fox, P. T., Laird, A. R., Amunts, K., … Eickhoff, C. R. (2015). Multimodal connectivity mapping of the human left anterior and posterior lateral prefrontal cortex. *Brain Structure and Function*. https://doi.org/10.1007/s00429-015-1060-5

Reitan, R. M., & Wolfson, D. (1994). A selective and critical review of neuropsychological deficits and the frontal lobes. *Neuropsychology Review*. https://doi.org/10.1007/BF01874891

Rigoli, D., Piek, J. P., Kane, R., & Oosterlaan, J. (2012). An examination of the relationship between motor coordination and executive functions in adolescents. *Developmental Medicine and Child Neurology*. https://doi.org/10.1111/j.1469-8749.2012.04403.x

Roski, C., Caspers, S., Lux, S., Hoffstaedter, F., Bergs, R., Amunts, K., & Eickhoff, S. B. (2014). Activation shift in elderly subjects across functional systems: An fMRI study. *Brain Structure and Function*. https://doi.org/10.1007/s00429-013-0530-x

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., … Eickhoff, S. B. (2012). Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage*, *60*(1), 830–846. https://doi.org/10.1016/j.neuroimage.2011.11.050

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative Diseases Target Large-Scale Human Brain Networks. *Neuron*. https://doi.org/10.1016/j.neuron.2009.03.024

Shallice, T. (1982). Specific Impairments of Planning. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *298*(1089), 199–209. https://doi.org/10.1098/rstb.1982.0082

Smith, S. M., Vidaurre, D., Beckmann, C. F., Glasser, M. F., Jenkinson, M., Miller, K. L., … Van Essen, D. C. (2013). Functional connectomics from resting-state fMRI. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.09.016

Staines, W. R., McIlroy, W. E., Graham, S. J., & Black, S. E. (2001). Bilateral movement enhances ipsilesional cortical activity in acute stroke: A pilot functional MRI study. *Neurology*. https://doi.org/10.1212/WNL.56.3.401

Stroop, J. R. (1935). Stroop color word test. *J. Exp. Physiol.*, (18), 643–662. https://doi.org/10.1007/978-0-387-79948-3

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual view. *Psychological Research*, *63*(3–4), 289–298. https://doi.org/10.1007/s004269900007

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., … Katz, D. I. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia*, *43*(3), 396–417. https://doi.org/10.1016/j.neuropsychologia.2004.06.010

Stuss, D. T., & Levine, B. (2002). Adult Clinical Neuropsychology: Lessons from Studies of the Frontal Lobes. *Annual Review of Psychology*, *53*(1), 401–433. https://doi.org/10.1146/annurev.psych.53.100901.135220

Swanson, J. (2005). The Delis-Kaplan Executive Function System: A Review. *Canadian Journal of School Psychology*, *20*(1–2), 117–128. https://doi.org/10.1177/0829573506295469

Tanaka, D. (1976). Thalamic projections of the dorsomedial prefrontal cortex in the rhesus monkey (Macaca mulatta). *Brain Research*, *110*(1), 21–38. https://doi.org/10.1016/0006-8993(76)90206-7

van den Heuvel, M. P., & Hulshoff Pol, H. E. (2010). Exploring the brain network: A review on resting-state fMRI functional connectivity. *European Neuropsychopharmacology*. https://doi.org/10.1016/j.euroneuro.2010.03.008

Van Den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20737

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.09.012

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology*, *100*(6), 3328–3342. https://doi.org/10.1152/jn.90355.2008

Zelazo, P. D., Carter, A., Reznick, J. S., & Frye, D. (1997). Early development of executive function: A problem-solving framework. *Review of General Psychology*, *1*(2), 198–226. https://doi.org/10.1037/1089-2680.1.2.198

Zelazo, P. D., & Müller, U. (2002). Executive function in typical and atypical development. *Blackwell Handbook of Childhood Cognitive Development*, (c), 445–469. https://doi.org/10.1002/9780470996652.ch20

STUDY 1

Multi-modal imaging of neural correlates of motor speed performance in the trail-making test

---

Julia A. Camilleri[1,2], Andrew T.Reid[1], Veronika I. Müller[1,2], Christian Grefkes[3],
Katrin Amunts[1,4], Simon B. Eickhoff[1,2]

[1]Research Centre Jülich, Institute of Neuroscience and Medicine (INM-1), Jülich, Germany

[2]Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf, Germany

[3]Department of Neurology, University Hospital Cologne, Cologne, Germany

[4]C. and O. Vogt Institute for Brain Research, Heinrich Heine University, Düsseldorf, Germany

Frontiers in Neurology (2015)
doi: 10.3389/fneur.2015.00219
Impact Factor (2016): 3.552

Own contributions	Conception and design of study
	Reviewing and adapting analysis code
	Statistical data analysis
	Interpretation of results
	Preparing figures
	Writing paper
	Total contribution 80%

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 October 2015
doi: 10.3389/fneur.2015.00219

Multi-modal imaging of neural correlates of motor speed performance in the trail making test

Julia A. Camilleri[1,2], Andrew T. Reid[1], Veronika I. Müller[1,2], Christian Grefkes[3], Katrin Amunts[1,4] and Simon B. Eickhoff[1,2]*

[1] Research Centre Jülich, Institute of Neuroscience and Medicine (INM-1), Jülich, Germany, [2] Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf, Germany, [3] Department of Neurology, University Hospital Cologne, Cologne, Germany, [4] C. and O. Vogt Institute for Brain Research, Heinrich Heine University, Düsseldorf, Germany

The assessment of motor and executive functions following stroke or traumatic brain injury is a key aspect of impairment evaluation and used to guide further therapy. In clinical routine, such assessments are largely dominated by pen-and-paper tests. While these provide standardized, reliable, and ecologically valid measures of the individual level of functioning, rather little is yet known about their neurobiological underpinnings. Therefore, the aim of this study was to investigate brain regions and their associated networks that are related to upper extremity motor function, as quantified by the motor speed subtest of the trail making test (TMT-MS). Whole-brain voxel-based morphometry and whole-brain tract-based spatial statistics were used to investigate the association between TMT-MS performance with gray-matter volume (GMV) and white-matter integrity, respectively. While results demonstrated no relationship to local white-matter properties, we found a significant correlation between TMT-MS performance and GMV of the lower bank of the inferior frontal sulcus, a region associated with cognitive processing, as indicated by assessing its functional profile by the BrainMap database. Using this finding as a seed region, we further examined and compared networks as reflected by resting state connectivity, meta-analytic connectivity modeling, structural covariance, and probabilistic tractography. While differences between the different approaches were observed, all approaches converged on a network comprising regions that overlap with the multiple-demand network. Our data therefore indicate that performance may primarily depend on executive function, thus suggesting that motor speed in a more naturalistic setting should be more associated with executive rather than primary motor function. Moreover, results showed that while there were differences between the approaches, a convergence indicated that common networks can be revealed across highly divergent methods.

Keywords: trail-making test, motor speed, inferior frontal sulcus, voxel-based morphometry, resting state fMRI, meta-analytic connectivity modeling, structural covariance, probabilistic tractography

OPEN ACCESS

Edited by:
Bruno J. Weder,
University of Bern, Switzerland

Reviewed by:
Olivier Godefroy,
Amiens University Hospital, France
Phil Clatworthy,
University of Bristol, UK

****Correspondence:***
Julia A. Camilleri
j.camilleri@fz-juelich.de

Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *15 May 2015*
Accepted: *05 October 2015*
Published: *27 October 2015*

Citation:
Camilleri JA, Reid AT, Müller VI, Grefkes C, Amunts K and Eickhoff SB (2015) Multi-modal imaging of neural correlates of motor speed performance in the trail making test. Front. Neurol. 6:219. doi: 10.3389/fneur.2015.00219

INTRODUCTION

Hand motor deficits are among the most common impairments following stroke (1). As a result, post-stroke assessment of motor functions is a key aspect of patient evaluation and is used to guide further therapy. In addition to fast but typically qualitative clinical assessments, this often involves neuropsychological tests of coordinated hand function. In practice, such assessments are still largely dominated by pen-and-paper tests. One example of such a simple pen-and-paper test is the motor speed subtest of the trail-making test (TMT-MS) from the Delis–Kaplan executive function system [D–KEFS; (2)]. This test measures the time that subjects take to manually trace a pre-specified trail. The TMT-MS requires the examinee to connect circles by following a dotted line, and aims to serve as a baseline measure of the motor component that should be shared by the other portions of the test. The results should thus provide information about the extent to which difficulty on the other TMT subtests probing higher, executive functions may be related to a motor deficit. However, the results of the TMT-MS cannot only be used as a baseline for other TMT subtests, but also provide information of drawing speed *per se*, and thus can be used by clinicians as an assessment of upper extremity motor function (2).

Pen-and-paper tests such as the TMT provide standardized and reliable valid measures of the individual level of functioning; however, rather little is yet known about their neurobiological underpinnings. Therefore, one aim of the current study is to investigate brain–behavior relationships with regard to upper extremity motor function, as quantified by the TMT-MS from the D–KEFS. Additionally, previous studies have demonstrated that while the brain can be subdivided into distinct modules based on functional and microstructural properties [reviewed in Ref. (3)], processes such as motor function are likely to involve the efficient integration of information across a number of such specialized regions. Due to this integrative nature of the brain, most higher mental functions are likely implemented as distributed networks (4), and it has therefore been suggested that an understanding of how a brain region subserves a specific task should require information regarding its interaction with other brain regions (3). Therefore, the current study additionally aims to investigate the networks associated with the regions we find to be related to TMT-MS performance.

A number of different approaches can be employed to investigate networks associated with a particular brain region. Task-free (seed-based) resting-state functional connectivity (RS-FC) refers to temporal correlations of a seed region with spatially distinct brain regions, when no task is presented (5, 6). Meta-analytic connectivity modeling (MACM) (7–9) investigates co-activation patterns between a seed region and the rest of the brain, by calculation of meta-analyses across many task-based fMRI experiments and paradigms stored in, e.g., the BrainMap database (10, 11). Structural covariance (SC) is based on the correlation patterns across a population of gray-matter characteristics such as volume or thickness (12, 13) that are thought to reflect shared mutational, genetic, and functional interaction effects of the regions involved (14, 15). While having conceptual differences, these three modalities all share the goal of delineating regions that interact functionally with a particular seed region. By contrast, probabilistic tractography (PT) focuses on white-matter anatomical connectivity obtained from diffusion-weighted images (DWI) by producing a measure of the likelihood that two regions are structurally connected (16, 17). Previous studies have reported convergence between RS and MACM (18–20), between RS and SC (21, 22), RS and fiber tracking (23–26), and between RS, MACM, and SC (27, 28). However, striking differences among the different connectivity approaches have also been found (26, 27).

In this study, we first used whole-brain voxel-based morphometry [VBM; (29)] and whole-brain tract-based spatial statistics [TBSS; (30)] to investigate the association between TMT-MS performance with gray-matter volume (GMV) and white-matter integrity, respectively. Using the result of these initial analyses as the seed region of interest, we further examined and systematically compared networks obtained through RS-fMRI, MACM, SC, and PT. The aim of these analyses was twofold. First, we sought to explore the relationship of brain morphology to a simple measure of hand motor function. Second, we aimed to characterize both the divergence and convergence of four unique approaches to quantifying brain connectivity.

MATERIALS AND METHODS

Subjects

Data from the Enhanced Nathan Kline Institute – Rockland Sample[1] (31) was used for all analyses except for meta-analytical connectivity modeling and functional characterization (where the BrainMap database was used). From this cohort, we used anatomical, RS, and DWI of subjects that had completed the TMT-MS, no current psychiatric diagnosis, a Beck depression inventory score (BDI) of less than 14 and did not exceed 3 SDs from the population mean. This resulted in a sample of 109 right-handed healthy volunteers between 18 and 75 years of age (mean age 40.39 ± 15.49; 37 males). First, effects of age, gender, handedness, and BDI score as known influences on hand motor speed (32, 33) were regressed out of the raw TMT-MS performance score (**Figure 1A**; **Table 1**). This resulted in an adjusted performance score, which indicated how much better or worse a subject performed than would be expected given these confounding factors (**Figure 1B**). The association of these adjusted scores with local GMV and white-matter integrity was then tested by carrying out whole-brain VBM and TBSS, respectively.

Delis–Kaplan Executive Function System: Trail-Making Test – Motor Speed

The Delis–Kaplan executive function system: trail-making test (D–KEFS TMT) consists of five different conditions (2). For the current study, we were exclusively interested in the TMT-MS, which requires participants to trace over a dotted line as quickly as possible while making sure that the line drawn touches every circle along the path. In particular, the participant is prompted to

---

[1] http://fcon_1000.projects.nitrc.org/indi/enhanced

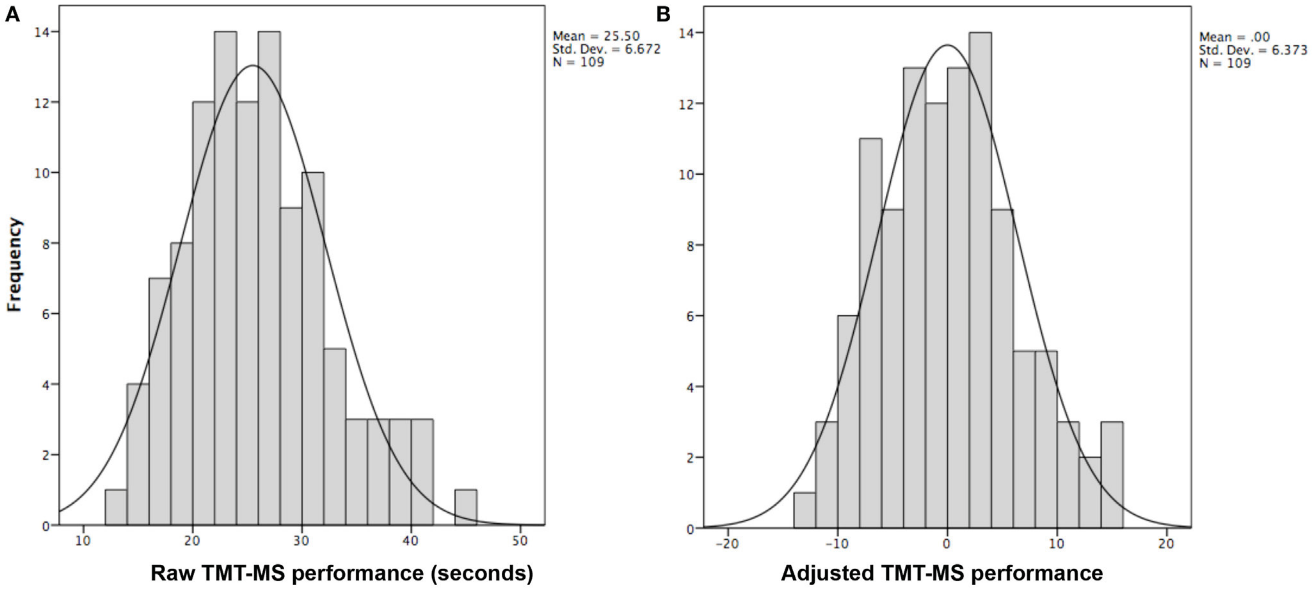

FIGURE 1 | Histograms showing distribution of TMT-MS performance. **(A)** The distribution of the raw TMT-MS performance. **(B)** The distribution of the adjusted TMT-MS performance after effects of age, gender, handedness, and BDI scores were regressed out of the raw scores.

focus on speed rather than neatness but has to make sure that the line touches every circle along the path. If the line departs from the dotted line or is not correctly connected to the next circle, the participant is stopped immediately and redirected to the dotted line while keeping the stopwatch running. The scoring measure is the time (in seconds) that the participant needs to complete the task.

Relationship Between TMT-MS Performance and Gray-Matter Volume

Whole-Brain VBM Analysis

The association between regional GMV and individual performance (adjusted for the potentially confounding effects of age, gender, handedness, and BDI), was investigated by performing a whole-brain VBM analysis. This analysis used the anatomical T1-weighted images of the 109 subjects described above. These scans were acquired in sagittal orientation on a Siemens TimTrio 3T scanner using an MP-RAGE sequence (TR = 1900 ms, TE = 2.52 ms, TI = 900 ms, flip angle = 9°, FOV = 250 mm, 176 slices, voxel size = 1 mm × 1 mm × 1 mm). Images were preprocessed using the VBM8 toolbox in SPM8 using standard settings, namely spatial normalization to register the individual images to ICBM-152 template space, and segmentation, wherein the different tissue types within the images are classified. The resulting normalized gray-matter segments, modulated only for the non-linear components of the deformations into standard space, were then smoothed using an 8 mm isotropic full-width-half-maximum (FWHM) kernel, and finally assessed for significant correlation between GMV and the adjusted TMT-MS performance scores. Age, gender, BDI scores, and Edinburgh handedness inventory (EHI) scores were used as covariates together with the adjusted TMT-MS performance scores, leading to an analysis of partial correlations between GMV and TMT-MS. As we modulated the gray-matter probability maps by the non-linear components only to represent the absolute amount of tissue corrected for individual brain size, we did not include total brain volume as an additional covariate in the analysis. That is, given that the correction for inter-individual differences in brain volume was applied directly to the data it was not performed (a second time) as part of the statistical model. Statistical significance using non-parametric permutation inference was assessed at $p < 0.05$ [family-wise error (FWE) corrected for multiple comparisons].

Whole-Brain TBSS Analysis

A TBSS whole-brain analysis was performed to investigate the association between white-matter volume and adjusted TMT-MS performance. DWI from the same group of 109 volunteers acquired on a 3T TimTrio Siemens scanner (137 directions, $b = 1{,}500\ \mathrm{s/mm^2}$) were used. Preprocessing was performed according to standard protocols using FSL[2]. The DWI data were first corrected for head-motion and eddy-current effects of the diffusion gradients. The b0 images were averaged and skull-stripped using BET (34) to create the analysis mask. Within this mask, a simple diffusion-tensor model was estimated for each voxel. Finally, non-linear deformation fields between the diffusion space and the ICBM-152 reference space were computed using FSL's linear (FLIRT) (35, 36), and non-linear (FNIRT) image registration tools (37). These allow mapping between the individual (native) diffusion space and the ICBM-152 reference space; i.e., the same space

---

[2] www.fmrib.ox.ac.uk/fsl

TABLE 1 | Characteristics of the cohort.

Age	Gender	BDI	EHI
26	Male	4	80
20	Male	0	95
53	Male	0	55
48	Female	9	100
62	Female	5	90
18	Female	7	75
54	Female	0	95
18	Female	1	90
21	Male	4	85
62	Female	1	100
53	Male	3	75
22	Male	4	90
62	Female	12	100
54	Female	0	95
24	Female	1	85
44	Female	8	90
57	Female	2	95
44	Female	3	70
51	Male	7	70
63	Female	0	80
26	Female	1	60
59	Male	4	95
30	Male	0	85
50	Female	1	90
26	Female	2	75
18	Male	0	80
24	Female	10	95
64	Female	0	95
47	Male	4	100
38	Female	0	80
23	Female	1	70
42	Female	8	85
59	Female	2	100
26	Male	5	100
18	Male	3	90
19	Male	1	100
27	Female	12	60
20	Female	3	100
56	Female	5	100
18	Male	4	85
30	Male	4	55
58	Female	6	95
52	Female	3	85
38	Male	1	65
64	Male	5	80
41	Female	2	100
49	Female	5	60
57	Female	8	60
40	Female	3	80
48	Female	0	100
36	Female	1	100
20	Male	5	90
60	Female	3	75
59	Male	2	85
52	Female	8	100
41	Male	1	70
26	Female	7	75
51	Female	5	75
61	Female	0	80
58	Male	5	80
56	Female	0	65
54	Female	4	95
27	Male	5	60
42	Female	9	70
31	Female	7	100
21	Female	1	100
18	Male	3	90
48	Female	3	85
20	Female	5	55
60	Female	1	100
20	Female	1	90
50	Female	2	90
62	Male	7	70
18	Male	2	85
57	Female	1	100
24	Female	0	95
26	Female	0	80
57	Female	5	85
19	Male	2	70
49	Male	0	60
23	Female	2	85
58	Female	5	55
55	Male	4	80
41	Female	5	100
41	Female	0	100
25	Female	2	75
49	Female	0	90
49	Female	1	100
21	Female	6	75
50	Male	1	85
19	Male	3	65
59	Male	3	85
41	Male	0	80
44	Male	13	100
20	Female	13	85
47	Male	5	90
21	Male	2	55
47	Female	7	55
55	Female	1	90
23	Female	13	100
61	Male	1	80
52	Female	0	100
20	Male	10	60
51	Female	0	65
42	Female	0	100
21	Female	0	80
36	Female	8	100
43	Female	9	85
43	Female	5	95

to which also the VBM and RS (as described below) data are also registered. The FA images were hereby normalized into standard space and then merged to produce a mean FA image. This was in turn used to generate a skeleton representing all fiber tracts common to all subjects included in the study (30, 38). The maximal FA scores of each individual FA image were then projected onto the mean FA skeleton. This projection aims to resolve any residual alignment problems after the initial non-linear registration (38). The resulting skeleton was then used to perform a multi-covariate analysis, using age, gender, BDI scores, EHI scores, and TMT-MS scores. Statistical significance using non-parametric permutation inference was again assessed at $p < 0.05$ multiple comparisons.

Seed Definition and Functional Characterization

The regions revealed by the initial VBM analysis were functionally characterized based on the behavioral domain meta-data from the BrainMap database[3] (10, 11, 39), using both forward and reverse inference, as performed in previous studies (40, 41). Behavioral domains, which have been grouped for the purpose of the database, describe the cognitive processes probed by an experiment. Forward inference is the probability of observing activity in a brain region, given knowledge of the psychological process; whereas reverse inference is the probability of a psychological process being present, given knowledge of activation in a particular brain region. The results of both the forward and reverse inferences will be defined by the number and frequency of tasks in the database. In the forward inference approach, the functional profile was determined by identifying taxonomic labels for which the probability of finding activation in the respective region/set of regions was significantly higher than the overall (*a priori*) chance across the entire database. That is, we tested whether the conditional probability of activation given a particular label [P(Activation|Task)] was higher than the baseline probability of activating the region(s) in question *per se* [P(Activation)]. Significance was established using a binomial test [$p < 0.05$, corrected for multiple comparisons using false discovery rate (FDR)]. In the reverse inference approach, the functional profile was determined by identifying the most likely behavioral domains, given activation in a particular region/set of regions. This likelihood P(Task|Activation) can be derived from P(Activation|Task) as well as P(Task) and P(Activation) using Bayes' rule. Significance (at $p < 0.05$, corrected for multiple comparisons using FDR) was then assessed by means of a chi-squared test.

Multi-Modal Connectivity Analyses

Multi-modal connectivity analyses were used to further characterize the results from the initial VBM analysis. In particular, we investigated; (1) RS-FC, inferred through correlations in the blood–oxygen-level-dependent (BOLD) signal obtained during a task-free, endogenously controlled state (5, 6); (2) MACM, revealing co-activation during the performance of external task demands (7, 8); (3) SC, identifying long-term coordination of brain morphology (15); and (4) probabilistic fiber tracking, providing information about anatomical connectivity by measuring the anisotropic diffusion of water in white-matter tracts (16, 17).

All the analyses were approved by the local ethics committee of the Heinrich Heine University Düsseldorf.

Task-Independent Functional Connectivity: Resting-State

A seed-based RS analysis was used to investigate the task-independent FC of the seed region (5, 6). RS-fMRI images of the 109 subjects described above were used. During the RS acquisition, subjects were instructed to not think about anything in particular but not to fall asleep. Images were acquired on a Siemens TimTrio 3T scanner using BOLD contrast [gradient-echo EPI pulse sequence, TR = 1.4 s, TE = 30 ms, flip angle = 65°, voxel size = 2.0 mm × 2.0 mm × 2.0 mm, 64 slices (2.00 mm thickness)].

Data were processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London[4]). The first four scans were excluded prior to further analyses and the remaining EPI images were then corrected for head movement by affine registration which involved the alignment to the initial volumes and then to the mean of all volumes. No slice time correction was applied. The mean EPI image for each subject was then spatially normalized to the ICBM-152 reference space by using the "unified segmentation" approach. (42). The resulting deformation was then applied to the individual EPI volumes. Furthermore, the images were smoothed with a 5-mm FWHM Gaussian kernel so as to improve the signal-to-noise ratio and to compensate for residual anatomic variations. The time-series of each voxel were processed as follows: spurious correlations were reduced by excluding variance that could be explained by the following nuisance variables: (i) the six motion parameters derived from the re-alignment of the image; (ii) their first derivatives; (iii) mean gray matter, white matter, and CSF signal. All nuisance variables entered the model as both first- and second-order terms. The data were then band-pass filtered preserving frequencies between 0.01 and 0.08 Hz. The time-course of the seed was extracted for every subject by computing the first eigenvariate of the time-series of all voxel within the seed. This seed time-course was then correlated with the time-series of all the other gray-matter voxels in the brain using linear (Pearson) correlation. The resulting correlation coefficients were transformed into Fisher's z-scores and tested for consistency across subjects by using a second-level ANOVA including age, gender, BDI scores, and EHI scores as covariates of no interest. Results were corrected for multiple comparisons using threshold-free cluster enhancement, a method that has been suggested to improve sensitivity and provide more interpretable output than cluster-based thresholding [TFCE; (43)], and FWE-correction at $p < 0.05$.

Task-Dependent Functional Connectivity: Meta-Analytic Connectivity Modeling

The whole-brain connectivity of the seed was characterized using a task-dependent approach by carrying out MACM. This method looks at FC as defined by task activation from previous fMRI studies and benefits from the fact that a large number of such studies are normally presented in a highly standardized format and stored in large-scale databases (9). Thus, MACM is based on the assessment of brain-wise co-activation patterns of a seed region across a large number of neuroimaging experiment results (7). All experiments that activate the particular seed region are first identified and then used in a quantitative meta-analysis to test for any convergence across all the activation foci reported in these experiments (9). Any significant convergence of reported foci in other brain regions as the seed was considered to indicate consistent co-activation with the seed. For this study, we used the BrainMap database to identify

---

[3] http://www.brainmap.org

[4] http://www.fil.ion.ucl.ac.uk/spm/software/spm8/

studies reporting neural activation within our seed region[5] (10). A coordinate based meta-analysis was then used to identify consistent co-activations across the experiments identified by using activation likelihood estimation (ALE) (44–46). This algorithm treats the activation foci reported in the experiments as spatial probability distributions rather than single points, and aims at identifying areas that show convergence across experiments. The results were corrected using the same statistical criteria as for the RS imaging data, i.e., using TFCE (43) and FWE-correction at $p < 0.05$.

Structural Covariance

Structural covariance was used to investigate the pattern of cortical gray-matter morphology across the whole brain by measuring the correlations of GMV, obtained through VBM, between different regions. This method assumes that such morphometric correlations carry some information about the structural or functional connectivity between the regions involved (13–15, 21). SC analysis was performed using the GMV estimates obtained from the VBM pipeline, as described above. Following preprocessing of the anatomical images, we first computed the volume of the seed region by integrating the (non-linear) modulated voxel-wise gray-matter probabilities of all voxels of the seed, which was then used as our covariate of interest for the group analysis. A whole-brain general linear model (GLM) analysis was applied using the GMV of the seed, along with the same additional covariates (of no interest) as for the RS-FC analysis. The results were corrected using the same statistical criteria as for the other connectivity modalities, i.e., using TFCE (43) and FWE-correction at $p < 0.05$.

Probabilistic Tractography

Probabilistic tractography was used to investigate white-matter anatomical connectivity from our seed region to the rest of the brain. The PT analysis was performed based on the same DWI as used for the TBSS analysis using the Diffusion Toolbox FDT implemented in FSL (16, 47). Fiber orientation distributions in each voxel were estimated according to Behrens et al. (48), i.e., using the BEDPOSTX crossing fiber model. Linear and subsequent non-linear deformation fields between each subject's diffusion space and the MNI152 space as the location of the seeds and subsequent output were computed using the FLIRT and FNIRT tools, respectively. For PT, 100,000 samples were generated for each seed voxel and the number of probabilistic tracts reaching each location of a cortical gray matter. Importantly, we did not investigate the number of tracts reaching specific ROIs, but rather analyzed the number of tracts reaching each gray-matter voxel of the ICBM-152 template. The distance of each target (i.e., whole-brain gray matter) voxel from the seed voxel was computed using the ratio of the distance-corrected and non-corrected trace counts [cf. (49)]. This allowed us to address a limitation of structural connectivity profiles generated by PT, namely the fact that trace counts show a strong distance-dependent decay. That is, voxels close to the region of interest will inevitably feature higher connectivity values than even well-connected distant ones. These effects were adjusted by referencing each voxel's trace count to the trace counts of all other gray-matter voxels in the same distance (with a 5-step, i.e., 2.5 mm, tolerance) along the fiber tracts [for a detailed description see Ref. (49)]. We thus replaced each trace count by a rank-based *z*-score indicating how likely streamlines passed a given voxel relative to the distribution of trace counts at that particular distance. The ensuing images were tested for consistency across subjects by using a second-level ANOVA. Results were corrected using the same statistical criteria as for the other connectivity modalities, i.e., using TFCE (43) and FWE-correction at $p < 0.05$.

Comparison of Connectivity Measures

The similarities and differences amongst all the different connectivity maps were compared and contrasted. The overlap between all the four thresholded connectivity maps (RS, MACM, SC, and PT) was computed using a minimum statistic conjunction (50), in order to identify *common connectivity* with the seed across the different modalities. This was done by computing the conjunction between the maps of the main effects for each of the modalities. An additional minimal conjunction analysis was also performed across the three modalities used to investigate gray-matter regions, namely, RS, MACM, and SC. Furthermore, we looked at *specifically present connectivity* for each of the modalities. *Specifically present connectivity* refers to regions that were connected with the seed in one modality but *not* in the other three [cf. (27)]. This was assessed by computing differences between the connectivity map of the first modality and those of the other three, respectively. Then a conjunction of these three different maps was performed. For example, the *specifically present connectivity* for MACM was assessed by computing the difference between the MACM map and the RS map in conjunction with the difference between the MACM map and the SC map and the difference between the MACM map and the PT map. Conversely, *specifically absent connectivity* was investigated by computing differences between one modality and the other three in order to identify regions that were present in the latter three modalities but not in the former. A conjunction of these different maps was then performed. For example, the *specifically absent connectivity* for MACM was assessed by computing the difference between the RS and MACM maps in conjunction with the difference between the SC and MACM maps and the difference between PT and MACM. All resulting maps were additionally thresholded with a cluster extent threshold of 100 voxels.

Finally, the resulting *common connectivity*, *specifically present connectivity* and *specifically absent connectivity* networks were functionally characterized based on the behavioral domain data from the BrainMap database as previously described for the seed region.

RESULTS

Relationships Between TMT-MS Performance and Brain Structure: Whole-Brain VBM and TBSS Analyses

The whole-brain VBM analysis revealed a significant negative correlation between the adjusted TMT-MS score and the GMV of a region in the lower bank of the left inferior frontal sulcus (IFS)

---

[5] http://www.brainmap.org

Figure 2A). Since the TMT-MS score refers to task completion time, this negative correlation indicates that better performance was associated with higher GMV in this region (**Figure 2B**).

The functional profile (based on the BrainMap database) of this region showed a significant association with cognition, specifically reasoning, at $p < 0.05$ (**Figure 3**).

The TBSS analysis of white-matter associations did not yield any significant results.

Connectivity of the IFS

Whole-brain connectivity of the region showing a significant association with TMT-MS performance was mapped using RS-FC, MACM, SC, and PT. Both similarities and differences amongst all the different connectivity maps were observed.

Converging Connectivity

Connectivity of the IFS seed, as revealed through RS-FC, MACM, SC, and PT analyses, included a number of distinct brain regions (**Figure 4**). Investigation of common regions interacting with the IFS across the different connectivity modalities (calculated through a minimum statistical conjunction analysis across the four thresholded connectivity maps) revealed convergence in the left inferior frontal gyrus (IFG) extending into the left IFS. An additional cluster was observed in the right Brodmann Area 45 (**Figure 5A**; **Table 2**). Functional characterization of this network found across all four connectivity approaches indicated an association with processes related to language, including semantics, phonology, and speech. Additionally, associations with working memory and reasoning were also revealed (**Figure 5B**). On the other hand, a conjunction across the modalities used to investigate gray-matter regions (RS-FC, MACM, and SC) resulted in a broader convergence, including clusters in the IFG bilaterally extending into the precentral gyrus, together with clusters in the middle cingulate cortex, middle orbital gyrus, and insula lobe of the left hemisphere (**Figure 6**).

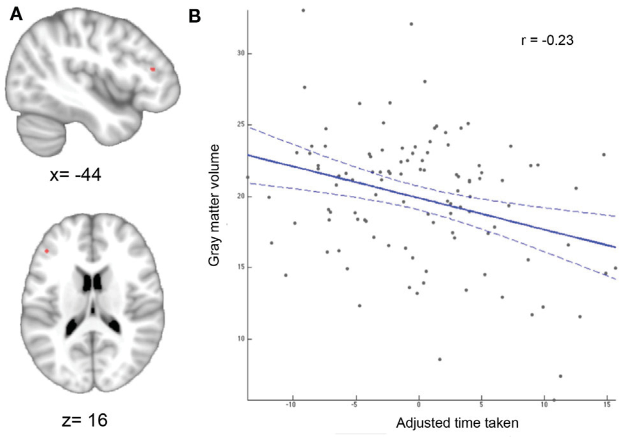

FIGURE 2 | Whole-brain VBM results. (A) Region showing significant correlation between gray-matter volume and adjusted time taken. Statistical significance using non-parametric permutation inference was assessed at $p < 0.05$ [family-wise error (few) corrected for multiple comparisons]. **(B)** Correlation between motor speed and gray-matter volume. The better (lower) the performance score the higher the gray-matter volume.

Specifically Present Connectivity for Each Modality

In the next step, we looked at the connectivity effects that were present in one modality but not in the other three (**Figure 7A**; **Table 3**).

For RS-FC, we found specific connectivity between the seed region and bilaterally in the inferior parietal lobule, IFG (pars opercularis and pars triangularis), middle frontal gyrus, inferior temporal gyrus, middle orbital gyrus, and supramarginal gyrus. Additionally, areas in the right IFG (p. orbitalis), cerebellum, superior orbital gyrus, middle occipital gyrus, and angular gyrus were also revealed by RS-FC. Moreover, specific RS-FC connectivity was found in areas of the left superior parietal lobule (**Figure 7A** in red). When functionally characterized using the BrainMap meta-data (**Figure 7B** in red) the components of this network were found to be mainly associated with cognitive functions, including working memory, attention, and action inhibition. In addition, fear was also found to be associated with this network.

Connectivity exclusively found using MACM was only observed in one region in the left hemisphere, namely in the insula lobe and adjacent IFG (p. triangularis), in an area slightly more posterior position to that found in RS-FC (**Figure 7A** in green). This region was found to be mainly associated with language functions, namely semantics, speech, and speech execution. Moreover, functions such as pain perception and music were also found to be related (**Figure 7B** in green).

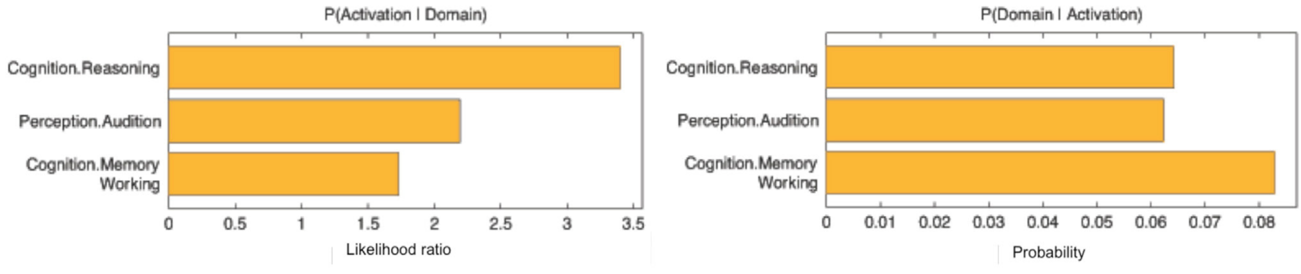

FIGURE 3 | Behavioral domains from the BrainMap database significantly associated with the seed, $p < 0.05$.

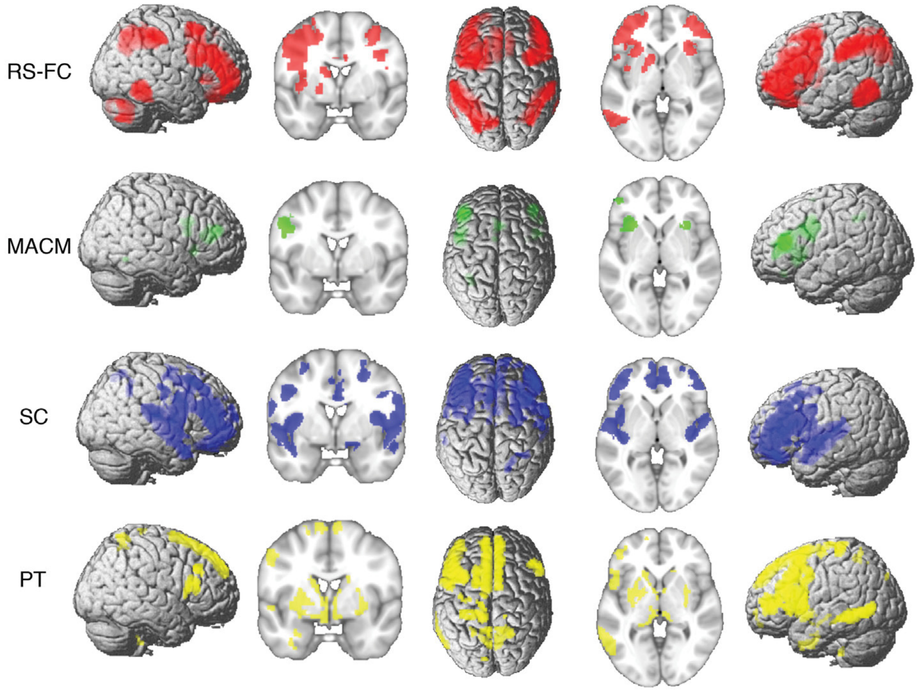

FIGURE 4 | Brain regions found to be significantly connected with the seed for each modality at $p < 0.05$, FWE corrected for multiple comparisons using threshold-free cluster enhancement (TFCE statistic).

Connectivity specific to SC was observed in the bilateral superior medial gyrus, temporal pole, superior temporal gyrus, Heschl's gyrus, rolandic operculum, supplementary motor area, superior and middle frontal gyri (more anterior to the effect found in RS-FC), IFG (p. orbitalis) (inferior to the area found in RS-FC on the right hemisphere) and middle orbital gyrus (bilaterally more anterior to the RS-FC effect). In the right hemisphere, specifically present SC connectivity included areas in the anterior cingulate cortex, insula lobe, middle temporal gyrus, supramarginal gyrus (more inferior to the area found in RS-FC), medial temporal pole, superior and inferior parietal lobules (the latter being more inferior to the area found in RS-FC), and superior orbital gyrus (more anterior to RS-FC specific connectivity in the same region). Additional connectivity was also observed in the left rectal gyrus, and left precentral gyrus (**Figure 7A** in blue). This network was found to be mainly functionally associated with functions related to emotion (fear, disgust, and sadness) and perception (audition and pain) (**Figure 7B** in blue).

The network specifically present for PT was found to be mainly functionally associated with functions related to emotion and pain. Additionally, functions such as action execution and action imagination were also found to be related (**Figures 7A,B** in yellow).

Specifically Absent Connectivity for Each Modality

Additionally, we looked at connectivity that was specifically absent in each modality, i.e., regions for which connectivity was absent in a particular modality but was observed in the other three (**Figure 8A**; **Table 4**). No regions were found to be specifically absent for the RS-FC modality. By contrast, for MACM we found specifically absent connectivity with areas of the left middle and inferior frontal gyri (p. triangularis) (**Figure 8A** in green). These regions were found to be functionally associated with cognitive functions, namely working and explicit memory but also with phonology, semantics, and syntax (**Figure 8B** in green).

Conversely, for SC specifically absent connectivity was found for an area in the left precentral gyrus (**Figure 8A** in blue; **Table 4**). This region was in turn found to be mainly functionally associated with language-related functions (phonology, semantics, speech, and syntax) together with working memory (**Figure 8B** in blue).

Connectivity specifically absent for PT was also found to be functionally associated with language-related functions (phonology, semantics, and speech) together with working memory, reasoning, and attention (**Figures 8A,B** in yellow).

DISCUSSION

The aim of this study was to employ a multi-modal approach to investigate the regions and associated networks related to upper extremity motor function, as quantified by the TMT-MS. In a first step, we therefore correlated local GMV with performance in motor speed. This analysis revealed a significant correlation between TMT-MS performance and GMV in a small region in the IFS, which was functionally characterized as being involved in cognitive tasks. In turn, the TBSS analysis of local WM associations yielded no significant result. We then further investigated the connectivity of the left IFS seed using a multi-modal approach. Functional interactions with other gray-matter

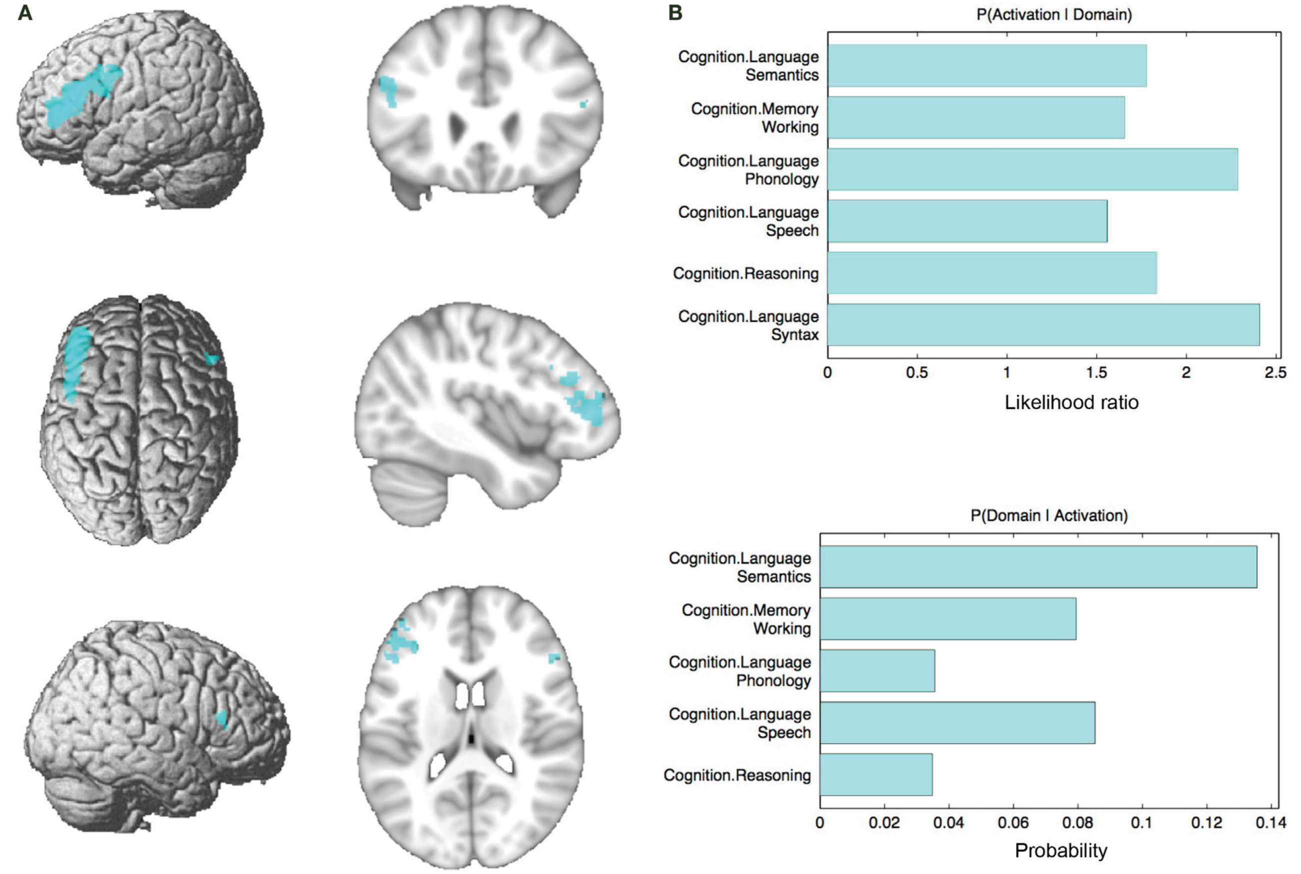

FIGURE 5 | Conjunction analysis and functional characterization of seed. **(A)** Conjunction across RS-FC, MACM, SC, and PT. **(B)** Behavioral domains from the BrainMap database significantly associated with the commonly connected regions shown in **(A)** (FDR-corrected for multiple comparisons, $p < 0.05$).

TABLE 2 | Converging connectivity of the IFS seed.

Region	x	y	z	Cytoarchitectonic assignment
Cluster 1 (780 voxels)				
L middle orbital gyrus	−46	46	−2	
Cluster 2 (1,235 voxels)				
R Inferior frontal gyrus (p. triangularis)	52	28	14	Area 45

x, y, and z coordinates refer to the peak voxel in MNI space. R, right; L, left.

regions and white-matter structural connections were assessed using RS-FC, MACM, SC, and PT approaches. The networks that emerged revealed both similarities and differences between the different modalities. A conjunction analysis between the four connectivity approaches was used to delineate a core network. Further analyses were used to investigate connectivity patterns specific to each of the modalities.

Relationships Between TMT-MS Performance and Brain Structure

In this study, we found TMT-MS performance to be specifically related to the local brain volume of a region in the lower bank of the left IFS. That is, across subjects better performance (lower completion time) was associated with higher GMV in this cluster. The left IFG, including IFS, has been formerly described as part of a multiple-demand system responsible for multiple kinds of cognitive demand, in which goals are achieved by assembling a series of sub-tasks, each separately defined and solved (51). An objective definition of this "multi-demand network" has recently been proposed by Müller et al. (52) based on a conjunction across three large-scale neuroimaging meta-analyses to identify regions consistently involved in sustained attention (53), working

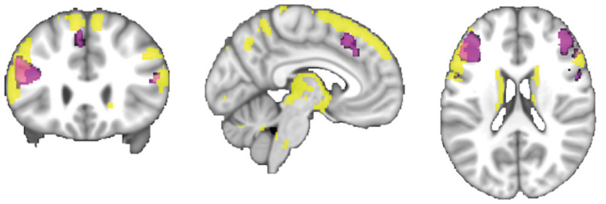

FIGURE 6 | A comparison of the conjunction across RS-FC, MACM, and SC (purple) with brain regions found to be significantly connected with the seed region when using PT (yellow) at $p < 0.05$, FWE corrected for multiple comparisons using threshold-free cluster enhancement (TFCE statistic).

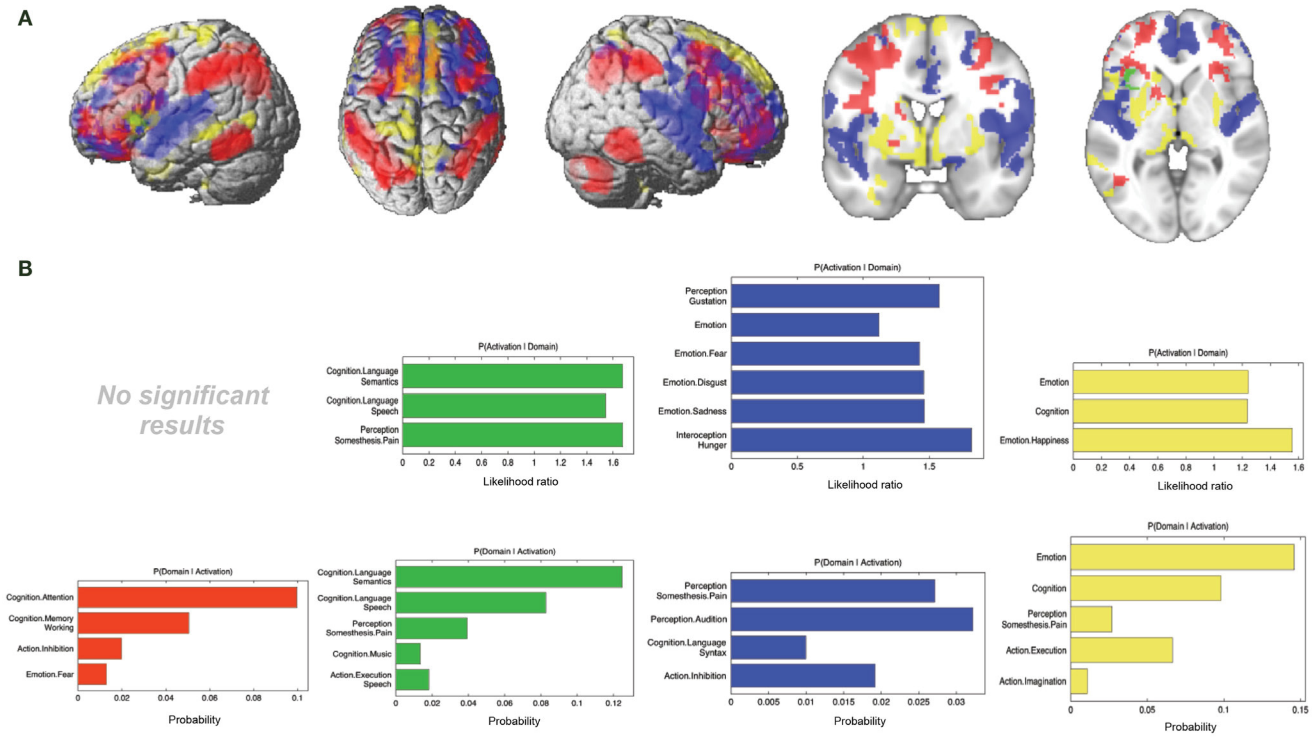

FIGURE 7 | Specific connectivity of seed and functional characterization. **(A)** Specific connectivity for RS-FC (red), MACM (green), SC (blue), and PT (yellow). An additional cluster extent threshold of 100 voxels was applied. **(B)** Behavioral domains from the BrainMap database significantly associated with the specifically connected regions shown in **(A)** (FDR-corrected for multiple comparisons, $p < 0.05$).

memory (54), and inhibitory control (55). Importantly, the IFS location identified in the current study was found to be part of this multi-demand network, indicating that TMT-MS performance is related to brain structure in a region involved in executive rather than motor functions. This association between certain aspects of motor performance and cognitive or executive functions has already been suggested in earlier studies (56, 57).

At first glance, these results contradict the intention of the TMT-MS to measure motor speed, and to serve as a baseline measure for higher, executive aspects of the test (2). However, one may argue that since subjects are given specific instructions to follow a dotted line while making sure that the line drawn touches every circle along the path, the accurate completion of this task should in fact draw heavily on executive control processes. It may hence not surprise that performance in a task requiring a relatively high degree of executive motor control and attention is related to a structure that is part of the multi-demand network involved in executive functions (51). In turn, there was no significant association between performance and GMV in cortical or subcortical motor structures as may have been expected. In this context, it must be noted that adequate hand motor abilities are a necessary prerequisite for performing the TMT-MS test successfully; i.e., subjects have to be able to use their hand to draw the required lines. Hence, the reliance of TMT-MS completion on an intact cortical and subcortical motor system is obvious. What we found, however, is that performance (i.e., the speed at which the task is completed) may seem to primarily depend on executive rather than more basic motor control processes. Does this contradict the assumption that the TMT-MS test is a baseline measure of motor speed? Not necessarily, but rather, given our findings, we would argue that motor speed in a more naturalistic setting should be more strongly associated with executive rather than primary motor function.

In congruence with the present results, previous studies have linked longer reaction times and motor slowing with sustained attention (58). However, lesion studies have associated slowing in motor processes with lesions in the right lateral frontal lobe (59, 60). Consequently, these results contrast with the findings of the present study. Additionally, the present results differ from those obtained using tasks that are commonly employed to investigate changes to the motor system following stroke; for instance, in functional neuroimaging studies using fist opening/closure paradigms (61, 62). Here, activation and interactions of the primary motor cortex as well as the lateral and medial pre-motor cortices are of essential importance. Similar regions were found in another functional neuroimaging study which used a finger tapping paradigm and focused on healthy subjects (63). In turn, activations involving the inferior frontal cortex and other regions of the executive, multi-demand network are not prominently seen. This implicates a potentially important distinction between neuroimaging assessments of stroke patients, in which more fundamental aspects of motor performance are usually tested, and paper-and-pencil tests that apparently, even when aimed at

TABLE 3 | Specifically present connectivity of IFS seed.

Region	x	y	z	Cytoarchitectonic assignment
RS-FC				
Cluster 1 (5322 voxels)				
L rectal gyrus	−4	24	−26	
Cluster 2 (4183 voxels)				
	−30	−72	20	
Cluster 3 (3958 voxels)				
	14	18	−28	
Cluster 4 (2318 voxels)				
	36	−64	24	
Cluster 5 (1630 voxels)				
R Cerebellum (Crus 2)	44	−66	−50	
Cluster 6 (1357 voxels)				
L inferior temporal gyrus	−52	−50	−26	
Cluster 7 (817 voxels)				
R inferior temporal gyrus	54	−50	−26	
MACM				
Cluster 1 (279 voxels)				
L insula lobe	−30	22	−10	
SC				
Cluster 1 (26511 voxels)				
R medial temporal pole	32	6	−33	
Cluster 2 (7299 voxels)				
	−39	3	−27	
Cluster 3 (2577 voxels)				
R superior frontal gyrus	21	33	30	
Cluster 4 (1710 voxels)				
L middle frontal gyrus	−40	51	10	
Cluster 5 (875 voxels)				
	−24	30	−23	
Cluster 6 (525 voxels)				
	28	−46	36	Area hIP1 (IPS)
Cluster 7 (341 voxels)				
L inferior frontal gyrus (p. Opercularis)	−57	15	7	Area 44
Cluster 8 (229 voxels)				
L SMA	−8	17	52	Area 6
Cluster 9 (153 voxels)				
L precentral gyrus	−33	−7	54	
Cluster 10 (122 voxels)				
L inferior frontal gyrus (p. Orbitalis)	−46	26	−5	
PT				
Cluster 1 (919 voxels)				
L superior medial gyrus	−8	54	28	
Cluster 2 (748 voxels)				
R superior medial gyrus	10	56	24	
Cluster 3 (387 voxels)				
L paracentral lobule	−10	−34	60	Area 4a
Cluster 4 (308 voxels)				
R precuneus	8	−66	40	Area 7A (SPL)
Cluster 5 (234 voxels)				
L inferior frontal gyrus (p. Orbitalis)	−48	22	−4	Area 45
Cluster 6 (232 voxels)				
L precuneus	−2	−72	36	Area 7P (SPL)
Cluster 7 (179 voxels)				
L middle temporal gyrus	−58	−28	−12	
Cluster 8 (111 voxels)				
	−4	−36	−48	
Cluster 9 (107 voxels)				
L middle occipital gyrus	*−52*	*−70*	*−2*	

x, y, and z coordinates refer to the peak voxel in MNI space. R, right; L, left.

testing basic motor speed, are more reflective of executive motor control. In summary, we would thus argue that the distinction between motor and "higher cognitive" tasks, which seems rather prevalent in (neuroimaging) stroke research, may be slightly misleading, as executive motor control functions may play a major role in the everyday impairments following stroke.

Core Network

Notably, all three FC approaches (RS-FC, MACM, and SC), together with locations revealed as structurally connected by PT, converged on a network comprising of the left inferior gyrus extending into the left IFS and an additional cluster in the right Brodmann Area 45. In combination with the observation of a fairly restrictive region associated with TMT-MS performance, these results suggest a core network of mostly regional connectivity that is in line with the current view on the role of the inferior frontal cortex in executive functioning (51).

Additionally, the right IFG, bilateral adjacent pre-motor cortices, and anterior insula were additionally found to converge when looking only at the FC approaches, namely, RS-FC, MACM, and SC (but not PT). Similar as the IFS seed, most of these clusters overlap with regions previously described to be part of the multiple-demand network (51, 52). In particular, the bilateral IFG, and left anterior insula as well as the MCC were the regions that overlapped with the multiple-demand network. Thus, we here show that, across different (functional) connectivity approaches the IFS shows robust interactions with regions associated with multiple cognitive demands. This is additionally supported by the functional characterization of the network robustly connected with the IFS across the different FC approaches, which show an association with multiple cognitive tasks. These observations thus continue to emphasize the important role of cognitive functions in the TMT-MS and thus suggest that this test might be tapping into executive rather than primary motor function.

Convergence and Differences Between Connectivity Measures

Convergence Among Modalities

Functional interactions can be probed by using different approaches, each having their own methodological features, and potentially also different biases even though the same statistical analyses and thresholds were used for each of the modalities. The use of the different modalities in the current study provided an opportunity to systematically compare all the different approaches. Despite the conceptual differences between the different modalities, a common network was revealed. When comparing the modalities RS-FC, MACM, and SC networks through a minimum statistic conjunction analysis, all three approaches converged on a core network that included adjacent parts of left IFG, its right-hemispheric homolog, right precentral gyrus, left middle cingulate cortex, middle orbital gyrus, and insular cortex. These results are in line with previous studies that used different seeds and therefore different networks, and also showed convergence between RS and MACM (18–20), between RS and SC (21, 22, 28), between RS and fiber tracking (23–26), and between RS, MACM, and SC (27, 64). As a result, it can be suggested that future studies could benefit from a multi-modal approach and

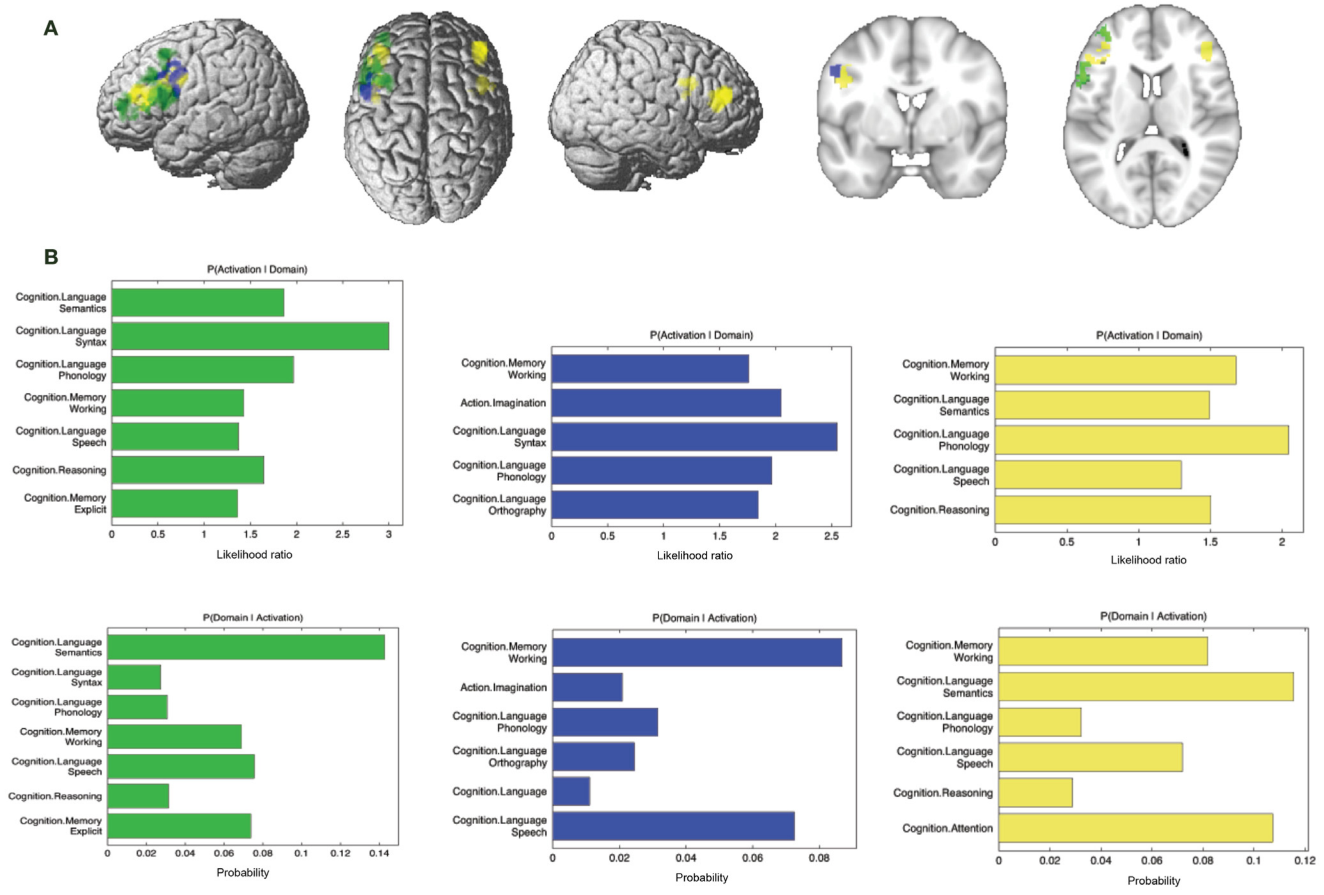

FIGURE 8 | Specifically missing connectivity of seed and functional characterization. **(A)** Specifically missing connectivity for MACM (green), SC (blue), and PT (yellow). An additional cluster extent threshold of 100 voxels was applied. **(B)** Behavioral domains from the BrainMap database significantly associated with the specifically missing regions shown in **(A)** (FDR-corrected for multiple comparisons, $p < 0.05$).

TABLE 4 | Specifically absent connectivity of IFS seed.

Region	*x*	*y*	*z*	Cytoarchitectonic assignment
MACM				
Cluster 1 (735 voxels)				
L inferior frontal gyrus (p. triangularis)	−42	40	−2	
L inferior frontal gyrus (p. triangularis)	−50	38	6	
L inferior frontal gyrus (p. triangularis)	−52	20	30	Area 45
Cluster 2 (166 voxels)				
L middle frontal gyrus	−44	12	38	Area 44
SC				
Cluster 1 (205 voxels)				
L precentral gyrus	−50	4	16	
PT				
Cluster 1 (629 voxels)				
L inferior frontal gyrus (p. triangularis)	−42	32	6	
Cluster 2 (339 voxels)				
R inferior frontal gyrus (p. triangularis)	46	34	6	Area 45
Cluster 3 (119 voxels)				
R precentral gyrus	54	6	18	Area 44

x, y, and z coordinates refer to the peak voxel in MNI space. R, right; L, left.

the consequent use and interpretation of the convergent network rather than focusing on a unimodal approach.

Furthermore, our resulting similarity between the SC and PT networks and the networks obtained from the other two modalities supports the idea that FC can be used to reflect structural connectivity and that SC of GMV can reflect functional networks in the brain (21, 22, 27). Consequently, our results together with previous findings provide evidence for the fact that SC is functional in nature.

Differences Among Modalities

Despite the convergence observed across all approaches, divergent connectivity patterns were also found when looking at contrasts of the different modalities. This is not surprising, given that the approaches use different data and methods in order to determine connectivity between a seed region and the rest of the brain. Previous studies have similarly reported striking differences between RS-FC and MACM connectivity approaches (20, 27). Clos et al. (27) and Jakobs et al. (20) have already argued that the differences that result from these two approaches may be the result of the conceptual differences between the methods. While RS-FC is based on correlation of fMRI time-series measured in the absence of an external stimulus (5, 65), MACM delineates networks that are conjointly recruited by a broad range of tasks (3). That is, RS and MACM derive FC from different mental states, in the absence and presence of a task, respectively. As a result, spontaneous networks related to self-initiated behavior and thought processes that can be captured in the task-free state may be largely missed in MACM analyses (3).

In particular, RS-FC of our seed was specifically found in a number of regions that have been predominantly associated with executive functions, such as working memory, attention, action inhibition, and spatial cognition. Importantly, there were no regions that were present in SC, PT, and MACM, but absent in RS-FC as revealed by the specifically absent RS-FC. This indicates that RS-FC captures the broadest network. By contrast, specific connectivity observed for MACM was found to be mainly associated with language-related functions such as semantics and speech. In turn, specifically absent regions in MACM were found to be mainly associated with cognitive functions such as working memory and explicit memory as well as language-related functions. As already mentioned above, these diverging patterns, with RS-FC capturing a broader network than MACM is possibly due to the conceptual differences. Moreover, these two approaches also differ in the subject groups assessed. While a group of 109 subjects were recruited for the RS-FC analysis, the MACM analysis relied on a large amount of published neuroimaging studies from the BrainMap database (10), with the selection criteria being activation of our identified seed region. Thus, it is possible that this difference in subject groups may have also contributed to the difference in results obtained.

In contrast to the FC approaches mentioned above, specific SC connectivity was observed in regions found to be mainly associated with functions related to emotion (fear, disgust, and sadness) and perception (pain, gustation, audition, hunger, and somesthesis). Additional functions observed included action inhibition and cognition. On the other hand, functional characterization of areas that were found to be specifically absent for SC connectivity revealed an association with functions related to cognition and language such as working memory, phonology, orthography, syntax, and speech. Given these results, it can be noted that the specific SC network showed a prominent association with perception and emotional processing. The strong association with emotional processing in SC is particularly interesting since the functional characterization of the seed region and the conjunction network did not indicate such an involvement. Moreover, while the specific RS-FC network revealed regions that were predominately related to cognition and the MACM network revealed regions that were predominantly related to language, the SC network found such regions to be specifically missing. These differences may be largely due to the conceptual differences between the FC modalities described above and SC. The exact biological basis of SC is still rather unclear (27), but it has been hypothesized that SC networks arise from synchronized maturational change that could be mediated by axonal connections forming and reforming over the course of development (66). Therefore, early and reciprocal axonal connectivity between regions is expected to have a mutually trophic effect on regional growth in an individual brain leading to covariance of regional volumes across subjects (14). That is, the correlation of anatomical structure between regions is the result of similarities in maturational trajectories (14). The specific connectivity pattern of the SC modality may thus be reflecting synchronized developmental patterns within a network of regions associated with perception and emotional processing. This could thus be the reason for particular regions to be present in the SC network and not in the MACM and RS-FC networks since the latter two modalities are more likely to highlight regions that are related to certain functions rather than long-term anatomical interactions. Additionally, SC is also likely to include other influences such as common genetic factors, developmental brain symmetry, neuromodulator distributions, and vascular territories (14, 15), which contribute to its more widespread distribution.

In congruence with the specific SC network, the PT network also showed a prominent association with perception and emotional processing while functional characterization of areas that were found to be specifically absent for PT connectivity revealed an association with functions related to cognition and language. These results further imply that the regions that were specifically associated with SC may reflect dominant long-term synchronized maturational patterns. However, despite the differences observed, it should be noted that the core network showed that the resulting SC network (also) revealed functional relations despite the fact that it was defined by anatomical covariance. SC may hence be regarded as a measure potentially bridging between structural and functional connectivity aspects. However, when comparing the PT to the other three networks, contrasting regions can be observed. This could be due to biases related to the use of conventional diffusion tensors. Such tensors can only capture the principal diffusion direction, and thus makes them prone to errors induced by crossing fibers (67). As a result, this could have limited the possible resulting convergence amongst the four modalities.

CONCLUSION

In summary, the present results demonstrate a significant correlation between TMT-MS performance and GMV in the lower bank of the IFS, which was functionally characterized as being involved in cognitive tasks. Additionally, all connectivity approaches used (RS-FC, MACM, SC, and PT) converged on a network comprising of regions that overlap with the multiple-demand network. Results therefore indicate that performance (i.e., the speed at which the task is completed) may primarily depend on executive function, thus suggesting that motor speed in a more naturalistic setting should be more strongly associated with executive rather than primary motor function. Moreover, the common connectivity resulting from the different modalities used verifies that common networks can be revealed across highly divergent methods.

ACKNOWLEDGMENTS

This study was supported by the Deutsche Forschungsgemeinschaft (DFG, EI 816/4-1, LA 3071/3-1; EI 816/6-1.), the National Institute of Mental Health (R01-MH074457), and the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 604102 (Human Brain Project).

REFERENCES

1. Raghavan P. The nature of hand motor impairment after stroke and its treatment. *Curr Treat Options Cardiovasc Med* (2007) **9**(3):221–8. doi:10.1007/s11936-007-0016-3
2. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: Psychological Corporation (2001).
3. Eickhoff SB, Grefkes C. Approaches for the integrated analysis of structure, function and connectivity of the human brain. *Clin EEG Neurosci* (2011) **42**(2):107–21. doi:10.1177/155005941104200211
4. Friston K. Functional integration and inference in the brain. *Prog Neurobiol* (2002) **68**(2):113–43. doi:10.1016/S0301-0082(02)00076-X
5. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* (2007) **8**(9):700–11. doi:10.1038/nrn2201
6. Smith SM, Vidaurre D, Beckmann CF, Glasser MF, Jenkinson M, Miller KL, et al. Functional connectomics from resting-state fMRI. *Trends Cogn Sci* (2013) **17**(12):666–82. doi:10.1016/j.tics.2013.09.016
7. Eickhoff SB, Bzdok D, Laird AR, Roski C, Caspers S, Zilles K, et al. Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *Neuroimage* (2011) **57**(3):938–49. doi:10.1016/j.neuroimage.2011.05.021
8. Laird AR, Eickhoff SB, Rottschy C, Bzdok D, Ray KL, Fox PT. Networks of task co-activations. *Neuroimage* (2013) **80**:505–14. doi:10.1016/j.neuroimage.2013.04.073
9. Fox PT, Lancaster JL, Laird AR, Eickhoff SB. Meta-analysis in human neuroimaging: computational modeling of large-scale databases. *Annu Rev Neurosci* (2014) **37**:409–34. doi:10.1146/annurev-neuro-062012-170320
10. Laird AR, Eickhoff SB, Kurth F, Fox PM, Uecker AM, Turner JA, et al. ALE meta-analysis workflows via the brainmap database: progress towards a probabilistic functional brain atlas. *Front Neuroinform* (2009) **3**:23. doi:10.3389/neuro.11.023.2009
11. Laird AR, Eickhoff SB, Fox PM, Uecker AM, Ray KL, Saenz JJ Jr, et al. The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. *BMC Res Notes* (2011) **4**:349. doi:10.1186/1756-0500-4-349
12. Albaugh MD, Ducharme S, Collins DL, Botteron KN, Althoff RR, Evans AC, et al. Evidence for a cerebral cortical thickness network anti-correlated with amygdalar volume in healthy youths: implications for the neural substrates of emotion regulation. *Neuroimage* (2013) **71**:42–9. doi:10.1016/j.neuroimage.2012.12.071
13. Lerch JP, Worsley K, Shaw WP, Greenstein DK, Lenroot RK, Giedd J, et al. Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. *Neuroimage* (2006) **31**(3):993–1003. doi:10.1016/j.neuroimage.2006.01.042
14. Alexander-Bloch A, Raznahan A, Bullmore E, Giedd J. The convergence of maturational change and structural covariance in human cortical networks. *J Neurosci* (2013) **33**(7):2889–99. doi:10.1523/JNEUROSCI.3554-12.2013
15. Evans AC. Networks of anatomical covariance. *Neuroimage* (2013) **80**:489–504. doi:10.1016/j.neuroimage.2013.05.054
16. Behrens T, Johansen-Berg H, Woolrich M, Smith S, Wheeler-Kingshott C, Boulby P, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci* (2003) **6**(7):750–7. doi:10.1038/nn1075
17. Parker GJ, Haroon HA, Wheeler-Kingshott CA. A framework for a streamline-based probabilistic index of connectivity (PICo) using a structural interpretation of MRI diffusion measurements. *J Magn Reson Imaging* (2003) **18**(2):242–54. doi:10.1002/jmri.10350
18. Cauda F, Cavanna AE, D'agata F, Sacco K, Duca S, Geminiani GC. Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. *J Cogn Neurosci* (2011) **23**(10):2864–77. doi:10.1162/jocn.2011.21624
19. Hoffstaedter F, Grefkes C, Caspers S, Roski C, Palomero-Gallagher N, Laird AR, et al. The role of anterior midcingulate cortex in cognitive motor control. *Hum Brain Mapp* (2014) **35**(6):2741–53. doi:10.1002/hbm.22363
20. Jakobs O, Langner R, Caspers S, Roski C, Cieslik EC, Zilles K, et al. Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus–context integration. *Neuroimage* (2012) **60**(4):2389–98. doi:10.1016/j.neuroimage.2012.02.037
21. He Y, Chen ZJ, Evans AC. Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* (2007) **17**(10):2407–19. doi:10.1093/cercor/bhl149
22. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron* (2009) **62**(1):42–52. doi:10.1016/j.neuron.2009.03.024
23. Koch MA, Norris DG, Hund-Georgiadis M. An investigation of functional and anatomical connectivity using magnetic resonance imaging. *Neuroimage* (2002) **16**(1):241–50. doi:10.1006/nimg.2001.1052
24. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex* (2009) **19**(1):72–8. doi:10.1093/cercor/bhn059
25. van den Heuvel MP, Mandl RC, Kahn RS, Pol H, Hilleke E. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum Brain Mapp* (2009) **30**(10):3127–41. doi:10.1002/hbm.20737
26. Damoiseaux JS, Greicius MD. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Struct Funct* (2009) **213**(6):525–33. doi:10.1007/s00429-009-0208-6
27. Clos M, Rottschy C, Laird AR, Fox PT, Eickhoff SB. Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. *Neuroimage* (2014) **99**:269–80. doi:10.1016/j.neuroimage.2014.05.030
28. Reid AT, Bzdok D, Langner R, Fox PT, Laird AR, Amunts K, et al. Multimodal connectivity mapping of the human left anterior and posterior lateral prefrontal cortex. *Brain Struct Funct* (2015):1–17. doi:10.1007/s00429-015-1060-5
29. Ashburner J, Friston KJ. Voxel-based morphometry – the methods. *Neuroimage* (2000) **11**(6):805–21. doi:10.1006/nimg.2000.0582
30. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* (2006) **31**(4):1487–505. doi:10.1016/j.neuroimage.2006.02.024
31. Nooner KB, Colcombe SJ, Tobe RH, Mennes M, Benedict MM, Moreno AL, et al. The NKI-rockland sample: a model for accelerating the pace of discovery science in psychiatry. *Front Neurosci* (2012) **6**:152. doi:10.3389/fnins.2012.00152
32. Kauranen K, Vanharanta H. Influences of aging, gender, and handedness on motor performance of upper and lower extremities. *Percept Mot Skills* (1996) **82**(2):515–25. doi:10.2466/pms.1996.82.2.515
33. Lawrie SM, MacHale SM, Cavanagh JT, O'CARROLL RE, Goodwin GM. The difference in patterns of motor and cognitive function in chronic fatigue syndrome and severe depressive illness. *Psychol Med* (2000) **30**(02):433–42. doi:10.1017/S0033291799001816
34. Fagiolo G, Waldman A, Hajnal J. A simple procedure to improve FMRIb software library brain extraction tool performance. *Br J Radiol* (2008) **81**(963):250–1. doi:10.1259/bjr/12956156
35. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal* (2001) **5**(2):143–56. doi:10.1016/S1361-8415(01)00036-6
36. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* (2002) **17**(2):825–41. doi:10.1006/nimg.2002.1132
37. Andersson JL, Jenkinson M, Smith S. *Non-Linear Registration, Aka Spatial Normalisation FMRIB Technical Report*. Oxford: FMRIB Analysis Group of the University of Oxford (2007).
38. Smith SM, Johansen-Berg H, Jenkinson M, Rueckert D, Nichols TE, Miller KL, et al. Acquisition and voxelwise analysis of multi-subject diffusion data with tract-based spatial statistics. *Nat Protoc* (2007) **2**(3):499–503. doi:10.1038/nprot.2007.45
39. Fox PT, Lancaster JL. Mapping context and content: the BrainMap model. *Nat Rev Neurosci* (2002) **3**(4):319–21. doi:10.1038/nrn789
40. Müller VI, Cieslik EC, Laird AR, Fox PT, Eickhoff SB. Dysregulated left inferior parietal activity in schizophrenia and depression: functional connectivity and characterization. *Front Hum Neurosci* (2013) **7**:268. doi:10.3389/fnhum.2013.00268
41. Rottschy C, Caspers S, Roski C, Reetz K, Dogan I, Schulz J, et al. Differentiated parietal connectivity of frontal regions for "what" and "where" memory. *Brain Struct Funct* (2013) **218**(6):1551–67. doi:10.1007/s00429-012-0476-4

42. Ashburner J, Friston KJ. Unified segmentation. *Neuroimage* (2005) **26**(3):839–51. doi:10.1016/j.neuroimage.2005.02.018
43. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage* (2009) **44**(1):83–98. doi:10.1016/j.neuroimage.2008.03.061
44. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate – based activation likelihood estimation meta-analysis of neuroimaging data: a random – effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* (2009) **30**(9):2907–26. doi:10.1002/hbm.20718
45. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. *Neuroimage* (2012) **59**(3):2349–61. doi:10.1016/j.neuroimage.2011.09.017
46. Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. *Hum Brain Mapp* (2012) **33**(1):1–13. doi:10.1002/hbm.21186
47. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* (2004) **23**:S208–19. doi:10.1016/j.neuroimage.2004.07.051
48. Behrens T, Berg HJ, Jbabdi S, Rushworth M, Woolrich M. Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? *Neuroimage* (2007) **34**(1):144–55. doi:10.1016/j.neuroimage.2006.09.018
49. Caspers S, Eickhoff SB, Rick T, von Kapri A, Kuhlen T, Huang R, et al. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *Neuroimage* (2011) **58**(2):362–80. doi:10.1016/j.neuroimage.2011.06.027
50. Nichols T, Brett M, Andersson J, Wager T, Poline J. Valid conjunction inference with the minimum statistic. *Neuroimage* (2005) **25**(3):653–60. doi:10.1016/j.neuroimage.2004.12.005
51. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci* (2010) **14**(4):172–9. doi:10.1016/j.tics.2010.01.004
52. Müller VI, Langner R, Cieslik EC, Rottschy C, Eickhoff SB. Interindividual differences in cognitive flexibility: influence of gray matter volume, functional connectivity and trait impulsivity. *Brain Struct Funct* (2015) **220**(4):2401–14. doi:10.1007/s00429-014-0797-6
53. Langner R, Eickhoff SB. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. *Psychol Bull* (2013) **139**(4):870. doi:10.1037/a0030694
54. Rottschy C, Langner R, Dogan I, Reetz K, Laird AR, Schulz JB, et al. Modelling neural correlates of working memory: a coordinate-based meta-analysis. *Neuroimage* (2012) **60**(1):830–46. doi:10.1016/j.neuroimage.2011.11.050
55. Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. *Neurosci Biobehav Rev* (2015) **48**:22–34. doi:10.1016/j.neubiorev.2014.11.003
56. Diamond A. Close interrelation of motor development and cognitive development and of the cerebellum and prefrontal cortex. *Child Dev* (2000) **71**(1):44–56. doi:10.1111/1467-8624.00117
57. Rigoli D, Piek JP, Kane R, Oosterlaan J. An examination of the relationship between motor coordination and executive functions in adolescents. *Dev Med Child Neurol* (2012) **54**(11):1025–31. doi:10.1111/j.1469-8749.2012.04403.x
58. Godefroy O, Lhullier-Lamy C, Rousseaux M. SRT lengthening: role of an alertness deficit in frontal damaged patients. *Neuropsychologia* (2002) **40**(13):2234–41. doi:10.1016/S0028-3932(02)00109-4
59. Godefroy O, Spagnolo S, Roussel M, Boucart M. Stroke and action slowing: mechanisms, determinants and prognosis value. *Cerebrovasc Dis* (2010) **29**(5):508–14. doi:10.1159/000297968
60. Stuss DT, Alexander MP, Shallice T, Picton TW, Binns MA, Macdonald R, et al. Multiple frontal systems controlling response speed. *Neuropsychologia* (2005) **43**(3):396–417. doi:10.1016/j.neuropsychologia.2004.06.010
61. Grefkes C, Nowak DA, Eickhoff SB, Dafotakis M, Küst J, Karbe H, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol* (2008) **63**(2):236–46. doi:10.1002/ana.21228
62. Staines WR, McIlroy WE, Graham SJ, Black SE. Bilateral movement enhances ipsilesional cortical activity in acute stroke: a pilot functional MRI study. *Neurology* (2001) **56**(3):401–4. doi:10.1212/WNL.56.3.401
63. Roski C, Caspers S, Lux S, Hoffstaedter F, Bergs R, Amunts K, et al. Activation shift in elderly subjects across functional systems: an fMRI study. *Brain Struct Funct* (2014) **219**(2):707–18. doi:10.1007/s00429-013-0530-x
64. Hardwick RM, Lesage E, Eickhoff CR, Clos M, Fox P, Eickhoff SB. Multimodal connectivity of motor learning-related dorsal premotor cortex. *NeuroImage* (2015) **123**:114–28. doi:10.1016/j.neuroimage.2015.08.024
65. Deco G, Corbetta M. The dynamical balance of the brain at rest. *Neuroscientist* (2011) **17**(1):107–23. doi:10.1177/1073858409354384
66. Mechelli A, Friston KJ, Frackowiak RS, Price CJ. Structural covariance in the human cortex. *J Neurosci* (2005) **25**(36):8303–10. doi:10.1523/JNEUROSCI.0357-05.2005
67. Yoldemir B, Ng B, Abugharbieh R. Effects of tractography approach on consistency between anatomical and functional connectivity estimates. *Biomedical Imaging (ISBI), 2014 IEEE 11th International Symposium*. Beijing (2014). p. 250–53.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2015 Camilleri, Reid, Müller, Grefkes, Amunts and Eickhoff. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

STUDY 2

Definition and characterization of an extended multiple-demand network

---

Julia A. Camilleri[1,2,3], Veronika I. Müller[1,2,3], Peter Fox[4], Angela R. Laird[5], Felix Hoffstaedter[1,2,3], Tobias Kalenscher[6], Simon B. Eickhoff[1,2,3]

[1]Research Centre Jülich, Institute of Neuroscience and Medicine (INM-1, 7), Jülich, Germany

[2]Institute of Systems Neuroscience, Heinrich Heine University, Düsseldorf, Germany

[3]Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Düsseldorf, Germany

[4]Research Imaging Institute, University of Texas Health Science Center at San Antonio, Texas, United States

[5]Department of Physics, Florida International University, Miami, United States

[6]Institute of Comparative Psychology, Heinrich Heine University, Düsseldorf Germany

NeuroImage (2018)
doi: 10.1016/j.neuroimage.2017.10.020
Impact Factor (2016): 5.835

Own contributions	Conception and design of study
	Reviewing and adapting analysis code
	Statistical data analysis
	Interpretation of results
	Preparing figures
	Writing paper
	Total contribution 80%

NeuroImage 165 (2018) 138–147

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Definition and characterization of an extended multiple-demand network

J.A. Camilleri [a,b,c,*], V.I. Müller [a,b,c], P. Fox [d], A.R. Laird [e], F. Hoffstaedter [a,b,c], T. Kalenscher [f], S.B. Eickhoff [a,b,c]

[a] *Research Centre Jülich, Institute of Neuroscience and Medicine (INM-1,7), 52425 Jülich, Germany*
[b] *Institute of Systems Neuroscience, Heinrich Heine University, Universitätstraße 1, 40225 Düsseldorf, Germany*
[c] *Institute of Clinical Neuroscience and Medical Psychology, Heinrich Heine University, Universitätstraße 1, 40225 Düsseldorf, Germany*
[d] *Research Imaging Institute, University of Texas Health Science Center at San Antonio, Texas, United States*
[e] *Department of Physics, Florida International University, Miami, United States*
[f] *Institute of Comparative Psychology, Heinrich Heine University, Universitätstraße 1, 40225 Düsseldorf Germany*

ARTICLE INFO

Keywords:
Executive functioning
Functional connectivity
Hierarchical clustering
Higher cognitive functions
Meta-analytical connectivity modeling

ABSTRACT

Neuroimaging evidence suggests that executive functions (EF) depend on brain regions that are not closely tied to specific cognitive demands but rather to a wide range of behaviors. A multiple-demand (MD) system has been proposed, consisting of regions showing conjoint activation across multiple demands. Additionally, a number of studies defining networks specific to certain cognitive tasks suggest that the MD system may be composed of a number of sub-networks each subserving specific roles within the system. We here provide a robust definition of an extended MDN (eMDN) based on task-dependent and task-independent functional connectivity analyses seeded from regions previously shown to be convergently recruited across neuroimaging studies probing working memory, attention and inhibition, i.e., the proposed key components of EF. Additionally, we investigated potential sub-networks within the eMDN based on their connectional and functional similarities. We propose an eMDN network consisting of a core whose integrity should be crucial to performance of most operations that are considered higher cognitive or EF. This then recruits additional areas depending on specific demands.

1. Introduction

Executive functioning is central to coordinated, goal-directed behavior and thought to play a major role in a wide range of different psychiatric and neurological diseases (Zelazo and Müller, 2002). However, despite its significance and the consequent effort directed towards investigating it, the true nature of executive abilities remains rather elusive. One of the main reasons for this is that executive functioning is probably not a single process but should be rather regarded as a “macro-construct” that includes different aspects of mental functioning (Zelazo et al., 1997). Moreover, the lack of a clear formal definition of executive functioning is also due to the nature of the aspects that constitute it, the relationship among these and their contribution to the overall concept (Lezak, 1982). Mirroring this lack of formal definition of executive functioning, several brain regions and networks have been implicated as the brain's underpinning of executive functioning. In this perspective, the network aspect is particularly important, as there is a growing consensus that higher cognitive, including “executive”, functions depend on distributed networks rather than any particular region in isolation (Corbetta and Shulman, 2002). In addition, it has been shown that “executive networks” seem to sustain a wide range of cognitive functions (Fedorenko et al., 2013; Cabeza and Nyberg, 2000), prompting the term multiple-demand network (MD; Duncan and Owen, 2000; Duncan, 2010). Unfortunately, different perspectives, operationalizations and traditions have resulted in a rather diverse co-existence of labels for brain networks associated with executive control. One is the aforementioned multiple-demand network as defined by convergent activation across multiple cognitive tasks in fMRI (Duncan, 2010). A very similar example is the cognitive control network, which has been described as a network that includes a set of cortical regions that are consistently co-active during cognitive control tasks (Cole and Schneider, 2007). Other comparable networks include the fronto-parietal control system (Vincent et al., 2008), the superordinate cognitive control network (Niendam et al., 2012), the task-positive network (Fox et al., 2005), and the extrinsic mode network (Hugdahl et al., 2015). In addition, there seems to be some convergence with concepts such as the salience network (Seeley et al., 2007), the ventral attention network (VAN) (Vossel et al., 2014; Japee et al., 2015) and the dorsal attention

---

[*] Corresponding author. Research Centre Jülich, Institute of Neuroscience and Medicine (INM-1,7), 52425 Jülich, Germany.
E-mail address: julia.camilleri@uni-duesseldorf.de (J.A. Camilleri).

https://doi.org/10.1016/j.neuroimage.2017.10.020
Received 28 July 2017; Received in revised form 6 October 2017; Accepted 9 October 2017
Available online 13 October 2017
1053-8119/© 2017 Elsevier Inc. All rights reserved.

network (DAN) (Corbetta et al., 2008; Corbetta and Shulman, 2002), besides other functional networks such as the working memory network (Rottschy et al., 2012), the vigilant attention network (Langner and Eickhoff, 2013), and the inhibitory control network (Cieslik et al., 2015).

Inspecting these various networks, it quickly becomes evident, that virtually all of them indicate the posterior-medial frontal cortex [pre-supplementary motor area and adjacent middle cingulate cortex (pre-SMA/MCC)], the bilateral anterior insula (aINS), intraparietal sulcus (IPS), and posterior inferior frontal sulcus (IFS) as regions contributing to executive processing. Interestingly, these regions were suggested as part of a multiple-demand network (MDN) by Duncan (2010) and emerged from a recent integration (Müller et al., 2015) of three large-scale neuroimaging meta-analyses on working memory (Rottschy et al., 2012), vigilant attention (Langner and Eickhoff, 2013), and inhibitory control (Cieslik et al., 2015).

In turn, there are also several brain regions not included in these rather conservative definitions of regions of the MDN but can nevertheless be found in several of the aforementioned networks. These include, e.g., the basal ganglia and thalamus, the more anterior IFS/dorsolateral prefrontal cortex, or the dorsal premotor cortex. In addition, the MDN as suggested by Duncan (2010) or Müller et al. (2015) are based on the (most robust) convergence of activation data and do not directly consider the perspective of a distributed neural network. In light of these two observations, it seems likely that the previously established regions of the MDN entertains close interactions with several other regions that may be considered as an extended MDN (eMDN) complementing the original regions.

Mapping and characterizing this broader MDN is the core aim of this study. In more detail, this entails the computation of robust connectivity maps for each original MDN region by combining task-free and task-based functional connectivity analyses. The eMDN is then identified by convergence across multiple of these robust connectivity maps for the seed regions. Next, we functionally characterize the ensuing eMDN regions by an objective analysis of experimental paradigms that evoke activation of these regions. Finally, we investigate potential cliques of regions within the extended MDN based on similarities in connectional and functional profiles.

2. Methods

2.1. Seed definition

The seed regions for this work were based on the meta-analytically defined multiple-demand network of Müller et al. (2015), which was defined by performing a conjunction across three large-scale neuroimaging meta-analyses on working memory (Rottschy et al., 2012, covering e.g., n-back, Sternberg or delayed match-to sample tasks), vigilant attention (Langner and Eickhoff, 2013, covering e.g., stimulus detection or simple reaction tasks), and inhibitory control (Cieslik et al., 2015; covering, e.g., Stroop, Simon or Flanker tasks). The regions present in the resulting conjunction consist of the bilateral anterior insula, bilateral inferior frontal junction/gyrus, right middle frontal gyrus, right intraparietal sulcus and the posterior medial frontal cortex extending from the midcingulate cortex to the (pre-) supplementary motor area.

To ensure that the functional connectivity analyses of all seed regions were based on the same number of voxels, in spite of unequal cluster sizes, we represented each seed by a 5 mm sphere around its center of gravity. The only exception to this approach was the posterior medial frontal cortex cluster whose center of gravity was located between MCC and pre-SMA. Given the presence of distinct peaks within both MCC and pre-SMA, both of these were retained as seed coordinates. Thus, eight seed coordinates (Fig. 1; Table 1) were used for whole-brain resting-state and meta-analytic connectivity modeling analyses that were intersected to define the robust, state-independent connectivity map for each seed.

2.2. Resting-state functional connectivity

Seed-based RS analysis was used to investigate the task-independent functional connectivity of each original MDN region. Resting-state fMRI images of 192 healthy volunteers were obtained from the Enhanced Nathan Kline Institute – Rockland Sample (Nooner et al., 2012). The local ethics committee of the Heinrich-Heine University in Düsseldorf approved re-analysis of the data. During RS acquisition, subjects were instructed to look at a fixation cross, not think about anything in particular and not to fall asleep. Images were acquired on a Siemens TimTrio 3T scanner using BOLD contrast [gradient-echo EPI pulse sequence, TR = 1.4 s, TE = 30 ms, flip angle = 65°, voxel size = 2.0 mm × 2.0 mm × 2.0 mm, 64 slices]. Physiological and movement artifacts were removed from the RS data by using FIX (FMRIB's ICA-based Xnoiseifier, version 1.061 as implemented in FSL 5.0.9; Salimi-Khorshidi et al., 2014; Griffanti et al., 2014), which decomposes the data into independent components (ICs) and identifies noise components using a large number of distinct spatial and temporal features via pattern classification. Unique variance related to the identified artefactual ICs is then regressed from the data together with 24 movement parameters (including derivatives and 2nd order effects as previously described and evaluated; cf. Satterthwaite et al., 2013). Data were further preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London) and in-house Matlab scripts. The first four scans were excluded prior to further analyses, the remaining EPI images corrected for head movement using a two-pass (alignment to the initial volume followed by alignment to the mean after the first pass) affine registration. The mean EPI image for each subject was then spatially

Table 1
Seed coordinates derived from the meta-analytically defined multiple-demand network by Müller et al. (2015).

	x	y	z
Right aINS	38	22	−2
Left aINS	−36	18	−2
Right IFJ/IFG	48	10	28
Left IFJ/IFG	−48	10	30
Right MFG	44	38	20
Right IPC/IPS	44	−44	46
MCC	4	20	44
pre-SMA	−2	6	58

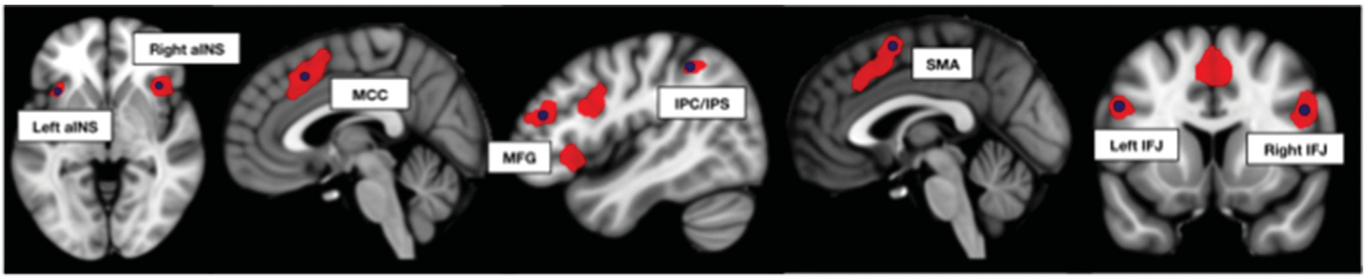

Fig. 1. Seed regions (shown in dark blue) derived from the meta-analytically defined multiple-demand network by Müller et al., (2015) (shown in red).

normalized to the ICBM-152 reference space using the "unified segmentation" approach (Ashburner and Friston, 2005). The resulting deformation was applied to the individual EPI volumes, which were subsequently smoothed with a 5-mm FWHM Gaussian kernel to improve the signal-to-noise ratio and to compensate for residual anatomic variations. The time-course of each seed was extracted per subject by computing the first eigenvariate of the time-series of all voxel within 5 mm of the seed coordinate. To reduce spurious correlations, variance explained by the mean white matter and cerebral spinal fluid signal were removed from the time series, which was subsequently band-pass filtered preserving frequencies between 0.01 and 0.08 Hz. The processed time-course of each seed was then correlated with the (identically processed) time-series of all other gray-matter voxels in the brain using linear (Pearson) correlation. The resulting correlation coefficients were transformed into Fisher's *z*-scores, which were entered in a second-level ANOVA for group analysis including age and gender as covariates of no interest. The data was then subjected to non-parametric permutation based inference and thresholded at $p < 0.05$ corrected for multiple comparisons on the cluster level.

2.3. *Meta-analytical connectivity modeling (MACM)*

Meta-analytical connectivity modeling (MACM) was used to characterize the whole-brain connectivity of each seed region during the execution of experimental tasks through the identification of significant co-activations with the seed across many individual experiments

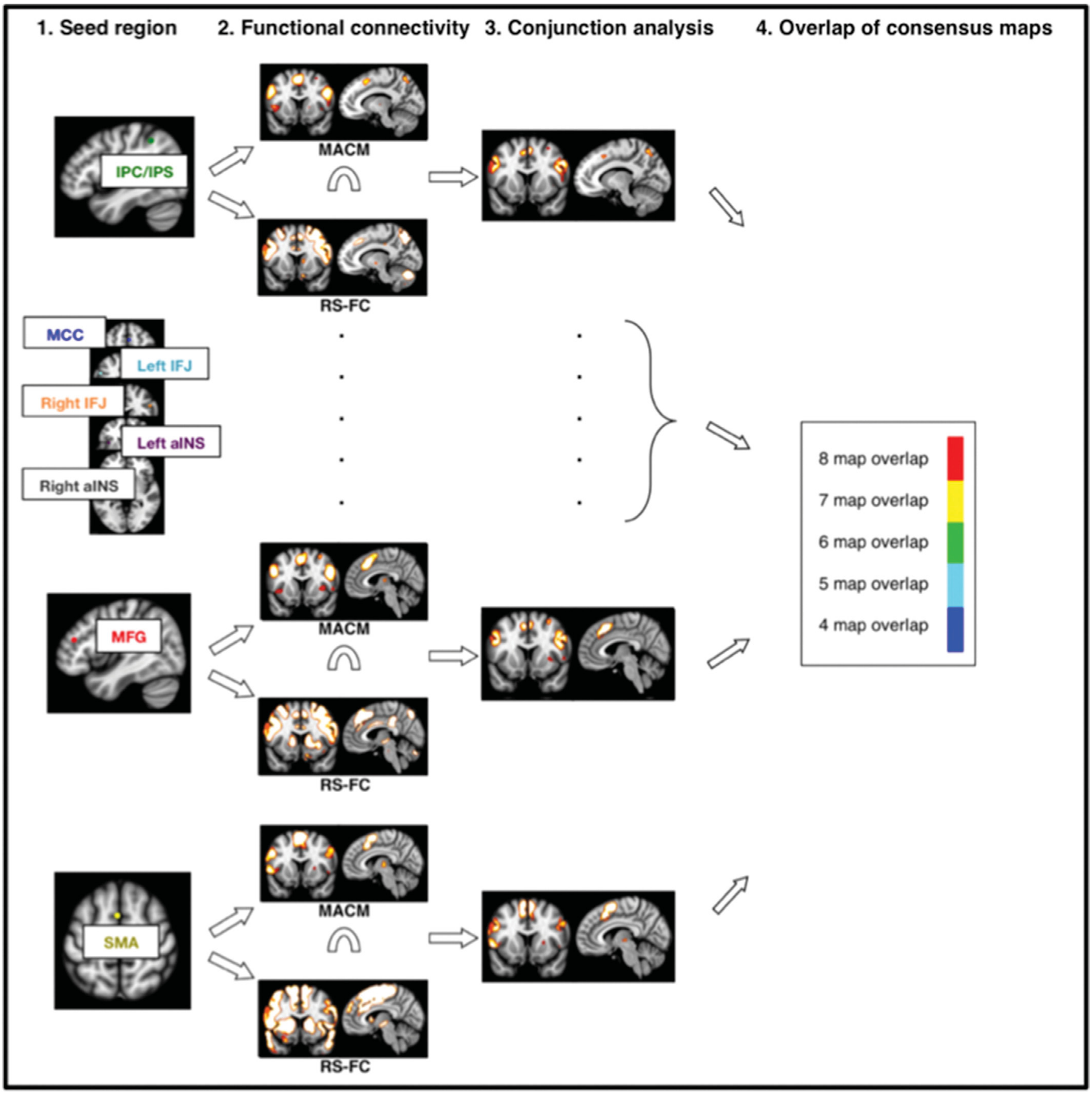

Fig. 2. Workflow used for the delineation of the extended multiple demand network entailing the computation of task-free (RS-FC) and task-based (MACM) connectivity maps for each seed region which were then converged to identify the eMDN.

(Eickhoff et al., 2009; Laird et al., 2013). It thus benefits from the fact that a large number of such studies are now available in a highly standardized format through the BrainMap database (Fox et al., 2014; Laird et al., 2011). First, all experiments that feature at least one focus of activation in a particular seed region were identified in BrainMap. Next, the retrieved experiments were subjected to a quantitative meta-analysis using the revised activation likelihood estimation (ALE) algorithm (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012). This algorithm treats the activation foci reported in the experiments as spatial probability distributions rather than single points, and aims at identifying brain areas that show convergence of activation across experiments. Importantly, convergence was assessed across all the activation foci reported in these experiments. Consequently, any significant convergence outside the seed indicates consistent co-activation and hence functional connectivity. Statistical significance was assessed at $p < 0.05$ after correction for multiple comparisons (Eickhoff et al., 2016).

2.4. Identification of the extended multiple-demand network

The key aim of our study was the definition of an extended multiple-demand system by identifying the brain regions that are strongly connected to multiple of the original MDN regions as defined by Müller et al. (2015). We identified areas that show robust task-independent as well as task-dependent functional connectivity with multiple of the seeds (Amft et al., 2015) using the workflow outlined in Fig. 2. First we generated the task-independent (RS) and task-dependent (MACM) whole-brain functional connectivity map for each seed. Then a conjunction analysis was performed across the RS and MACM functional connectivity maps for each seed using the minimum statistic (Nichols et al., 2005). This resulted in eight consensus functional connectivity maps, showing the areas consistently interacting with each seed across different brain states (cf. Clos et al., 2014; Hardwick et al., 2015). The extended multiple-demand network was then delineated by identifying all regions that were significantly connected with multiple seeds, i.e., regions in which the consensus connectivity maps of at least half of the seeds overlapped. In order to exclude smaller regions of putatively spurious overlap an additional extent-threshold of 10 continuous voxels was applied.

2.5. Functional characterization of extended MDN regions

The resulting regions (represented by their peak coordinates) of the extended multiple-demand network were then functionally characterized based on the meta-data from the BrainMap database (Laird et al., 2009, 2011; Fox and Lancaster, 2002), using both forward and reverse inference, as performed in previous studies (Müller et al., 2013; Rottschy et al., 2013). The key idea behind this approach is to identify all experiments that activate a particular region of interest and then analyze the experimental meta-data describing the experimental settings that were employed in these. This allows statistical inference on the type of tasks that evoke activation in a particular region.

In BrainMap, tasks are coded along two dimensions. Behavioral domains (BD) describe the cognitive processes probed by an experiment, while paradigm classes (PC) label the respective task used. In the forward inference approach, the functional profile was determined by identifying taxonomic labels for which the probability of finding activation in the respective region/set of regions was significantly higher than the overall (*a priori*) chance across the entire database. That is, we tested whether the conditional probability of activation given a particular label [P(Activation|Task)] was higher than the baseline probability of activating the region(s) in question *per se* [P(Activation)]. Significance was established using a binomial test [$p < 0.05$, corrected for multiple comparisons using false discovery rate (FDR)]. In the reverse inference approach, the functional profile was determined by identifying the most likely behavioral domains, given activation in a particular region/set of regions. This likelihood P(Task|Activation) can be derived from P(Activation|Task) as well as P(Task) and P(Activation) using Bayes' rule. Significance (at $p < 0.05$, corrected for multiple comparisons using FDR) was then assessed by means of a chi-squared test.

2.6. Clustering of extended MDN regions

The last objective was to elucidate the relationships between eMDN regions and to identify potential cliques among them, i.e., sub-networks within the eMDN. To this end, we performed hierarchical cluster analysis of the eMDN regions based on their: (1) resting-state functional connectivity patterns, (2) whole-brain co-activation maps, and (3) functional profiles yielded by the BrainMap based decoding. Resting-state functional connectivity between all regions of the identified eMDN was computed using the FSLNets toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). Partial temporal correlations between all regions' time series data were computed to estimate pairwise functional connectivity (Marrelec et al., 2006). For each pairwise connection, Fisher's Z–transformed functional connectivity values were submitted to one-sample t-tests. The resulting t values, reflecting connection strength as well as consistency across the sample, were z-transformed (into units of the standard normal distribution). This connectivity matrix was then fed into the WARD clustering.

Of note, all features entered the analyses without any thresholding for significance, which is a distinction from the analyses described above but necessary in order to preserve the full pattern of the respective connectional and functional profiles. The concept behind hierarchical clustering is to group the initial elements (regions) in a stepwise fashion such that elements within a cluster have features that are as homogeneous as possible while different clusters are maximally distinct from each other. This was achieved through an agglomerative approach in which clusters initially formed by individual regions that are subsequently merged according to their similarity using standardized Euclidean distances and Ward's incremental sum of squares method (Eickhoff et al., 2011; Timm, 2002). This hierarchical approach then revealed cliques of eMDN regions at different level of granularity based on resting-state connectivity, MACM co-activation and functional activation patterns.

2.7. Contrast analyses of functional differences

Finally, to examine the specificity of the functional profiles of the three different cliques we performed contrast analyses which were constrained to the experiments in BrainMap that activated the regions belonging to each of the 3 clusters. This was done using the “Behavioural Domain” meta-categories in the BrainMap database and forward inference to compare the activation probabilities between each pair of cliques given a particular behavioural domain, compared with the *a priori* probability of any focus to lie in either of the two compared cliques. This was done by means of a binomial test ($p < 0.05$, FDR-corrected for multiple comparisons).

3. Results

3.1. The extended multiple-demand network

The extended multiple-demand network was defined in a stepwise fashion, first identifying regions that were robustly connected with all of the seed regions, i.e., found in all eight consensus connectivity maps. This yielded six clusters located in the bilateral inferior frontal junction (IFJ) extending into the inferior frontal gyrus, the bilateral anterior insula (aINS), and the bilateral pre-SMA (Fig. 3 in red). When reducing the required overlap to seven consensus connectivity maps, four additional clusters emerged. These were located in the bilateral intraparietal sulcus (IPS), right middle frontal gyrus (MFG) extending into the inferior frontal sulcus (IFS), as well as in the left dorsal pre-motor cortex (dPMC) (Fig. 3 in yellow). At a threshold of six overlapping consensus connectivity maps an additional cluster in the left MFG/IFS was observed (Fig. 3 in green).

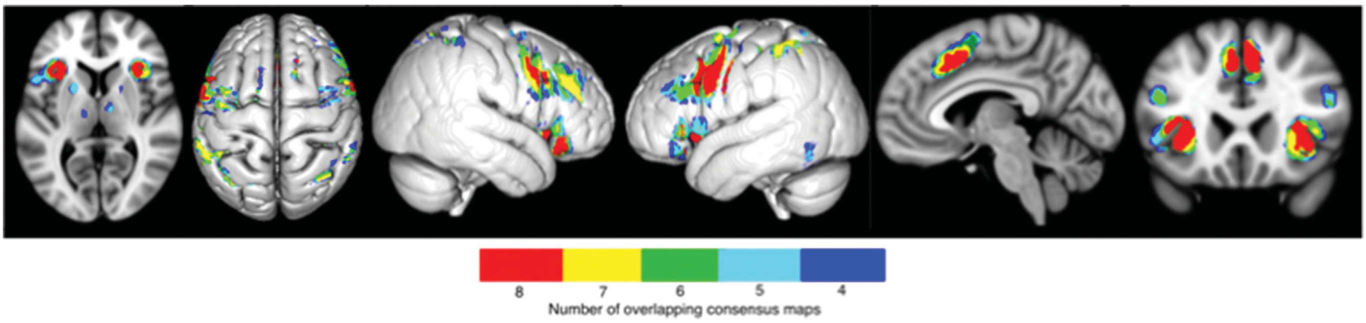

Fig. 3. Results showing the different resulting extended networks depending on the number of overlapping consensus maps. Eight overlapping consensus maps yielded clusters located in the bilateral IFJ/IFG, bilateral aINS, and bilateral pre-SMA (in red). Seven overlapping maps resulted in the addition of the bilateral IPS, right MFG/IFS and left dPMC (in yellow). Six overlapping maps resulted in the addition of the left MFG/IFS (in green). Five overlapping maps additionally included the right dPMC, left putamen, left thalamus and left ITG (in cyan). Four overlapping maps resulted in the addition of the right putamen and right thalamus (in blue).

The network formed from five overlapping connectivity maps additionally included the right dorsal premotor cortex, the left putamen, the left thalamus and the left ITG (Fig. 3 in cyan). Finally, when reducing the required overlap to four, i.e., half of the computed consensus connectivity maps, clusters in the right putamen and in the right thalamus were additionally observed (Fig. 3 in blue). The peak coordinates of all the resulting regions can be found in Table 2.

3.2. Functional characterization

The functional profiles of each of the eMDN regions were characterized based on the behavioral domain and paradigm class meta-data from the BrainMap database. This revealed that the left IFJ was associated with language and working memory, where as the right IFJ was associated with spatial cognition and attention. Both IPS clusters were associated with working memory while the right IPS was found to be associated to functions related to spatial cognition, reasoning, perception, attention, action control and language. Both aINS clusters showed associations with language. The right aINS showed additional associations with action preparation, cognition and sensation. The bilateral pre-SMA were associated with language and working memory. Moreover, the left pre-SMA was associated with speech exection while the right pre-SMA was associated with working memory and attention. The subcortical clusters, namely the bilateral putamen and the bilateral thalamus, were all found to be associated with sensation and action. The cluster in the right MFG/IFS was linked to cognition and working memory, that in the left MFG/IFS to reasoning and working memory. Both dPMC clusters were related to action, perception, working memory, action control. In addition, the left dPMC cluster was linked to attention, the right to spatial cognition. Finally, the cluster in the left ITG was linked to emotion, perception, language, and memory.

Table 2
Peak coordinates of resulting regions of the extended multiple demand network.

Number of overlapping consensus maps	Region	Coordinates of main peak		
		x	y	z
8	Left IFJ	−46	6	30
	Right IFJ	50	12	28
	Left aINS	−32	20	2
	Right aINS	36	22	0
	Left SMA/pre-SMA	−4	14	44
	Right SMA/pre-SMA	6	18	46
7	Left IPS	−32	−52	46
	Right IPS	32	−58	48
	Right MFG/IFS	44	36	20
	Left dPMC	−28	−4	52
6	Left MFG/IFS	−44	32	22
5	Right dPMC	32	0	52
	Left Putamen	−20	6	4
	Right Thalamus	10	−12	8
	Left ITG	−46	−60	−10
4	Right Putamen	22	6	4
	Left Thalamus	−10	−16	6

3.3. Clustering of extended MDN regions

The hierarchical clustering revealed several cliques within the eMDN that were present across the different features, i.e., resting-state connectivity, MACM co-activation and function but also feature-specific patterns (Fig. 4).

Across all analyses, the bilateral thalamus and putamen were consistently grouped together. In turn, the bilateral aINS and bilateral pre-SMA showed high similarity in resting-state connectivity and co-activation profiles but were slightly more divergent in terms of their functional profile. In the latter, the bilateral pre-SMA formed a cluster with the left IPS, which was then joined by the bilateral MFG/IFS and later by the bilateral aINS. In clustering based on MACM co-activation, the bilateral MFG/IFS also showed a close connection to the aINS and pre-SMA cluster. Conversely, in RS clustering the bilateral MFG/IFS showed a closer association with the bilateral IFJ. Additionally, the bilateral IFJ, the bilateral IPS and the left ITG showed high similarity in the co-activation and functional clustering. However, when the feature being assessed was RS connectivity the bilateral IPS was first closely grouped with the ITG, which was then joined by clusters consisting of the bilateral IFJ and the bilateral MFG/IFS and another cluster consisting of the bilateral dPMC. On the other hand, the bilateral dPMC formed a rather separate cluster in the clustering based on function and co-activation as highlighted in purple in Fig. 4.

The hierarchical clustering results thus revealed three main cliques within the eMDN, namely a subcortical cluster, i.e., bilateral putamen and thalamus, a cluster consisting of the pre-SMA, aINS and the MFG/IFS and another cluster consisting of the IFJ, IPS, dPMC and left ITG, with the latter being less consistent across features.

3.4. Contrast analyses of functional differences

The results of the contrast analyses of the functional profiles of the three cliques further highlighted some functional differences between the sub-networks. Namely, the results indicated that the subcortical cluster showed the strongest associations with functions that are related to perception and action execution when compared to the other two clusters. Additionally, the cluster consisting of the bilateral IFJ, IPS, dPMC and left ITG was strongly associated with functions such as action execution, spatial cognition, action observation and motor learning when compared to the cluster consisting of the bilateral pre-SMA, aINS and the MFG/IFS. Inversely, the latter cluster was found to be more strongly associated with functions such as interoception, speech execution, social cognition and emotion when compared to the cluster consisting of the

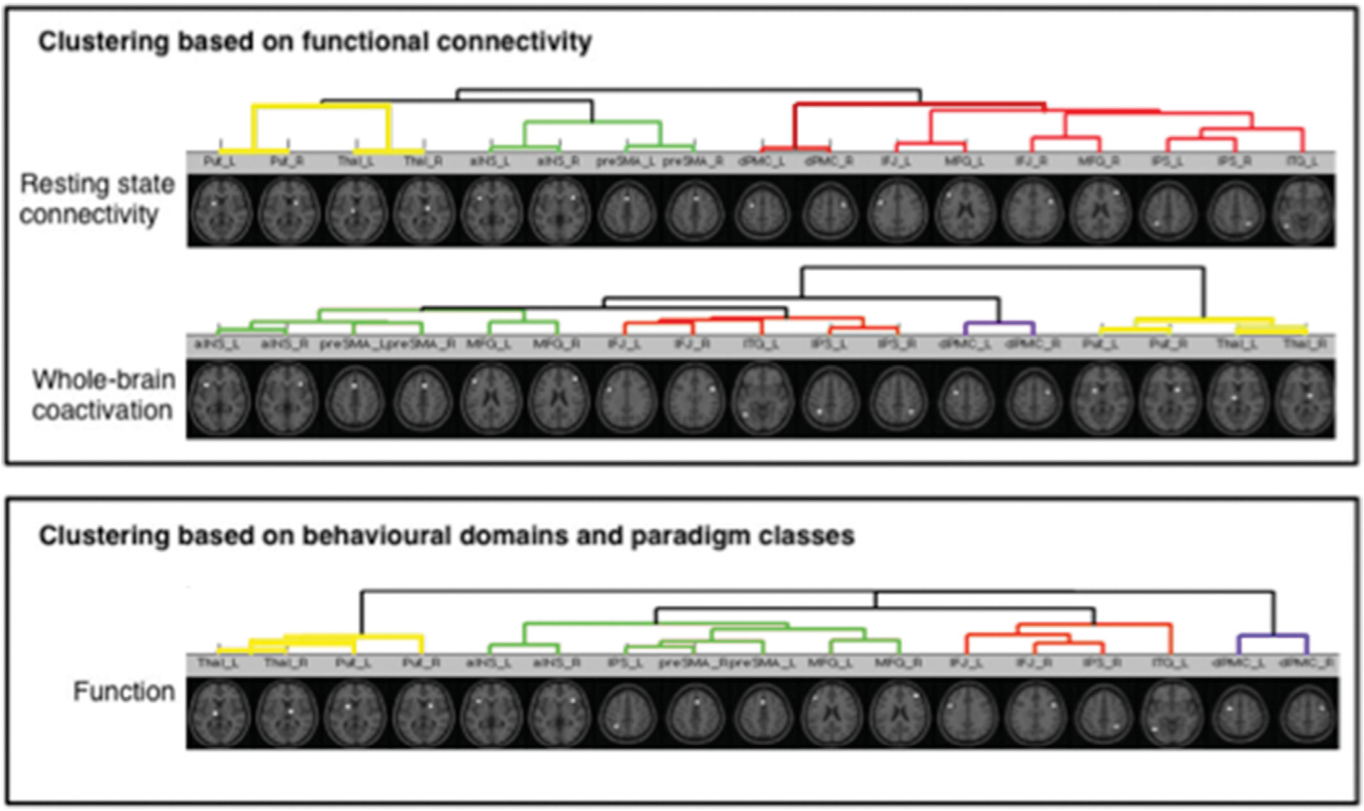

Fig. 4. Clustering of the extended MDN regions based on resting state connectivity, whole brain co-activation and behavioural domains and paradigm classes. The different colours represent the grouping that resulted from the different clustering analyses.

bilateral IFJ, IPS, dPMC and left ITG. The results of these analyses are shown in Fig. 5.

4. Discussion

The goal of the current study was to establish a robust definition of the extended multiple-demand network (eMDN) comprising regions that are either part of the previously meta-analytically defined MDN (Müller et al., 2015) or closely connected to multiple of these regions. To achieve this we first performed task-dependent and task-independent functional connectivity analyses seeded from the original MDN regions and performed a per-seed conjunction analysis resulting in a consensus connectivity map of each seed region. Subsequently, eMDN regions were defined by identifying those locations where at least half of these consensus connectivity map overlapped. The delineated eMDN regions where then functionally characterized by the paradigms that evoke activation in these regions. Finally, we employed hierarchical clustering based on similarities in task-dependent and task-independent functional connectivity as well as functional profiles to identify cliques of regions within this eMDN.

4.1. The extended multiple-demand network

In total, we identified 17 regions in which the consensus functional connectivity maps of more than half of the seed-regions overlapped and which we hence consider part of the eMDN. All these regions resonate

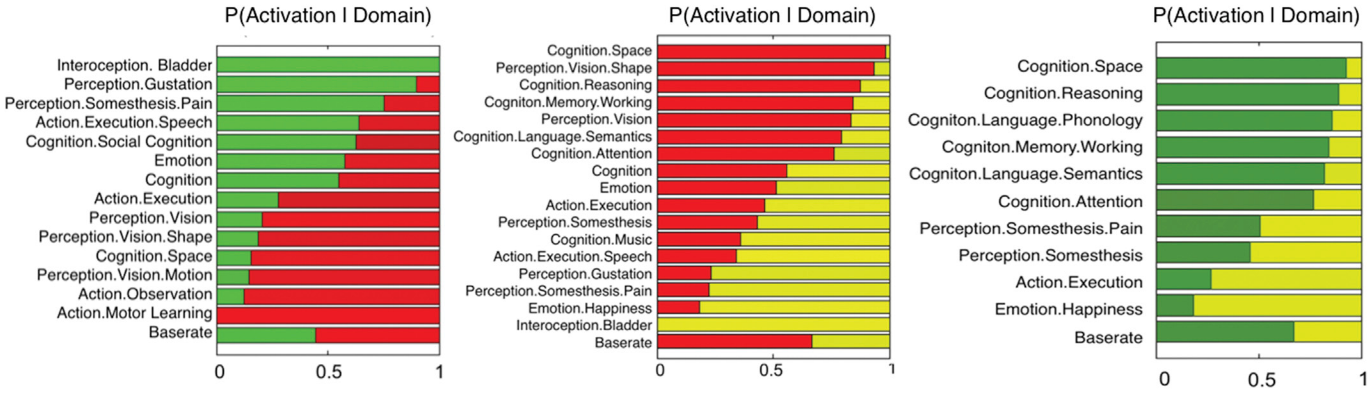

Fig. 5. Functional differences between each pair of sub-networks (cluster consisting of the pre-SMA, aINS and the MFG/IFS is shown in green; cluster consisting of the IFJ, IPS, dPMC and left ITG is shown in red; sub-cortical cluster i.e., bilateral putamen and thalamus is shown in yellow). "Behavioral Domain" meta-categories in the BrainMap database were used to perform forward inference to determine the above-chance differences in activating either set of regions given a particular behavioural domain. The baserate denotes the general probability of BrainMap activation of the given seeds.

well with regions previously implicated as part of the multiple-demand system by Duncan (2010, 2013) based on various task-activation studies and results from non-human primates. That is, by taking a complementary approach starting from a network that was robustly defined over hundreds of neuroimaging findings and mapping regions consistently connected to these across mental states (cf. Amft et al., 2015), we corroborated previous views of the multiple-demand system. We would argue that our work reconciles previous accounts of an MDN (Müller et al., 2015; Duncan, 2010) together with the reported involvement of several additional areas in "executive" networks. In particular, we note that a full overlap of all consensus connectivity maps was only found in regions that were part of the original network resulting from a conjunction across three large-scale meta-analyses dealing of activation data for working memory (Rottschy et al., 2012), attention (Langner and Eickhoff, 2013) and inhibitory control (Cieslik et al., 2015). In turn, however, two regions implicated as MDN regions from the activation data (right MFG and IPS) did not show a full overlap of all consensus connectivity maps and were thus not part of the connectivity core. From this, we would argue that only the bilateral inferior frontal junction (IFJ) extending into the inferior frontal gyrus, the bilateral anterior insula (aINS), and the bilateral pre-SMA extending into the anterior mid-cingulate cortex (aMCC) should be considered the core eMDN based on consistent activation in executive control tasks and strong interconnectivity. Such core networks have been suggested to play a key role in enabling high levels of functional diversity and functional synchronization between brain regions (van den Heuvel and Sporns, 2013). Most evidently, this core eMDN is made up of regions that make up the saliency network, namely the bilateral pre-SMA and bilateral aINS (Seeley et al., 2007). This network has been previously shown to play an important role in executive processing and cognitive control by initiating and maintaining cognitive sets, coordination behavioural responses and guiding behavior in general (Menon and Uddin, 2010) and is thus of no surprise that it forms part of our core eMDN. Interestingly the bilateral pre-SMA and the bilateral aINS are here joined by the bilateral IFJ. The inclusion of the IFJ in the eMDN core might be related to the role that it plays in task switching and cognitive control in general (Brass et al., 2005).

Our core eMDN is then complemented by a range of other regions that are likewise robustly connected and involved in various aspects of executive processes as detailed below, forming the extended multi-demand network.

Moreover, the regions that have been found to be part of the eMDN all seem to converge with other networks that have been found in previous studies to represent regions involved in executive functioning. Such networks include the cognitive control network (Cole and Schneider, 2007), the fronto-parietal control system (Vincent et al., 2008), the superordinate cognitive control network (Niendam et al., 2012), and the task-positive network (Fox et al., 2005) among others. This convergence, together with the fact that the eMDN is defined by looking at functional connectivity across different brain states might suggest a possible integration of such networks.

4.2. Hierarchical clustering

The hierarchical clustering revealed several cliques within the eMDN that were largely consistent across features, i.e., resting-state connectivity, MACM co-activation and function. Most notably, the subcortical structures, i.e., bilateral putamen and thalamus always clustered together. Furthermore, pre-SMA, aINS and MFG/IFS showed close associations, as did the IFJ, IPS, dPMC and left ITG, though the latter was less consistent across features (Fig. 6). These results noticeably disrupt the aforementioned core eMDN.

4.2.1. The subcortical sub-group: putamen and thalamus

The four subcortical nodes of the eMDN, i.e., regions in the bilateral putamen and the mediodorsal nucleus of the thalamus, formed the most consistent clique within the delineated executive network as they were clustered together based on resting-state connectivity, task co-activation and functional recruitment patterns. As evidenced by the functional decoding and contrast analyses via the BrainMap database, all of these regions are associated to sensorimotor processes, such as action execution and inhibition, as well as the perception of music, pain and visual stimuli. These results are thus well in line with the current literature describing the thalamus as a station, which relays nearly all incoming information from the outside world to the cortex (McCormick and Bal, 1994; Behrens et al., 2003). Furthermore, both the putamen and the thalamus have been frequently linked to pain perception (Starr et al., 2011; Kogler et al., 2015) and pain-related motor responses (Jones et al., 1991; Coghill et al., 1994). Additionally, consistent with our findings implicating this subgroup to action-related functions, both the putamen (Arsalidou et al., 2013). and the thalamus (Sommer, 2003; Guillery and Sherman, 2002) have been previously linked to motor functions and movement regulation.

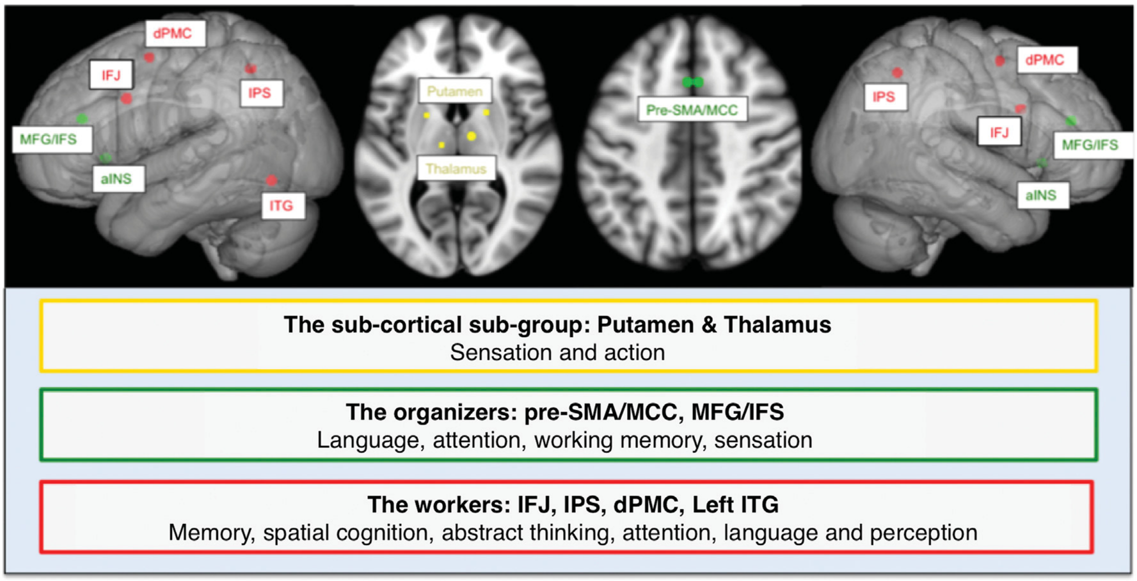

Fig. 6. Summary figure illustrating results obtained from hierarchical clustering and functional decoding analyses revealing three main cliques.

Importantly in the context of the eMDN, several studies have already implicated both the thalamus and the putamen to hold key roles in executive functioning as part of a system that links different regions, including the (pre-) frontal cortex, via subcortical loop including the struatum and thalamus (Alexander et al., 1986; Alvarez and Emory, 2006). This view has been supported by tracer studies in experimental animals revealing dense connections between prefrontal and subcortical structures (Alexander and Crutcher, 1990; Joel and Weiner, 1994; Middleton and Strick, 1997; Tanaka, 1976; Markowitsch et al., 1985). Likewise patients with basal ganglia pathology, e.g., those suffering from Huntington's and Parkinson's disease, have well documented deficits in executive functioning (Elliott, 2003), highlighting the critical role of cortico-striatal-thalamic circuits for executive processes. In summary, the presence of a subcortical clique within the eMDN is well supported by several streams of previous literature. Its interaction with (pre-) frontal and parietal cortices is classically conceptualized as parallel segregated processing loops, each connected to a different area of the cortex (Alexander et al., 1986). One is the motor loop that connects premotor and sensory areas to the primary motor cortex via the putamen and the ventral lateral thalamus (Alexander et al., 1986; Lehericy et al., 2006). In contrast, a cognitive loop connects (pre-)frontal areas, the caudate nucleus and the mediodorsal thalamus (Alexander et al., 1986; Tanaka, 1976). At first glance, these studies seem to contradict our findings which highlighted the role of the putamen and the mediodorsal thalamus in executive functioning. However more recent anatomical and physiological evidence has extended the classical view of the cortico-striatal loops and suggests substantial interaction between these loops (Houk, 2001; Seger, 2006). Consequently, cortico-striatal-thalamic circuits are now described as a spiral through which information cascading from one loop to the next rather than individual segregated loops (Haber and Knutson, 2010).

In conclusion, the presence of a distinct clique of subcortical nodes within the eMDN reflects the integration of cortico-striatal-thalamic loops into the executive system. We would argue that within a framework of interacting subcortical processing loops, these regions should play a key role in processing information from the outside environment and interacting with it.

4.2.2. Pre-SMA/MCC, aINS and MFG/IFS

Bilateral pre-SMA/MCC, aINS and MFG/IFS formed another clique that was associated with a broad functional profile including many higher cognitive processes such as language, working memory, sensation, action preparation, and attention. In contrast to the subcortical group this set showed some heterogeneity based on the assessed feature, which may be best described as a tight clustering of aINS and pre-SMA/MCC based on functional connectivity whereas the MFG/IFS shows similarities to these particularly in task-based features, i.e. function and co-activation profiles.

The broad cognitive profile of this group is consistent with previous findings from a wide range of brain imaging studies associating these regions, especially the aINS and the pre-SMA/MCC (often referred to as dACC, see Müller et al., 2015), to numerous, cognitive and affective processes (for review see: Menon and Uddin, 2010). Moreover and in line with our clustering results these two regions are well recognized as being closely related to each other, forming together what has been termed the salience network (Menon and Uddin, 2010). This network has been discussed in the initiation and maintenance of cognitive sets (Dosenbach et al., 2006), the coordination of behavioral responses (Medford and Critchley, 2010) and more general the guidance of behavior by identifying the most relevant among several intra- and extra-personal stimuli (Seeley et al., 2007). All of these processes are essential aspects of executive functioning and cognitive control. Hence, our observation that the “saliency regions” aINS and pre-SMA/MCC form the core of the MDN is well in line with the rich literature on this network. We would thus focus on two aspects that may be of particular relevance to the current findings. First, it has been argued that the “saliency network” bridges sensory, emotional and cognitive information (Craig, 2009; Gogolla et al., 2014; Menon and Uddin, 2010) through switching between the executive and the default mode network (Sridharan et al., 2008). Therefore, the aINS and pre-SMA/MCC may not only represent core regions of the eMDN but moreover initiate and orchestrate the engagement of other regions in the eMDN upon commencement of cognitive tasks. Second, it has been shown, that these regions form a convergent morphological substrate of mental illness as only the aINS and pre-SMA/MCC showed consistent atrophy in a large scale meta-analysis over structural neuroimaging studies in a wide range of psychiatric disorders (Goodkind et al., 2015). The core role of these regions within the executive eMDN as demonstrated in the current study thus resonates well with the widespread impairments in executive functioning across various mental disorders (Elliott, 2003).

The MFG in turn has not been discussed in the context of the saliency network. This fits with our observation that while being part of the same clique, albeit not consistently, this region is neither part of the MDN core based on convergent activation in executive tasks nor by virtue of consistent interaction with all seeds. This position as a relative outsider in the clique matches the fact that the MFG has previously been discussed as part of a ventral attention network (Corbetta and Shulman, 2002). Interestingly, however, this network has been often associated with functions that overlap with those attributed to the salience network, namely identifying and responding to behaviorally relevant stimuli (Vossel et al., 2014; Japee et al., 2015). As moreover the aINS is likewise often considered part of the ventral attention network, we would argue that the integration of the MFG/IFS into the clique formed by the aINS and pre-SMA/MCC may reflect often-neglected convergence between the concept of the salience and ventral attention network, respectively. In this context, it is interesting to note, that in contrast to the salience network, the ventral attention network has been reported to be strongly right-lateralized. This bodes well with our observation in the clustering on functional properties revealing close similarities between the right MFG/IFS and the salience regions while the left MFG/IFS joins this group at a later stage.

We therefore conclude that the bilateral pre-SMA/MCC, bilateral aINS and bilateral MFG/IFS form the core of the multi demand system that is not only relevant for integrating different information on the internal and external environment but also plays a key role in engaging the eMDN by regulating activity of other networks. These regions thus can be thought of as the managers of the eMDN, explaining their involvement in virtually all cognitive tasks.

4.2.3. IFJ, IPS, dPMC and left ITG

The remaining regions of the eMDN, i.e., the bilateral IFJ, IPS, dPMC and the left ITG were less consistently organized into any distinct cliques than the previously discussed sets. We would see this as an indication that these regions form, in contrast to the subcortical nodes related to sensorimotor processes and the core aINS, pre-SMA/MCC, MFG/IFS cluster, more flexible, most likely task- and brain-state dependent associations. In other words, whereas the regions above represent the coordinating core of the eMDN and are hence consistently (co-) recruited by cognitive tasks, the regions discussed in this section are integrated more flexibly into the system.

In the task-based based clustering we found a relatively close association between the IFJ and IPS. This mirrors previous findings that have linked these regions to higher-level processes (Neubert et al., 2014) such as the processing of infrequent stimuli (Verbruggen et al., 2010), preparatory cognitive control (Chikazoe et al., 2009), spatial orientating and re-orientating (Corbetta et al., 1998; Thiel et al., 2004), information updating (Vossel et al., 2011) and feedback processing (Hirose et al., 2009). Convergently, our functional decoding also associated this sub-group with functions such as spatial cognition, reasoning, and working memory.

Interestingly, the clustering analysis based on RS-FC linked the IPS with the dPMC. While at odds with the task-based results discussed previously, this association is also well supported by literature proposing that the IPS and dPMC are part of a dorsal attention network related to the top-down control of visual attention and motor preparation (Corbetta et al., 2008; Corbetta and Shulman, 2002; Genon et al., 2016). Within this dorsal attention network, the IPS and the dPMC are thought to be involved in shifting maintaining spatial attention to peripheral locations (Hopfinger et al., 2000; Kelley et al., 2008). In our view, the fact that two incongruent findings of the current study, linking the IPS with either the IFJ or the dPMC are both well supported by the current literature serves to highlight the proposed flexible recruitment of different components within this clique during the performance of cognitive tasks depending presumably on the exact demands. Our results and findings of previous studies therefore indicate that the nodes within this rather loose group fulfill specific roles needed for the implementation of higher cognitive functions while under the coordination and recruitment by previously discussed core regions and can thus be compared to the workers of a system.

5. Conclusion

In this study we provide a robust definition of an extended multiple-demand network (eMDN) based on task-dependent and task-independent functional connectivity analysis seeded from regions previously shown to be convergently recruited across neuroimaging studies probing working memory, attention and inhibition, i.e., the proposed key components of executive functioning. The eMDN was differentiated into three cliques, including a subcortical group mainly related to sensorimotor processing, a core of potential organizers (bilateral pre-SMA/MCC, aINS, MFG/IFS), and a more heterogeneous set of workers dynamically recruited based on task demands.

The proposed structure of the eMDN as the most likely neurobiological substrate for executive processes also holds important implications for the understanding of the psychological structure of executive functions. In particular, we would propose a core system whose integrity should be crucial to performance of most operations that may be considered higher cognitive or executive functions. This explains the inter-correlation of performance in different executive function tests and is consistent with the general factor of intelligence (g) (Jensen, 1998). The core network then dynamically recruits additional areas of the eMDN depending on the demands of the individual tasks, explaining divergences between the performance in different tasks probing the executive system and the presence of isolated clinical impairment. In this regard, further studies should be carried out in order to corroborate these findings and link the different regions and sub-networks to executive performance in health and disease.

Financial disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This study was supported by the Deutsche Forschungsgemeinschaft (DFG, EI 816/4–1, LA 3071/3-1), the National Institute of Mental Health (R01-MH074457), the Helmholtz Portfolio Theme “Supercomputing and Modelling for the Human Brain” and the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 7202070 (HBP SGA1).

References

Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13, 266–271.

Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9, 357–381.

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42.

Amft, M., Bzdok, D., Laird, A.R., et al., 2015. Definition and characterization of the extended default mode network. Brain Struct. Funct. 220, 103–1049.

Arsalidou, M., Duerden, E.G., Taylor, M.J., 2013. The centre of the brain: topographical model of motor, cognitive, affective, and somatosensory functions of the basal ganglia. Hum. Brain Mapp. 34, 3031–3054.

Ashburner, J., Friston, K.J., 2005. Unified segmentation. Neuroimage 26, 839–851.

Behrens, T., Johansen-Berg, H., Woolrich, M., Smith, S., Wheeler-Kingshott, C., Boulby, P., Barker, G., Sillery, E., Sheehan, K., Ciccarelli, O., 2003. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat. Neurosci. 6, 750–757.

Brass, M., Derrfuss, J., Forstmann, B., von Cramon, D.Y., 2005. The role of the inferior frontal junction area in cognitive control. Trends Cogn. Sci. (Regul. Ed.) 9, 314–316.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12, 1–47.

Chikazoe, J., Jimura, K., Hirose, S., Yamashita, K., Miyashita, Y., Konishi, S., 2009. Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J. Neurosci. 29, 15870–15877.

Cieslik, E.C., Mueller, V.I., Eickhoff, C.R., Langner, R., Eickhoff, S.B., 2015. Three key regions for supervisory attentional control: evidence from neuroimaging meta-analyses. Neurosci. Biobehav. Rev. 48, 22–34.

Clos, M., Rottschy, C., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2014. Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. Neuroimage 99, 269–280.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., Duncan, G.H., 1994. Distributed processing of pain and vibration by the human brain. J. Neurosci. 14, 4095–4108.

Cole, M.W., Schneider, W., 2007. The cognitive control network: integrated cortical regions with dissociable functions. Neuroimage 37, 343–360.

Corbetta, M., Akbudak, E., Conturo, T.E., Snyder, A.Z., Ollinger, J.M., Drury, H.A., Linenweber, M.R., Petersen, S.E., Raichle, M.E., Van Essen, D.C., 1998. A common network of functional areas for attention and eye movements. Neuron 21, 761–773.

Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. Neuron 58, 306–324.

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

Craig, A.D., 2009. How do you feel—now? the anterior insula and human awareness. Nat. Rev. Neurosci. 10.

Dosenbach, N.U., Visscher, K.M., Palmer, E.D., Miezin, F.M., Wenger, K.K., Kang, H.C., Burgund, E.D., Grimes, A.L., Schlaggar, B.L., Petersen, S.E., 2006. A core system for the implementation of task sets. Neuron 50, 799–812.

Duncan, J., 2013. The structure of cognition: attentional episodes in mind and brain. Neuron 80, 35–50.

Duncan, J., 2010. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. Trends Cogn. Sci. Regul. Ed. 14, 172–179.

Duncan, J., Owen, A.M., 2000. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends Neurosci. 23, 475–483.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Kurth, F., Fox, P.T., 2012. Activation likelihood estimation meta-analysis revisited. Neuroimage 59, 2349–2361.

Eickhoff, S.B., Bzdok, D., Laird, A.R., Roski, C., Caspers, S., Zilles, K., Fox, P.T., 2011. Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. Neuroimage 57, 938–949.

Eickhoff, S.B., Laird, A.R., Grefkes, C., Wang, L.E., Zilles, K., Fox, P.T., 2009. Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. Hum. Brain Mapp. 30, 2907–2926.

Eickhoff, S.B., Nichols, T.E., Laird, A.R., Hoffstaedter, F., Amunts, K., Fox, P.T., Bzdok, D., Eickhoff, C.R., 2016. Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. Neuroimage 137, 70–89.

Elliott, R., 2003. Executive functions and their disorders. Br. Med. Bull. 65, 49–59.

Fedorenko, E., Duncan, J., Kanwisher, N., 2013. Broad domain generality in focal regions of frontal and parietal cortex. Proc. Natl. Acad. Sci. U. S. A. 110, 16616–16621.

Fox, P.T., Lancaster, J.L., 2002. Mapping context and content: the BrainMap model. Nat. Rev. Neurosci. 3, 319–321.

Fox, P.T., Lancaster, J.L., Laird, A.R., Eickhoff, S.B., 2014. Meta-analysis in human neuroimaging: computational modeling of large-scale databases. Annu. Rev. Neurosci. 37, 409–434.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102, 9673–9678.

Genon, S., Li, H., Fan, L., Muller, V.I., Cieslik, E.C., Hoffstaedter, F., Reid, A.T., Langner, R., Grefkes, C., Fox, P.T., Moebus, S., Caspers, S., Amunts, K., Jiang, T., Eickhoff, S.B., 2016. The right dorsal premotor mosaic: organization, functions, and connectivity. Cereb. Cortex 27, 2095–2110.

Gogolla, N., Takesian, A.E., Feng, G., Fagiolini, M., Hensch, T.K., 2014. Sensory integration in mouse insular cortex reflects GABA circuit maturation. Neuron 83, 894–905.

Goodkind, M., Eickhoff, S.B., Oathes, D.J., Jiang, Y., Chang, A., Jones-Hagata, L.B., Ortega, B.N., Zaiko, Y.V., Roach, E.L., Korgaonkar, M.S., 2015. Identification of a common neurobiological substrate for mental illness. JAMA psychiatry 72, 305–315.

Griffanti, L., Salimi-Khorshidi, G., Beckmann, C.F., Auerbach, E.J., Douaud, G., Sexton, C.E., Zsoldos, E., Ebmeier, K.P., Filippini, N., Mackay, C.E., 2014. ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging. Neuroimage 95, 232–247.

Guillery, R., Sherman, S.M., 2002. Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. Neuron 33, 163–175.

Haber, S.N., Knutson, B., 2010. The reward circuit: linking primate anatomy and human imaging. Neuropsychopharmacology 35, 4–26.

Hardwick, R.M., Lesage, E., Eickhoff, C.R., Clos, M., Fox, P., Eickhoff, S.B., 2015. Multimodal connectivity of motor learning-related dorsal premotor cortex. Neuroimage 123, 114–128.

Hirose, S., Chikazoe, J., Jimura, K., Yamashita, K., Miyashita, Y., Konishi, S., 2009. Sub-centimeter scale functional organization in human inferior frontal gyrus. Neuroimage 47, 442–450.

Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3, 284–291.

Houk, J.C., 2001. Neurophysiology of frontal-subcortical loops. Frontal-Subcortical Circuits psychiatry Neurol. 92–113.

Hugdahl, K., Raichle, M.E., Mitra, A., Specht, K., 2015. On the existence of a generalized non-specific task-dependent network. Front. Hum. Neurosci. 9.

Japee, S., Holiday, K., Satyshur, M.D., Mukai, I., Ungerleider, L.G., 2015. A role of right middle frontal gyrus in reorienting of attention: a case study. Front. Syst. Neurosci. 9, 23.

Jensen, A.R., 1998. The G Factor: the Science of Mental Ability.

Joel, D., Weiner, I., 1994. The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. Neuroscience 63, 363–379.

Jones, A.K., Brown, W.D., Friston, K.J., Qi, L.Y., Frackowiak, R.S., 1991. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc. Biol. Sci. 244, 39–44.

Kelley, T.A., Serences, J.T., Giesbrecht, B., Yantis, S., 2008. Cortical mechanisms for shifting and holding visuospatial attention. Cereb. Cortex 18, 114–125.

Kogler, L., Müller, V.I., Chang, A., Eickhoff, S.B., Fox, P.T., Gur, R.C., Derntl, B., 2015. Psychosocial versus physiological stress—meta-analyses on deactivations and activations of the neural correlates of stress reactions. Neuroimage 119, 235–251.

Laird, A.R., Eickhoff, S.B., Kurth, F., Fox, P.M., Uecker, A.M., Turner, J.A., Robinson, J.L., Lancaster, J.L., Fox, P.T., 2009. ALE meta-analysis workflows via the brainmap database: progress towards a probabilistic functional brain atlas. Front. Neuroinformatics 3, 23.

Laird, A.R., Eickhoff, S.B., Rottschy, C., Bzdok, D., Ray, K.L., Fox, P.T., 2013. Networks of task co-activations. Neuroimage 80, 505–514.

Laird, A.R., Eickhoff, S.B., Fox, P.M., Uecker, A.M., Ray, K.L., Saenz Jr., J.J., McKay, D.R., Bzdok, D., Laird, R.W., Robinson, J.L., Turner, J.A., Turkeltaub, P.E., Lancaster, J.L., Fox, P.T., 2011. The BrainMap strategy for standardization, sharing, and meta-analysis of neuroimaging data. BMC Res. Notes 4, 349–0500-4-349.

Langner, R., Eickhoff, S.B., 2013. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol. Bull. 139, 870.

Lehericy, S., Bardinet, E., Tremblay, L., Van de Moortele, P.F., Pochon, J.B., Dormont, D., Kim, D.S., Yelnik, J., Ugurbil, K., 2006. Motor control in basal ganglia circuits using fMRI and brain atlas approaches. Cereb. Cortex 16, 149–161.

Lezak, M.D., 1982. The problem of assessing executive functions. Int. J. Psychol. 17, 281–297.

Markowitsch, H.J., Emmans, D., Irle, E., Streicher, M., Preilowski, B., 1985. Cortical and subcortical afferent connections of the primate's temporal pole: a study of rhesus monkeys, squirrel monkeys, and marmosets. J. Comp. Neurol. 242, 425–458.

Marrelec, G., Krainik, A., Duffau, H., Pélégrini-Issac, M., Lehéricy, S., Doyon, J., Benali, H., 2006. Partial correlation for functional brain interactivity investigation in functional MRI. Neuroimage 32, 228–237.

McCormick, D.A., Bal, T., 1994. Sensory gating mechanisms of the thalamus. Curr. Opin. Neurobiol. 4, 550–556.

Medford, N., Critchley, H.D., 2010. Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct. Funct. 214, 535–549.

Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214, 655–667.

Middleton, F.A., Strick, P.L., 1997. Cerebellar output channels. Int. Rev. Neurobiol. 41, 61–82.

Müller, V.I., Cieslik, E.C., Laird, A.R., Fox, P.T., Eickhoff, S.B., 2013. Dysregulated left inferior parietal activity in schizophrenia and depression: functional connectivity and characterization. Front. Hum. Neurosci. 7.

Müller, V.I., Langner, R., Cieslik, E.C., Rottschy, C., Eickhoff, S.B., 2015. Interindividual differences in cognitive flexibility: influence of gray matter volume, functional connectivity and trait impulsivity. Brain Struct. Funct. 220, 2401–2414.

Neubert, F., Mars, R.B., Thomas, A.G., Sallet, J., Rushworth, M.F., 2014. Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. Neuron 81, 700–713.

Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J., 2005. Valid conjunction inference with the minimum statistic. Neuroimage 25, 653–660.

Niendam, T.A., Laird, A.R., Ray, K.L., Dean, Y.M., Glahn, D.C., Carter, C.S., 2012. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cognitive, Affect. Behav. Neurosci. 12, 241–268.

Nooner, K.B., Colcombe, S., Tobe, R., Mennes, M., Benedict, M., Moreno, A., Panek, L., Brown, S., Zavitz, S., Li, Q., 2012. The NKI-Rockland sample: a model for accelerating the pace of discovery science in psychiatry. Front. Neurosci. 6, 152.

Rottschy, C., Caspers, S., Roski, C., Reetz, K., Dogan, I., Schulz, J., Zilles, K., Laird, A., Fox, P., Eickhoff, S., 2013. Differentiated parietal connectivity of frontal regions for "what" and "where" memory. Brain Struct. Funct. 218, 1551–1567.

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A.R., Schulz, J.B., Fox, P.T., Eickhoff, S.B., 2012. Modelling neural correlates of working memory: a coordinate-based meta-analysis. Neuroimage 60, 830–846.

Salimi-Khorshidi, G., Douaud, G., Beckmann, C.F., Glasser, M.F., Griffanti, L., Smith, S.M., 2014. Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers. Neuroimage 90, 449–468.

Satterthwaite, T.D., Elliott, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., Eickhoff, S.B., Hakonarson, H., Gur, R.C., Gur, R.E., 2013. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. Neuroimage 64, 240–256.

Seeley, W.W., Menon, V., Schatzberg, A.F., Keller, J., Glover, G.H., Kenna, H., Reiss, A.L., Greicius, M.D., 2007. Dissociable intrinsic connectivity networks for salience processing and executive control. J. Neurosci. 27, 2349–2356.

Seger, C.A., 2006. The basal ganglia in human learning. Neuroscientist 12, 285–290.

Sommer, M.A., 2003. The role of the thalamus in motor control. Curr. Opin. Neurobiol. 13, 663–670.

Sridharan, D., Levitin, D.J., Menon, V., 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc. Natl. Acad. Sci. U. S. A. 105, 12569–12574.

Starr, C.J., Sawaki, L., Wittenberg, G.F., Burdette, J.H., Oshiro, Y., Quevedo, A.S., McHaffie, J.G., Coghill, R.C., 2011. The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions. Brain 134, 1987–2004.

Tanaka, D., 1976. Thalamic projections of the dorsomedial prefrontal cortex in the rhesus monkey (Macaca mulatta). Brain Res. 110, 21–38.

Thiel, C.M., Zilles, K., Fink, G.R., 2004. Cerebral correlates of alerting, orienting and reorienting of visuospatial attention: an event-related fMRI study. Neuroimage 21, 318–328.

Timm, N., 2002. Applied Multivariate Analysis.

Turkeltaub, P.E., Eickhoff, S.B., Laird, A.R., Fox, M., Wiener, M., Fox, P., 2012. Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. Hum. Brain Mapp. 33, 1–13.

van den Heuvel, Martijn P., Sporns, O., 2013. Network hubs in the human brain. Trends Cogn. Sci. Regul. Ed. 17, 683–696.

Verbruggen, F., Aron, A.R., Stevens, M.A., Chambers, C.D., 2010. Theta burst stimulation dissociates attention and action updating in human inferior frontal cortex. Proc. Natl. Acad. Sci. U. S. A. 107, 13966–13971.

Vincent, J.L., Kahn, I., Snyder, A.Z., Raichle, M.E., Buckner, R.L., 2008. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. J. Neurophysiol. 100, 3328–3342.

Vossel, S., Weidner, R., Fink, G.R., 2011. Dynamic coding of events within the inferior frontal gyrus in a probabilistic selective attention task. J. Cogn. Neurosci. 23, 414–424.

Vossel, S., Geng, J.J., Fink, G.R., 2014. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist 20, 150–159.

Zelazo, P.D., Carter, A., Reznick, J.S., Frye, D., 1997. Early development of executive function: a problem-solving framework. Rev. general Psychol. 1, 198.

Zelazo, P.D., Müller, U., 2002. Executive Function in Typical and Atypical Development.

6. Summary and General Discussion

The two studies presented here have used multimodal neuroimaging analysis to better understand the concept of EF in the broader sense. This was specifically done by investigating the neurobiological underpinnings of a sub-test of the D-KEFS TMT, a commonly used test to measure EF, and later, by defining and characterizing a robust network of brain regions associated with EF based on functional connectivity.
Study 1 employed a multi-modal approach to investigate the regions and associated networks related to performance on the D-KEFS TMT-MS. In Study 2 the focus was on functional connectivity and how this can be used to define a broad and robust network that identifies the brain regions associated with EF.

6.1 Relationship between TMT-MS and EF

The VBM analysis in Study 1 found TMT-MS performance to be specifically related to the local brain volume of a small region in the lower bank of the left IFS. That is, better performance was associated with higher GMV in this cluster, across subjects. This region has been previously reported to be part of the Multiple Demand System defined by Duncan, (2010), and is also part of the Multiple Demand Network by Müller et al., (2015), which was defined by performing a conjunction across three large-scale meta-analyses. Additionally, our functional characterization of the region that emerged from the VBM analysis, found a significant association with cognitive processes such as reasoning and working memory. This suggests that performance on the TMT-MS may be related to brain structure in a region that is usually associated to EF rather than motor functions. This finding is not surprising since the TMT-MS requires subjects to follow a dotted line and thus accurate completion of this task should in fact heavily involve EF processes such as attention and executive motor control. However, this does not necessarily contradict the assumption that the TMT-MS test is a baseline measure of motor speed. Rather, given the current findings, it would be argued that motor speed in a more naturalistic setting should be more strongly associated with executive rather than primary motor function. In fact, the close relationship between certain aspects of motor performance and cognitive or EF has already been reported in previous studies (Diamond, 2000; Rigoli et al., 2012). However, the findings reported here contrast findings of fMRI studies that used less naturalistic settings such as fist opening/closure or finger tapping paradigms (Grefkes et al., 2008; Roski et al., 2014; Staines et al., 2001), which reported activations and interactions of the primary motor cortex as well as the lateral and medial pre-motor cortices. This divergence in findings from different studies using more or less naturalistic settings coincides with the challenges associated with EF, described earlier. Additionally, it implicates a key difference between neuroimaging motor assessments, such as the opening/closing or finger tapping paradigms, and pen-and-paper tests, with the latter being more reflective of executive motor control and thus having a greater challenge with disentangling EF processes from the more basic primary motor functions.

6.2 A distributed network associated with EF

Based on the integrative view of the brain, which suggests that mental processes depend on the dynamic interaction and exchange of information between multiple brain regions (Eickhoff & Grefkes, 2011), both Study 1 and Study 2 identified brain networks based on the functional (and structural) connectivity of brain regions.

6.2.1 The extended MDN

Specifically, Study 2 defined a broad and robust network associated with EF including a total of 17 regions in which the consensus functional connectivity maps of more than half of the seed-regions overlapped and were therefore considered to be part of the eMDN. All these regions coincide with the regions that were previously reported to be part of the Multiple-Demand System by Duncan (2010; 2013), based on various task-activation studies and results from non-human primates. Furthermore, the regions that have been found to be part of the eMDN all seem to converge with the afore-mentioned networks including the cognitive control network

(Cole & Schneider, 2007), the fronto-parietal control system (Vincent et al., 2008), and the superordinate cognitive control network (Niendam et al., 2012)(Angela R. Laird et al., 2013), among others. Hence, Study 2 succeeded to corroborate previous views of brain regions associated with EF by taking a complementary approach starting from a network that was robustly defined over a large number of neuroimaging findings and mapping regions consistently connected to these across mental states (cf. Amft et al., 2015).

Following further observation of the eMDN, it can be noticed that a full overlap of all consensus connectivity maps was only found in regions that were part of the original MDN network by Müller et al., (2015). In turn, however, two regions implicated as MDN regions from the activation data in Müller et al., 2015 (right MFG and IPS) did not show a full overlap of all consensus connectivity maps and were thus not part of the connectivity core. From this, we would suggest that only the bilateral inferior frontal junction (IFJ) extending into the inferior frontal gyrus, the bilateral anterior insula (aINS), and the bilateral pre-SMA extending into the anterior midcingulate cortex (aMCC) should be considered the core eMDN based on consistent activation in executive control tasks and strong interconnectivity. Such core networks have been suggested to play a key role in enabling high levels of functional diversity and functional synchronization between brain regions (van den Heuvel & Sporns, 2013). Our core eMDN is then complemented by a range of other regions that are likewise robustly connected and involved in various aspects of executive processes, forming the extended multiple demand network. Importantly, the presence of such a broad multiple demand network associated with multiple cognitive processes may explain the challenges associated with measuring EF and the inter-correlation of performance in different executive function tests.

Furthermore, the region that was found to be associated with TMT-MS performance, together with the regions that were found to be part of the associated core network in Study 1 converge with the regions of the core eMDN defined in Study 2. This suggests that the region in the IFS that was found to be associated with the TMT-MS dynamically interacts with regions that are also associated with EF, thus further emphasizing the involvement of EF in the successful completion of the TMT-MS.

6.2.2 Sub-networks within the eMDN

The secondary goal of Study 2 was to further investigate the dynamic interaction of the regions defined in the eMDN by investigating the presence of any potential sub-networks. This was done by using hierarchical clustering analyses, based on similarities in RS-FC, MACM co-activation, and function. Additionally, the regions within the network were functionally characterized in order to identify the functions associated with each of the regions based on a large number of neuroimaging studies in BrainMap. Collectively, the clustering analyses suggested the presence of three main sub-networks within the eMDN. Namely, a sub-cortical group mainly related to sensorimotor processing, a core of organizing regions, and a more heterogeneous set of regions dynamically recruited based on task demands. Consequently, the eMDN can be considered to be a system of brain regions interacting with each other to fulfill multiple cognitive processes, composed of a number of sub-networks specialized to particular functions. The defined eMDN thus corresponds with the widely accepted view of the brain being topographically organized into distinct areas that are integrated into networks. Details regarding each of the sub-networks can be found in the Discussion section of Study 2.

6.3 Convergences across modalities

A number of different approaches can be used to investigate the functional integration of the brain, each of which has its own conceptual underpinnings, methodological features and potential biases. Both studies presented here have made use of multiple approaches to define brain networks in accordance with the aim of the specific study. Study 1 used four different modalities to investigate the connectivity of a seed region in the IFS and systematically examined the convergences and differences that resulted from the comparison of the different approaches. Although strong conceptual differences exist among these different modalities, a common network was revealed. When using a minimum statistical conjunction to compare the networks resulting from the three modalities that focus on functional connectivity, namely RS-FC, MACM, and SC, all three approaches converged on a core network that included adjacent parts of left IFG, its right-hemispheric homolog, right precentral gyrus, left middle cingulate cortex, middle orbital gyrus, and insular cortex. These results coincide with previous studies that also showed convergence between RS and MACM (Cauda et al., 2011; Hoffstaedter et al., 2014; Jakobs et al., 2012), between RS and SC (He et al., 2007; Reid et al., 2015; Seeley et al., 2009), and between RS, MACM and SC (Clos et al., 2014; Hardwick et al., 2015). Additionally, convergence was also found when carrying out a minimum statistical conjunction across all four connectivity approaches. This is in line with previous findings that reported convergences between RS and fiber tracking (Damoiseaux & Greicius, 2009; Greicius et al., 2009; Koch et al., 2002; Van Den Heuvel et al., 2009) and suggests that FC can be used to reflect structural connectivity. As a result, Study 1 suggests that future studies could benefit from a multi-modal approach and should thus focus on using and interpreting convergent networks rather than focusing on unimodal approaches.

Following suggestions and evidence provided by Study 1, showing that strong convergences do exist across modalities, Study 2 used multimodal analyses to define a robust and broad network of regions associated with EF irrespective of brain state.

6.4 Conclusion

EF is crucial for an independent, and socially productive life and its impairment is thought to play a major role in a wide range of different psychiatric and neurological disorders. Due to its importance and pervasive nature, a number of studies have focused on investigtaing the various aspects of EF including the development of valid and reliable tests that can be used to measure it and the definition of networks of brain regions associated with EF. The two studies presented here have used multimodal neuroimaging analysis in the attempt to better understand the concept of EF in the broader sense.

Results of Study 1, demonstrating a significant correlation between TMT-MS performance and GMV in a region that was associated more to EF than to motor speed, suggest that performance on the TMT-MS may primarily depend on EF, thus insinuating that motor speed in a more naturalistic setting may be more strongly associated with executive rather than primary motor function. Additionally, all connectivity approaches used converged on a network made of regions that were also found to be functionally associated with cognitive processes.

Study 2 provides a robust definition of an extended multiple demand network (eMDN). The eMDN was characterized into three cliques by means of hierarchical clustering, including a subcortical group mainly related to sensorimotor processing, a core of potential organizers (bilateral pre-SMA/MCC, aINS, MFG/IFS), and a more heterogeneous set of workers dynamically recruited based on task demands. We propose the eMDN to be the most likely neurobiological substrate for EF. This system is composed of a core whose integrity should be critical for performance of higher cognitive functions, which then dynamically recruits additional areas of the eMDN depending on the demands of the individual tasks, explaining discrepancies between the performance in different EF tasks.

Additionally, the fact that the region that was found to be associated with TMT-MS performance, together with the regions that were found to be part of the associated core network in Study 1 converge with the regions of the core eMDN defined in Study 2, strongly suggest that the region in the IFS that was found to be associated with the TMT-MS dynamically interacts with regions that are also associated with EF and thus further emphasizing the involvement of EF in the successful completion of the TMT-MS.

Furthermore, both studies verified that common networks could be revealed across highly divergent connectivity approaches. Together, these studies thus stress the importance of multi-modal analysis when attempting to reveal underlying brain networks. Additionally, taken together, these studies confirm the complexity of the concept of EF while verifying the need for further studies investigating the neural correlates of commonly used pen-and-paper tests.

References

Amft, M., Bzdok, D., Laird, A. R., Fox, P. T., Schilbach, L., & Eickhoff, S. B. (2015). Definition and characterization of an extended social-affective default network. *Brain Structure and Function*. https://doi.org/10.1007/s00429-013-0698-0

Cauda, F., Cavanna, A. E., D'agata, F., Sacco, K., Duca, S., & Geminiani, G. C. (2011). Functional Connectivity and Coactivation of the Nucleus Accumbens: A Combined Functional Connectivity and Structure-Based Meta-analysis. *Journal of Cognitive Neuroscience*. https://doi.org/10.1162/jocn.2011.21624

Clos, M., Rottschy, C., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2014). Comparison of structural covariance with functional connectivity approaches exemplified by an investigation of the left anterior insula. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2014.05.030

Cole, M. W., & Schneider, W. (2007). The cognitive control network: Integrated cortical regions with dissociable functions. *NeuroImage*, *37*(1), 343–360. https://doi.org/10.1016/j.neuroimage.2007.03.071

Damoiseaux, J. S., & Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure & Function*, *213*(6), 525–533. https://doi.org/10.1007/s00429-009-0208-6

Diamond, A. (2000). Close Interrelation of Motor Development and Cognitive Development and of the Cerebellum and Prefrontal Cortex. *Child Development*. https://doi.org/10.1111/1467-8624.00117

Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2010.01.004

Eickhoff, S. B., & Grefkes, C. (2011). Approaches for the Integrated Analysis of Structure, Function and Connectivity of the Human Brain. *Clinical EEG and Neuroscience*, *42*(2), 107–121. https://doi.org/10.1177/155005941104200211

Fedorenko, E., Duncan, J., & Kanwisher, N. (2013). Broad domain generality in focal regions of frontal and parietal cortex. *Proceedings of the National Academy of Sciences*, *110*(41), 16616–16621. https://doi.org/10.1073/pnas.1315235110

Grefkes, C., Nowak, D. A., Eickhoff, S. B., Dafotakis, M., Küst, J., Karbe, H., & Fink, G. R. (2008). Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Annals of Neurology*. https://doi.org/10.1002/ana.21228

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cerebral Cortex*, *19*(1), 72–78. https://doi.org/10.1093/cercor/bhn059

Hardwick, R. M., Lesage, E., Eickhoff, C. R., Clos, M., Fox, P., & Eickhoff, S. B. (2015). Multimodal connectivity of motor learning-related dorsal premotor cortex. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2015.08.024

He, Y., Chen, Z. J., & Evans, A. C. (2007). Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhl149

Hoffstaedter, F., Grefkes, C., Caspers, S., Roski, C., Palomero-Gallagher, N., Laird, A. R., … Eickhoff, S. B. (2014). The role of anterior midcingulate cortex in cognitive motor control. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22363

Jakobs, O., Langner, R., Caspers, S., Roski, C., Cieslik, E. C., Zilles, K., … Eickhoff, S. B. (2012). Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus-context integration. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2012.02.037

Koch, M. A., Norris, D. G., & Hund-Georgiadis, M. (2002). An investigation of functional and anatomical connectivity using magnetic resonance imaging. *NeuroImage*. https://doi.org/10.1006/nimg.2001.1052

Laird, A. R., Eickhoff, S. B., Rottschy, C., Bzdok, D., Ray, K. L., & Fox, P. T. (2013). Networks of task co-activations. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2013.04.073

Müller, V. I., Langner, R., Cieslik, E. C., Rottschy, C., & Eickhoff, S. B. (2015). Interindividual differences in cognitive flexibility: influence of gray matter volume, functional connectivity and trait impulsivity. *Brain Structure and Function*, *220*(4), 2401–2414. https://doi.org/10.1007/s00429-014-0797-6

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective and Behavioral Neuroscience*, *12*(2), 241–268. https://doi.org/10.3758/s13415-011-0083-5

Reid, A. T., Bzdok, D., Langner, R., Fox, P. T., Laird, A. R., Amunts, K., … Eickhoff, C. R. (2015). Multimodal connectivity mapping of the human left anterior and posterior lateral prefrontal cortex. *Brain Structure and Function*. https://doi.org/10.1007/s00429-015-1060-5

Rigoli, D., Piek, J. P., Kane, R., & Oosterlaan, J. (2012). An examination of the relationship between motor coordination and executive functions in adolescents. *Developmental Medicine and Child Neurology*. https://doi.org/10.1111/j.1469-8749.2012.04403.x

Roski, C., Caspers, S., Lux, S., Hoffstaedter, F., Bergs, R., Amunts, K., & Eickhoff, S. B. (2014). Activation shift in elderly subjects across functional systems: An fMRI study. *Brain Structure and Function*. https://doi.org/10.1007/s00429-013-0530-x

Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative Diseases Target Large-Scale Human Brain Networks. *Neuron*. https://doi.org/10.1016/j.neuron.2009.03.024

Staines, W. R., McIlroy, W. E., Graham, S. J., & Black, S. E. (2001). Bilateral movement enhances ipsilesional cortical activity in acute stroke: A pilot functional MRI study. *Neurology*. https://doi.org/10.1212/WNL.56.3.401

Van Den Heuvel, M. P., Mandl, R. C. W., Kahn, R. S., & Hulshoff Pol, H. E. (2009). Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Human Brain Mapping*. https://doi.org/10.1002/hbm.20737

van den Heuvel, M. P., & Sporns, O. (2013). Network hubs in the human brain. *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2013.09.012

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a Frontoparietal Control System Revealed by Intrinsic Functional Connectivity. *Journal of Neurophysiology*, *100*(6), 3328–3342. https://doi.org/10.1152/jn.90355.2008

7. Acknowledgements

First and foremost, I would like to express my sincere gratitude to Prof. Simon Eickhoff for providing me with the opportunity to work in his group and for his continuous support and patience. His guidance was of great help and his dedication for science has inspired me significantly. I could not have imagined having a better advisor and supervisor for my Ph.D study.

Additionally, I would also like to thank Prof. Tobias Kalenscher for his willingness to mentor and assess my dissertation. His help, insight and expertise were greatly appreciated.

My sincere thanks also goes to Dr. Veronika Müller (Moni) for being an excellent guide and source of information. I have learnt a lot from her insightful comments and her questions have helped me to view my work more critically. She has also provided constant support and has been a great source of encouragement whenever things got a bit tough. This whole journey would have been close to impossible without her!

I am also very thankful to Dr Felix Hoffstaedter, Dr Edna Cieslik and Dr Robert Langner who have all contributed to this thesis in some way. Felix for his technical help and interesting conversations, Edna for her invaluable support when things felt difficult and stressful and Robert for some very insightful conversations and expertise. I am also very grateful to all my fellow members of the INM-7 who collectively, with all their different educational backgrounds and nationalities, make up a very interesting and stimulating workplace.

I am also deeply thankful to all the support I had from my office mates, Rachel Pläschke, Alessandra Nostro and Deepthi Varikuti, who have now become very dear friends! I have beautiful memories of the time we spent together in the office as well as the experiences we've had outside the office.

Last but definitely not least, I would like to thank my parents and sisters, Rachel and Roberta, for their endless support from afar, as well as Marcus for his constant encouragement. Their help has made this whole experience a lot easier.