Structural Correlates of Visuospatial and Verbal Working Memory

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Abstract

Working memory (WM) is referred to as the ability to temporarily store and manipulate information (Baddeley, 2012). A key aspect of WM organization is the division into a visuospatial and verbal component. While functional neural correlates of both components have been studied extensively, the structural underpinnings of WM remain unclear. This study aims to investigate gray matter (GM) correlates of visuospatial and verbal WM, conceptualized as performance on the Block tapping task and Digit span task. Whole brain and regional voxel-based morphometry (VBM) analyses were used to investigate the association of GM volume (GMV) with performance on both forward and backward recall versions of both tasks. Analyses were performed on T1-weighted imaging data of 765 subjects (age: 55 – 80 years, 413 male) from the "1000BRAINS" study (Caspers et al., 2014). Regional analyses included regions of the extended multiple demand network (Camilleri et al., 2018) which can be seen as a substrate of executive processes, subsuming WM. Age and gender were included as covariates of no interest. None of the whole-brain analyses yielded any significant correlation between GMV and task performance. For the Block tapping task, regional analyses showed no correlation between GMV and performance. For the Digit span task, forward recall was positively correlated with GMV in the left inferior temporal gyrus (ITG). Backward recall was positively correlated with GMV in the right anterior insula (aINS) and left ITG. The left ITG has been linked to verbal WM before (Nishiyama, 2018). The association between GMV in the right aINS and backward recall supports the assumption that backward recall involves more executive control than forward recall (Donolato, Giofre, & Mammarella, 2017). However, all of the results had small effect sizes, possibly indicating a weak association of visuospatial and verbal WM and GMV. Together with the lack of significant results on a whole-brain level, the results suggest that GMV is not the relevant neural substrate of WM aspects such as the visuospatial and verbal components.

Keywords: working memory, voxel-based morphometry, visuospatial working memory, verbal working memory

Working memory is a central cognitive function which entails the short-term storage and manipulation of information. It underlies the successful execution of goal-directed behavior and functions such as planning, problem-solving, speech comprehension and production (Engle, 2002; Page, Madge, Cumming, & Norris, 2007). Working memory also accounts for a significant part of variance in general intelligence (Conway, Kane, & Engle, 2003).

Its importance furthermore becomes evident when seeing the struggles in activities of daily living of those whose working memory functioning is impaired, which is the case in many neurological and psychiatric disorders. Working memory impairment was shown in neurodegenerative diseases (Amici et al., 2007), Parkinson's disease (Gilbert, Belleville, Bherer, & Chouinard, 2005; Possin, Filoteo, Song, & Salmon, 2008), Huntington's disease (Huber & Paulson, 1987; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004), dementia (Huntley & Howard, 2010), dyslexia (Majerus & Cowan, 2016) schizophrenia (Berberian et al., 2009; Driesen et al., 2008; Fuller et al., 2009; Horan et al., 2008; Johnson et al., 2013) and depression (Joormann & Gotfib, 2008; Rose & Ebmeier, 2006). Apart from clinical syndromes, negative life events were shown to impair working memory (Klein & Boals, 2001).

Research on working memory is vast and has a more than forty years long history during which different brain regions and networks have been implied in working memory function. However, the effect of structural variance in the brain on working memory function and performance is still not clear. This study aims to fill this gap by investigating the relationship of grey matter volume on a whole-brain and regional level with two widely-used tasks assessing visuospatial and verbal working memory. In the following introduction to this study I will first describe the multicomponent model of working memory which was chosen as a theoretical framework and discuss the assessment of working memory. Then I will give a short overview of the brain regions that so far could be associated with the components of the multicomponent model and explain how networks, in particular the extended multiple demand network, might give more insight into working memory function. Lastly, I will illustrate the relevance of investigating not only functional, but structural correlates of working memory.

Working memory

The term ‘working memory’ was first introduced by Miller, Galanter and Pribram (1960) to describe the kind of memory that is used for the execution of plans. Since then, many different models and theories on working memory structure and function have been proposed over the years (e.g. Cowan, 2008, 2010, for an overview see Miyake & Shah, 1999). The maybe most influential of these is the multicomponent model of working memory (Baddeley and Hitch, 1974, see figure 1). It constitutes a framework for conceptualizing general short-term information storage for a broad range of cognitive tasks (Baddeley, 2000). Until then this kind of storage was assumed to use a unitary store, the so-called short-term memory (Atkinson & Shiffrin, 1968; Broadbent, 1958). Baddeley and Hitch (1974) instead proposed a model consisting of three components, which are the central executive and its two subsystems, the visuospatial sketchpad and the phonological loop. The central executive has four functions appointed to it: focusing attention, dividing attention between two important targets, switching between tasks and interfacing with long-term memory. The subsystems are hypothesized to store domain-specific information with the visuospatial sketchpad holding visual, spatial and visuo-spatial information, and the phonological loop holding verbal and acoustic information (Baddeley and Hitch, 1974). Dual-task experiments supported the introduction of these subsystems by showing that while secondary tasks from the same domain interfere with performance on the primary tasks (e.g. verbal – verbal), secondary tasks from a different domain do not nearly as much (e.g. verbal

– visuospatial) (Logie, Zucco, & Baddeley, 1990). The phonological loop again is comprised of two components, a phonological store and an articulatory rehearsal system. Similarly, after controversy about whether the visuospatial sketchpad stores visual or spatial information, two components within the visuospatial sketchpad were postulated: the "visual cache" for storing visual information and the "inner scribe" for storage of dynamic information (such as movement), which is considered spatial (Logie, 1995). The visuospatial sketchpad is assumed to interact with long-term memory specific for visual semantic, while the phonological loop is assumed to interact with long—term memory specific for language. Both long-term memory systems are in turn associated with episodic long-term memory. In a later version of the multicomponent model (Baddeley, 2000), a fourth component was added. The episodic buffer was introduced to account for the need of a storage that goes beyond the separated visuospatial sketchpad and phonological loop but cannot be provided by the central executive. It is conceptualized as a multidimensional store that binds different features into one integrated episode and serves as an interface between the central executive and episodic long-term memory (Baddeley, 2000).

The critical idea behind the multicomponent model is the differentiation into separable components for visuospatial and verbal working memory which are governed by an attentional resource. Importantly, the working memory system is considered to have a limited capacity.

Span tasks

This capacity is the metric of working memory and refers to the maximal number of items which an individual can successfully retain in working memory. There has been a lot of discussion on the absolute limit of working memory capacity, with claims ranging from four plus/minus one (Cowan, 2010; Luck & Vogel, 1997; Vogel, Woodman, & Luck, 2001) to seven plus/minus two (G. A. Miller, 1956). These estimates vary depending on whether the number of separate items that can be retained is assessed, or the number of chunks. Chunks are groups of items that have been combined into a larger, meaningful unit (Cowan, Morey, Chen, Gilchrist, & Saults, 2008). This quantification of working memory gives valuable insight into interindividual differences in cognition. For example. interindividual differences in working memory capacity correlate with general fluid intelligence and executive attention (Kane & Engle, 2002), making working memory capacity a good predictor of performance in many other cognitive tasks.

To asses working memory capacity, span tasks are a widely-used measure (Conway et al., 2005). In these tasks, participants are asked to recall an increasingly longer sequence of stimuli. The longest sequence is representative of the subject's working memory span. Span tasks can be used to assess both visuospatial and verbal working memory. For example, the Block tapping task (Schellig, 1997) taps visuospatial working memory, whereas the Digit span task (Oswald & Fleischmann, 1997) examines verbal working memory. Furthermore, two recall conditions exist: a forward condition, in which the stimuli have to be repeated in the same order as presented; and a backward condition, in which the stimuli have to be repeated in the reverse order as presented, staring from the last and ending with the first.

In theory, both conditions probe the storage component of working memory. However, the backward condition is assumed to have a higher executive demand compared to forward recall (Carlesimo, Fadda, Lorusso, & Caltagirone, 1994). Studies suggest that this effect might be dependent on the probed working memory component, as participants typically achieve higher scores in the forward compared to backward recall only in a verbal working memory task (Li & Lewandowsky, 1995). Despite not finding this effect for visuospatial working memory (Kessels, van den Berg, Ruis, & Brands, 2008; Ylioja, Baird, & Podell, 2009), here as well different processes seem to be involved in forward versus backward recall. In a study of participants with high versus low spatial ability, performance on backward but not forward recall on a visuospatial span task differentiated between both groups (Cornoldi & Mammarella, 2008), suggesting that backward recall relies stronger on spatial processes.

In this study, the aforementioned Block tapping task and Digit span task are used to asses visuospatial and verbal working memory capacity, respectively. The original Block tapping task by Corsi (1972) was developed as a nonverbal analogue to Hebb's recurring digits task (Hebb, 1961). It could be shown that patients with temporal lobe lesions in the left hemisphere (which is dominant for speech processes) suffer from impairments in verbal learning and memory (Meyer & Yates, 1955), while patients with temporal lobe lesion in the right hemisphere showed impairment for non-verbal information storage (Kimura, 1962; Milner, 1968). These impairments were selective – left hemispheric lesions did not impair storage of non-verbal information and right hemispheric lesions did not impair verbal information storage. To investigate these lateralized processes, Corsi (1972) assessed incidental learning in epilepsy patients who had undergone resection of the left or right temporal lobe, using the recurring digit task and Block tapping task to test verbal and non-verbal memory processes. Indeed, a double dissociation between the digit task and the Block tapping task was found in the two patient groups, affirming a domain-specific lateralization of memory processes. Today, the tasks are used in clinical, health and neuropsychology to assess symptoms of working memory disturbances or developmental changes. Furthermore, as working memory has become a critical construct in many psychological and neuroscientific research fields, the use of span tasks for research purposes likewise has increased (Conway et al., 2005).

Neural correlates

Corsi's (1972) work already introduced an important difference in the neural correlates of working memory: that visuospatial working memory is associated with the right hemisphere, while verbal working memory is associated with the left hemisphere. This was supported by later work on the multicomponent model (Baddeley, 2003). As the multicomponent model was proposed as a broad theoretical framework and an information-processing model, it initially did not make any inherent assumptions about the neural implementation of its components. Functional and lesion studies later started filling this gap.

The brain region most often implied in working memory is the prefrontal cortex. Studies on persistent neural activity in the prefrontal cortex support the notion that this region maintains representations relevant for goal-directed behavior (Courtney, Ungerleider, Keil, & Haxby, 1997; Fuster & Alexander, 1971; E. K. Miller, Erickson, & Desimone, 1996). The content of these representations seems to be variable with accounts for stimulus, rule and category information (Meyers, Freedman, Kreiman, Miller, & Poggio, 2008; Riggall & Postle, 2012; Stokes et al., 2013), leading to the overall assumption that the prefrontal cortex codes more abstract and goal-related information (D'Esposito & Postle, 2015). Concordantly, a recent meta-analysis indicated a fronto-parietal network as a "core" network for working memory and additional differential activations dependent on stimulus, task or contrast differences (Rottschy et al., 2012). The central executive and episodic buffer have both been associated with frontal lobe areas (Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000), with the latter being theorized to be implemented in the synchronous firing of neurons (Uhlhaas et al., 2009). Taken together, there is evidence for the prefrontal cortex to provide functions appointed to the central executive: the execution of top-down signals that guide activity in brain areas associated with the storage of stimulus representation (Sreenivasan, Curtis, & D'Esposito, 2014). The storage of stimulus representations in specific brain regions likewise goes well with the concept of separate components for visuospatial and verbal working memory.

Visuospatial working memory is associated with temporal and parietal association areas which is supported by the distinction of the visual processing stream into two pathways (Goodale & Milner, 1992; Goodale & Westwood, 2004). The dorsal stream arises from early visual areas in the occipital lobe and projects to the posterior parietal cortex. This stream, also termed the "where"-stream, is assumed to guide action and process spatial information. The ventral stream projects from early visual areas in the occipital lobe to areas in the temporal lobe. This stream is termed "what"-stream as it supports object recognition. Damage to either parietal or temporal areas within these pathways elicited selective impairments in short-term storage of either information on spatial relations or object discrimination, respectively (Mishkin & Ungerleider, 1982; Mishkin, Ungerleider, & Macko, 1983; Newcombe, Ratcliff, & Damasio, 1987). These deficits are in line with the idea that information stored in working memory is stored in the same sensory-specific association areas in which the cascade of initial stimulus processing ends; here, parietal and temporal association areas (Mishkin & Appenzeller, 1987). Continuous neural firing in these areas even when the stimulus is absent is interpreted as the maintenance of a stimulus representation (Fuster, 1990; Fuster & Jervey, 1982; Vidyasagar, Salzmann, & Creutzfeldt, 1991). Furthermore, research on a group of stroke patients indicated the right dorsolateral prefrontal cortex and the right posterior parietal cortex to be relevant for performance on the Block tapping task (van Asselen et al., 2006). In a voxel-based morphometry study on fibromyalgia patients who suffer from impaired working memory, performance on the Block tapping task was positively correlated with grey matter values in the left dorsolateral prefrontal cortex (Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008). Considering the role of the prefrontal cortex in working memory, deficits in these patients may additionally have been caused by impairment of function of the central executive.

A double dissociation between visuospatial and verbal working memory could be shown in further patient studies. Impaired visuospatial, but not verbal working memory was found in a patient suffering from a middle cerebral artery aneurysm in the right hemisphere (Hanley, Young, & Pearson, 1991). Vice versa, impaired verbal, but not visuospatial working memory was reported after left parietal injury (Warrington & Shallice, 1969) and ischemic lesion of the left hemispheric language area (Vallar & Baddeley, 1984).

The articulatory rehearsal system of the phonological loop is associated with Brodman areas 40 and 44 (Baddeley, 2000). The storage component historically has been associated first with the parietal lobe (Baddeley, 2003; Markowitsch et al., 1999; Paulesu, Frith, & Frackowiak, 1993) and later the superior temporal cortex (Takayama, Kinomoto, & Nakamura, 2004). However, as neither of them sufficed as a stand-alone neural correlate, a localist approach seemed unsustainable and the phonological store is rather seen to emerge from a sensory-motor speech processing system with one component being the left posterior planum temporale (Buchsbaum & D'Esposito, 2008). Studies on aphasic patients further support the subdivision of the phonological loop into a storage component and the articulatory rehearsal system (Baddeley, 2000). Patients suffering from Broca’s aphasia in which the left inferior frontal gyrus and anterior insula are damaged often experience a rehearsal deficit (Muller & Knight, 2006). Impairments in articulatory rehearsal could also be seen in a patient with lesion of the sub-cortical premotor and Rolandic regions (Vallar, DeBetta, & Silveri, 1997) and in a patient with loss of the right cerebellum (Silveri, Di Betta, Filippini, Leggio, & Molinari, 1998). Patients with conduction aphasia usually suffer from damage to the inferior parietal cortex and arcuate fasciculus (Damasio & Damasio, 1980). The arcuate fasciculus connects anterior and posterior language areas and its microstructure in the left hemisphere has been associated with verbal working memory performance in children (Yeatman et al., 2011). Conduction aphasics show impairments in the storage function of the phonological loop (Gvion, Biran, & Friedmann, 2002; Muller & Knight, 2006). Such impairments of storage could further be seen in a patient also suffering from lesion of the left angular gyrus (Markowitsch et al., 1999) and in a patient with lesion of the inferior parietal lobule together with superior and middle temporal gyri (Vallar et al., 1997). Apart from inferior parietal and nearby regions, one patient was similarly impaired after traumatic bi-frontal damage (Gruber et al., 2005). A study employing voxel-based morphometry in patients diagnosed with neurodegenerative disease showed a relation between grey matter volume in the left dorsolateral prefrontal cortex and inferior parietal lobe and performance on the backward Digit span task (Amici et al., 2007). In the same study on fibromyalgia patients as cited above, performance on the Digit span task backward was positively correlated with grey matter values in the medial frontal gyrus (Luerding et al., 2008). Here as well damage to prefrontal regions might have caused working memory deficits by impairment of the central executive additionally to impairment of the verbal working memory component.

Forward and backward span tasks.

This study employs forward and backward recall version of the Block tapping task and Digit span task, so I will further consider which neural correlates have been associated with these more specifically.

As mentioned above, the block tapping span has its origins in the investigation of unilateral temporal lobectomy and its effects on presumably lateralized cognitive functions, i.e. non-verbal and verbal memory processes. Impaired memory performance on the Block tapping task was associated with resection of the right temporal lobe, whereas impaired memory performance on the Digit span task was associated with resection of the left temporal lobe (Corsi, 1972). On a broader level spatial and verbal processes have also been associated with the right and left hemisphere, respectively.

When comparing neural correlates of visuospatial and verbal forward and backward recall, the pattern of lateralization is partially supported, and different brain areas were activated by the two working memory subcomponents (Donolato et al., 2017). For visuospatial working memory, research has mostly focused on forward recall and associated the right premotor region (Croize et al., 2004), the hippocampus (Toepper et al., 2010) and right dorsolateral prefrontal cortex (Toepper et al., 2014) with it.

For verbal working memory, Manan et al. (2014) found an activation in frontal areas, temporal areas and the cerebellum for both forward and backward recall. Backward recall was additionally associated with activation in parietal areas. However, the number of activated voxel within most of these regions was larger for backward compared to forward recall. An overall leftward asymmetry was reported for young subjects. Another study (Sun et al., 2005) equally reported differing activated regions for verbal forward and backward recall. Greater activation in the backward compared to forward recall here was found in the left occipital regions (BA 17/18/19) and left dorsolateral prefrontal cortex (BA 9), while more activation during forward compared to backward recall was found in the right inferior frontal gyrus (BA 44/45). These findings support the notion that verbal backward recall can be differentiated from forward recall also in its neural correlates and that backward recall is stronger associated with regions involving executive processes. Other studies investigating verbal working memory using span tasks report activation of the anterior cingulate cortex, left prefrontal cortex, left inferior frontal cortex, bilateral parietal cortex and left language area (Chein, Moore, & Conway, 2011; Kondo et al., 2004; Osaka et al., 2004).

When comparing both verbal and visuospatial working memory span tasks, Chein et al. (2011) found that both activated the prefrontal cortex, anterior cingulate cortex and superior parietal cortex, indicating a domain-general aspect that is present in both components. Taken together, there is evidence for participation of the central executive via prefrontal areas additionally to activation in regions which seem more specific to visuospatial or verbal working memory. At least for verbal working memory, forward and backward recall seems to be distinguishable in their activation patterns of brain regions.

Extended multiple demand network.

Considering all brain regions involved in working memory, not one specific structure can be termed the single neural correlate of any of the components. Rather, working memory emerges from a network supporting different necessary cognitive processes, some of them specific to the visuospatial or verbal domain, some domain-general (Zimmer, 2008). Rottschy et al. (2012) used coordinate-based meta-analyses to unify the sometimes inconsistent, but large amount of research on neural correlates of working memory and identify which network supports this function. They indeed found a core network but stated that this was probably not limited to working memory. As Baddeley's model likewise combines executive processes and working memory storages, it might be appropriate to consider a broader network when investigating working memory.

As such, the extended multiple demand network (Camilleri et al., 2018) can be regarded as a substrate of executive processes. Executive functions are cognitive processes which control and coordinate lower level cognitive processes to enable regulated and goal-directed behavior (Friedman & Miyake, 2017; Miyake et al., 2000). Commonly described as executive functions are abilities such as planning, task switching, dual tasking and working memory processes (Friedman & Miyake, 2017). Given this diversity in related functions, multiple brain regions and networks have been associated with executive functions. Despite the variability, similarity in recruited brain regions was found and termed multiple demand network (Duncan & Owen, 2000). This notion was taken up by Müller et al. (2015) who employed a conjunction analysis over three neuroimaging meta-analyses on vigilant attention (Langner & Eickhoff, 2013), working memory (Rottschy et al., 2012) and inhibitory control (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015). These functions have been named as core executive functions before (Alvarez & Emory, 2006). This convergence resulted in seven clusters which were consistently involved in all three core executive functions, namely the midcingulate cortex extending into pre- and supplementary motor area (MCC/SMA), left and right anterior insula (aINS), left and right inferior frontal junction/gyrus (IFG), right middle frontal gyrus and (MFG) right intraparietal sulcus (IPS). As this definition of a multiple demand network is rather conservative and does not include many regions which have otherwise been associated with specific executive functions, Camilleri et al. (2018) investigated the connections of the multiple demand network with other brain regions. Clusters that were found to be task-dependently and task-independently connected to the regions of the multiple demand network were the bilateral IFG, bilateral aINS, bilateral pre-SMA, bilateral IPS, bilateral MFG extending into the inferior frontal sulcus (IFS), bilateral dorsal pre-motor cortex (dPMC), bilateral putamen, bilateral thalamus and left inferior temporal gyrus (ITG). These regions together with the regions from the multiple demand network were termed extended multiple demand network and could later be divided into core regions which were consistently recruited over virtually all cognitive tasks and regions which were recruited by more specific task demands (see figure 2).

As the extended multiple demand network is tightly linked to working memory, but integrates further, related functions, it constitutes a suitable candidate for investigation of the neural correlates of working memory performance.

Structural correlates of working memory

Due to its great relevance, research on working memory dates back decades and is comprised of an ever-growing body of many thousand research articles. Despite the vast amount of attention that has been paid to working memory, one specific gap in the literature is that while the functional correlates of working memory are investigated thoroughly, little is found concerning its structural correlates.

But how could there be brain function without brain structure? Study of the macroscopic brain anatomy may give insight into inter-individual variability of performance on specific cognitive functions. The existence of a relationship between structural features of the brain and behaviour could be shown for motor behavior, sensory perception, intelligence, personality and high-level cognitive functions (Kanai & Rees, 2011). Commonly investigated are the structure of grey matter and white matter, often using voxel-based morphometry (VBM). VBM is a method that aims to identify differences in local concentration (or volume) of grey or white matter between two groups while disregarding global volumetric or positional differences (Ashburner & Friston, 2000). Intuitively, a larger cortical volume would be associated with better performance, as more volume might contain more processing units and thus have a higher computational efficacy. However, while many findings of studies employing VBM support this notion, not all do as there are studies in which less grey matter volume is correlated with better performance (Hyde et al., 2007; Hyde, Zatorre, Griffiths, Lerch, & Peretz, 2006). This might in part be explained by developmental processes, as grey matter volume develops non-linearly and is marked by earlier increases and later losses (Gogtay et al., 2004). Grey matter loss might partially be due to synaptic pruning (Huttenlocher, 1979), a process shown to remove weak synapses and thus enable efficient processing in a system with a limited number of synapses, such as the brain (Chechik, Meilijson, & Ruppin, 1998). Therefore, results on voxel-based morphometry studies have to be interpreted in the context of developmental processes but offer the opportunity to relate performance on cognitive tests to structural measures of the brain.

To this day it is not clear to which extent structural variation in grey matter volume associates with performance on working memory tasks. To examine this relationship, I used voxel-based morphometry on a large sample of 765 subjects. Whole-brain and regional analyses, using regions from the extended multiple demand network, were used to investigate the association of grey matter volume with performance on a visuospatial and a verbal working memory task. These tasks were the Block tapping task and Digit span task, respectively. In the light of the literature discussed above, I expected to find grey matter volume of regions in the right hemisphere to be associated with performance on the Block tapping task and grey matter volume of regions in the left hemisphere to be associated with performance on the Digit span task. Further, I expected the backward recall versions of both tasks to be associated with grey matter volume in frontal areas.

Methods

Participants

Participants were tested within the larger 1000BRAINS study (Caspers et al., 2014). In this cohort study, participants were recruited from the 10-year follow-up cohort of the German Heinz Nixdorf Recall (HNR) Study and the HNR MultiGeneration Study cohort consisting of spouses and offspring of HNR participants. Participants underwent comprehensive assessment of clinical, laboratory, socioeconomic and environmental data during the initial HNR study. Within the 1000BRAINS study, data was collected on neuropsychological tests of attention, memory, executive functions and language; motor skills; personality ratings; life quality; mood and daily activities; and magnetic resonance imaging (MRI) of the brain. To ensure safety during the MRI scan, exclusion criteria were coronary artery stents, cardiac pacemakers, surgical implants or protheses in the trunk or head, claustrophobia, a history of neurosurgery and the presence of tattoos or permanent make-up on the head. Subjects gave informed written consent to participate in all tests and measures.

For this study, data from 765 participants was used. Age ranged from 55 to 76 years (M: 65.87 years, SD: 5.61 years). 413 participants were male.

Measurements

Neuropsychological assessment.

Visuo-spatial working memory.

To assess visuospatial working memory capacity, participants completed the Block Tapping Task (Schellig, 1997). As display characteristics of this test such as colour, number of blocks, block size and block placement have lacked standardization for a long time (Berch, Krikorian, & Huha, 1998), I will further include specific descriptions of these task parameters. In the Block tapping task, 9 black synthetic blocks (edge length: 25mm) in fixed positions on a grey synthetic board (6 x 275 x 228mm) are presented. The x and y coordinates of the blocks measured in millimeters from the lower edge of the board are: 1. (145, 167), 2. (48, 181), 3. (216, 150), 4. (69, 128), 5. (157, 101), 6. (226, 63), 7. (29, 75), 8. (79, 24) and 9. (140, 39). The experimenter taps these blocks in a specific sequence. This sequence has to be repeated by the participant. The number of blocks tapped in a sequence increases with every trial, starting at three blocks and ending at eight blocks. A sequence with a higher number of blocks is always more difficult to reproduce than any sequence with a lower number of blocks. For every sequence, three items are presented. The test ends when the participant successfully repeats all three items of a sequence of eight blocks or when he or she fails to correctly reproduce three items in a row. The Block tapping span is calculated as the highest sequence in which the participant correctly reproduces at least two items. A span score of five or higher is considered normal. Forward and backward versions were employed.

Performance results can be seen in table 1. In the backward version, one participant attained a Block tapping span of nine. Because this is an impossible result, it is assumed that this was a mistake in the experimenter's documentation.

Verbal working memory.

Verbal working memory capacity was assessed using the Digit span task ("Zahlennachsprechen", from Nürnberger Alters-Inventar, Oswald and Fleischmann, 1997). In this task, participants have to verbally repeat a sequence of digits that were verbally presented to them by the experimenter. The number of digits in a sequence increases by trial. It starts at two digits and ends at nine. For every sequence, three items are presented. The test ends when the participant successfully repeats all three items of a sequence of nine digits or when he or she fails to repeat three consecutive items. The digit span is calculated as the highest sequence in which the participant correctly reproduces at least two items. Forward and backward versions were employed.

Performance results can be seen in table 1.

Magnetic Resonance Imaging (MRI).

Data acquisition.

Whole-brain T1-weighted structural MRI images (3D-MPRAGE, 176 slices, TR = 2.25 s, TE = 3.03 ms, TI = 900ms, FoV = $256 \times 256 \text{mm}^2$, flip angle = 9◦, voxel resolution = $1 \times 1 \times 1 \text{mm}^3$) were acquired for all participants on a 3 Tesla MR scanner (Tim-TRIO, Siemens Medical Systems, Erlangen, Germany) at the Research Center in Jülich.

Image analysis.

The T1-weighted images were pre-processed using the Computational Anatomy Toolbox (CAT12) in SPM software version 12 (Statistical Parametric Mapping; Wellcome Trust Center for Neuroimaging, University College London, 2014) on the basis of MATLAB R2017a (The MathWorks Inc., 2017). To account for global differences in brain structure, images need to be spatially registered into a common template space, ensuring that all images are within the same stereotactic space. Here, the ICBM-152 template from the Montreal Neurological Institute (MNI) template was chosen for spatial normalization. Then the images were segmented into grey matter (GM), white matter and cerebrospinal fluid. As my analysis focuses on differences in grey matter volume, only the grey matter segments were used for analysis. In the process of spatial normalization, information about the absolute volume of brain regions is lost and afterwards only relative grey matter concentrations may be compared. To compensate for this effect, a further processing step called modulation is added in which the spatially normalized grey matter is multiplied by its relative volume before and after normalization. This results in the preservation of the total amount of grey matter volume. For the whole-brain analysis, images were smoothed using an isotropic Gaussian kernel. After smoothing, each voxel contains the average amount of grey matter from around the voxel (within the Gaussian kernel). Smoothing increases the signal-to-noise ratio and thus makes large scale effects more apparent. The data becomes more normally-distributed, which increases the validity of parametric statistical tests. Kernel size is given as full width at half maximum (FWHM), and in this study, FWHM amounts to eight millimeters. For the regional analyses, no smoothing was performed as grey matter values were averaged over the defined areas. Regions from the extended multiple demand network were used. These were the bilateral IFG, bilateral aINS, bilateral pre-SMA, bilateral IPS, bilateral MFG extending into the inferior frontal sulcus (IFS), bilateral dorsal pre-motor cortex (dPMC), bilateral putamen, bilateral thalamus and left inferior temporal gyrus (ITG) (for peak coordinates see table 2).

Statistical analysis.

For the whole-brain analysis, a multiple linear regression of grey matter values on scores of forward and backward versions of both Block tapping task and Digit span task was calculated for each voxel. Voxel-wise grey matter volume was used as dependent variable, while performance scores were covariates of interest. This was done separately for the forward and backward recall version of the Block tapping task and the forward and backward version of the Digit span task, as collinearity between these measures was assumed.

For the regional analyses, a multiple linear regression of averaged grey matter values on scores of forward and backward versions of both Block tapping task and Digit span task was calculated for each region of the eMDN. Grey matter volume averaged over the region of interest was used as dependent variable, while again performance scores on forward and backward versions of both tasks were used as covariate of interest. Again, this was done separately for forward and backward recall versions of both Block tapping and Digit span task.

When multiple statistical tests are conducted simultaneously, the likelihood of incorrectly rejecting the null hypothesis (known as Type I error) increases, as rare events become more likely. While a certain alpha value may be appropriate for a single statistical test, it is not when encountering the problem of multiple comparisons. To compensate for this effect, the Bonferroni correction (Bonferroni, 1935) divides the original alpha value by the number of tests conducted. The result is taken as the new alpha value for the entire set of tests. Because the Bonferroni correction is the most conservative approach to correct for multiple comparisons, it was applied to all analyses. In all analyses, age and gender were used as covariates of no interest. Analyses were performed using the in-house scripts.

Results

Whole-brain results

On a voxel-wise whole-brain level, no significant correlations were found between grey matter volume and performance on the forward or backward version of either the Block tapping task or Digit span task.

Regional results

Block tapping task.

On a regional level, no significant correlations were found between grey matter volume in any of the regions of the eMDN and performance on the forward or backward version of the Block tapping task.

Digit span task.

For the forward version of the Digit span task, performance was positively correlated with grey matter volume in the left ITG (r=0.11, p=0.0026, Bonferroni-corrected). The left ITG can be seen in figure 3.

For the backward version of the Digit span task, performance was positively correlated with grey matter volume in the left ITG (r=0.12, p=0.0006, Bonferroni-corrected) and in the right aINS (r=0.12, p=0.0007, Bonferroni-corrected). The right aINS can be seen in figure 4.

Discussion

Working memory is a fundamental cognitive function that is important for any goal-directed behavior (Engle, 2002). The influential multicomponent model (Baddeley, 1974) subdivides working memory into an attentional, executive resource, a visuospatial and a verbal component. Despite vast research on functional correlates of working memory, the association between structural variance in the brain and working memory performance is still not clear. This study aims to fill this gap by investigating the relationship between grey matter volume on a voxel-wise whole-brain and regional level and performance on two widely-used span tasks assessing visuospatial and verbal working memory, the Block tapping task and Digit span task.

The most striking finding of this study is the mostly absence of significant correlations. In the regional analyses on visuospatial working memory and in whole-brain analyses of both visuospatial and verbal working memory, no significant correlations between task performance and grey matter volume were found.

This might indicate that there are no structural correlates which are specific to the visuospatial and verbal working memory components. It has been argued that working memory capacity (assessed by forward and backward digit span) and general intelligence share a common neuroanatomic framework (Colom, Jung, & Haier, 2007). Similarly, a common neural network has been proposed for working memory and fluid reasoning measured by Raven's progressive matrices (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). These findings are in line with the notion that working memory is an assembly of different processes provided by different structures in a variable fashion, depending on task demands (Zimmer, 2008). Considering that working memory processes in turn underlie many higher cognitive functions (Engle, 2002), it is unsurprising that these functions recruit similar brain areas. Complementary, regions involved in working memory most likely are not specific to working memory. When considering working memory as an emergent property of the brain that is supported by the same regions as other cognitive functions, the relevance of the functional interactions between these regions is emphasized. One option to investigate the role of the organization of complex brain networks in cognitive performance is to study measures of functional connectivity between brain regions. In short, functional connectivity refers to the correlation in activity of two or more brain regions (Friston, 2009). Importantly, there are differences in overall network organization between intrinsic (measured by resting state) and task-evoked brain networks (Bolt, Nomi, Rubinov, & Uddin, 2017). For working memory capacity, the intrinsic functional organization of a cognitive control network provides information about cognitive performance (Stevens, Tappon, Garg, & Fair, 2012). The authors conclude that a combination of efficient processing within relevant brain regions and interactions between these regions constitutes an organizational requirement for neural systems underlying complex cognitive tasks. Accordingly, resting-state functional connectivity measures of brain regions known to be engaged in working memory correlate with working memory performance (Liu et al., 2017). Task-dependent analyses revealed that communication between networks was critical for better working memory performance (J. R. Cohen & D'Esposito, 2016). Important for working memory accuracy was the efficiency of information flow between perceptual (here occipital) and attentional (here parietal) neural systems, again supporting a network perspective of working memory capacity (Weber, Hahn, Hilger, & Fiebach, 2017).

These findings support the notion that working memory is highly dependent on the functioning of brain networks. However, it is unlikely that there is no effect of “hardware” – the structure of the brain – at all. Concordantly, this study found significant results when correlating averaged grey matter volumes of each region of the extended multiple demand network with performance on the verbal working memory task.

Performance on the forward and backward recall version of the Digit span task showed a significant positive correlation with grey matter volume in the left inferior temporal gyrus. The inferior temporal gyrus has been implied in both visuospatial and verbal working memory (Bedwell et al., 2005; Fiebach, Rissman, & D'Esposito, 2006; Majerus et al., 2010; E. K. Miller, Li, & Desimone, 1993; Ranganath, 2006; Sugase-Miyamoto, Liu, Wiener, Optican, & Richmond, 2008). For visuospatial working memory, areas specialized to the processing of specific stimuli such as the fusiform face area or parahippocampal place area are involved in the maintenance of these stimuli in working memory (Courtney et al., 1997; Druzgal & D'Esposito, 2001; Postle, 2005; Postle, Druzgal, & D'Esposito, 2003; Ranganath, 2006). Similarly, a language area within the left inferior temporal cortex involved in verbal working memory was identified (Fiebach, FriederiCi, Smith, & Swinney, 2007; Fiebach et al., 2006). In the domain of language, a posterior-to-anterior axis for level of abstraction has been proposed within the inferior temporal cortex (L. Cohen & Dehaene, 2004). The posterior inferior temporal cortex is involved in basic differentiation of letter-strings and non-linguistic visual stimuli, while the anterior inferior temporal gyrus is associated with the differentiation of words and non-words and is sensitive to semantic context (Nobre, Allison, & McCarthy, 1994). Taken together, specialized areas in the inferior temporal cortex support both components of working memory. While support for visuospatial working memory seems to stem from right inferotemporal areas, verbal working memory is supported more by inferotemporal areas in the left hemisphere (Majerus et al., 2010), which could be confirmed by results from this study.

The same regional analyses as described above using performance on the backward recall version of the Digit span task additionally showed a significant positive correlation with grey matter volume in the right anterior insula. The anterior insula is associated with executive and attentional processes (Palva, Monto, Kulashekhar, & Palva, 2010; Petersen & Posner, 2012). It has been proposed as part of the “salience network” to detect the most relevant stimuli for goal-directed behavior (Eckert et al., 2009). Upon detection, the anterior insula initiates the engagement of brain areas involved in working memory, attentional processes and other higher cognitive processes (Eckert et al., 2009). Furthermore, the anterior insula is associated with cognitive control (Cole & Schneider, 2007; Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008). In general, the anterior insula seems to be recruited by multiple cognitive demands (Duncan & Owen, 2000). The finding of a positive correlation between grey matter volume in the right anterior insula and performance specifically on backward, but not forward, recall of the Digit span task therefore supports the assumption that backward recall requires more executive processes than forward recall

(Carlesimo et al., 1994). Moreover, the same result was obtained in a large sample study (Takeuchi et al., 2017), supporting the relationship between grey matter volume in the right anterior insula and backward recall of the Digit span task.

Strikingly, the significant correlations that were found in regional analyses on the Digit span task had small effect sizes. This finding is in line with a recent study investigating the relationship between regional grey matter volume and diverse complex cognitive functions in a likewise large sample (Takeuchi et al., 2017). The authors found a positive correlation between performance on most cognitive tasks and regional grey matter volume in widespread brain areas; however, the effect sizes of these correlation were in the same low range as they are found in this study. Other studies using large sample sizes and investigating the relationship between cognition and structural variance in the brain likewise reported only small effect sizes (Magistro et al., 2015; McDaniel, 2005; Salthouse et al., 2015; Takeuchi et al., 2015). This could in part be affected by the level of analysis employed. Salthouse et al. (2015) reason that findings on the relationships between neural measures and measures of cognitive functioning may be reduced after adjusting for shared variance between the measures. As both neural measures and cognitive measures each are likely to show collinearity among themselves, general factors may drive an apparently strong relation between a specific neural measure and a specific cognitive measure. When accounting for such general factors, the association between the specific neural measure and specific cognitive measure may turn out to be much weaker than it first seemed. The same notion was proposed and supported by an analysis of three morphometric indices of grey matter at three levels of the intelligence hierarchy (Roman et al., 2014). This effect in association with often small sample sizes (and hence not enough power) and a large variety in employed tasks and preprocessing methods likely leads to the substantial inconsistency in reports on the neural correlates of different cognitive functions (Takeuchi et al., 2017).

As this study examined a large sample (n=765), a lack of power is unlikely to account for the absence of significant correlations. However, one possible limitation is that only one task was used to assess each working memory component. Therefore, more general information on the effect of structural variance on visuospatial and verbal working memory performance may have been missed. The employed span tasks both probe working memory for serial information, but stronger patterns of lateralization in and clearer distinction of recruited brain regions have been shown for item compared to order information (Majerus et al., 2010). The resources for maintaining order information were also shown to be shared between the visuospatial and verbal component (Depoorter & Vandierendonck, 2009; Vandierendonck, 2016), making it harder to find features that distinguish both components, whereas item information is stored by separate processes (Depoorter & Vandierendonck, 2009). Therefore, using more tasks probing the two working memory components and focusing on recall of item information might have emphasized potential differences in the relationship of visuospatial and verbal working memory and structural variance in the brain. In the visuospatial domain, it has furthermore been argued that information about the location of objects is maintained by neither the visual cache nor inner scribe, but the episodic buffer (Zimmer, 2008) which again is a resource that is shared between visuospatial and verbal working memory. However, the employment of the Block tapping task and Digit span task enabled the investigation of forward vs backward recall versions. In doing so, a relationship between performance on the backward Digit span task and grey matter volume in a region highly associated with executive processes was shown, supporting existing literature and the assumption of a higher executive demand of backward recall in verbal working memory (Carlesimo et al., 1994). Moreover, it was shown before that in the Block tapping task, not spatial but sequential processes differentiated forward and backward recall (Higo, Minamoto, Ikeda, & Osaka, 2014), making order information a relevant feature.

In conclusion, no single brain region seems likely to be the exclusive neural correlate of either of the working memory components, which is in accordance with a network perspective on working memory (Zimmer, 2008). Moreover, this study indicates that grey matter volume is not the relevant structural correlate of working memory performance and the distinction between a visuospatial and a verbal component. To further investigate the role of structural variance on working memory performance in different subcomponents, it is important to employ different approaches. Insights into the relationship between grey matter and working memory may be gathered by investigating measures of cortical thickness (Colom et al., 2013; Martinez et al., 2015; Salthouse et al., 2015) and cortical surface area (Colom et al., 2013). Furthermore, an association between white matter and working memory was shown in healthy adults (Takeuchi et al., 2011), in developmental studies (Klingberg, 2006; Short et al., 2013; Vestergaard et al., 2011), in studies on aging (Charlton, Barrick, Lawes, Markus, & Morris, 2010) and in studies on disease (Coltman et al., 2011; Duong et al., 2005; Karlsgodt et al., 2008). For future studies, it is important to use large samples (Takeuchi et al., 2017), carefully consider the level of analysis (Salthouse et al., 2015) and be aware that methodological variations may cause inconsistent results even when examining the same measure in the same sample (Martinez et al., 2015).

Taken together, this study investigated the relationship between grey matter volume on a whole-brain and regional level with performance on backward and forward versions of a visuospatial and verbal working memory task. The positive correlation between grey matter volume in the left inferior temporal gyrus and performance on forward and backward Digit span task supports the domain-specific involvement of left inferior temporal regions in verbal working memory. This finding is in line with my hypothesis of finding grey matter volume of regions in the left hemisphere to be associated with performance on the Digit span task. However, no further results support a clear structural lateralization of visuospatial and verbal working memory. The positive correlation between grey matter volume in the right anterior insula and performance on the backward Digit span task gives evidence for the assumption that backward recall requires more executive processes than forward recall. This is in accordance with the hypothesis of grey matter volume of more frontal areas being associated with performance on the backward recall version, although again only in regard to verbal working memory. However, small effect sizes and the absence of significant correlations on a regional level for performance on the visuospatial working memory task and on a whole-brain level for both tasks indicates that grey matter volume is not the relevant neural correlate of the visuospatial and verbal subcomponents of working memory. Further investigation using different approaches for measuring structural variance in the brain is needed to clarify the relationship between brain structure and working memory function.

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Appendix

Table 1.

Descriptive statistics

Characteristic	Age	BTT forward	BTT backward	DST forward	DST backward
n	764	765	765	765	765
M	65.87	5.46	4.70	6.12	4.69
SD	5.61	0.90	1.07	1.08	1.14
Variance	31.49	0.81	1.14	1.17	1.30
Maximum	55.00	3.00	0.00	3.00	0.00
Minimum	76.00	8.00	9.00	9.00	9.00

Note. BTT = Block tapping task. DST = Digit span task. In the backward version of the BTT, one participant attained a block tapping span of nine. Because this is an impossible result, it is assumed that this was a mistake in the experimenter's documentation.

Table 2.

Peak coordinates of regions of the extended multiple demand network

Region	Coordinates of main peak		
	x	y	z
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
Left IPS	-32	-52	46
Right IPS	32	-58	48
Right MFG/IFS	44	36	20
Left dPMC	-28	-4	52
Left MFG/IFS	-44	32	22
Right dPMC	32	0	52
Left Putamen	-20	6	4
Right Thalamus	10	-12	8
Left ITG	-46	-60	-10
Right Putamen	22	6	4
Left Thalamus	-10	-16	6

Note. Coordinates in MNI space. IFJ = inferior frontal junction; aINS = anterior insula; SMA = supplementary motor area; IPS = intraparietal sulcus; MFG/IFS = middle frontal gyrus/inferior frontal sulcus; dPMC = dorsal pre-motor cortex; ITG = inferior temporal gyrus.

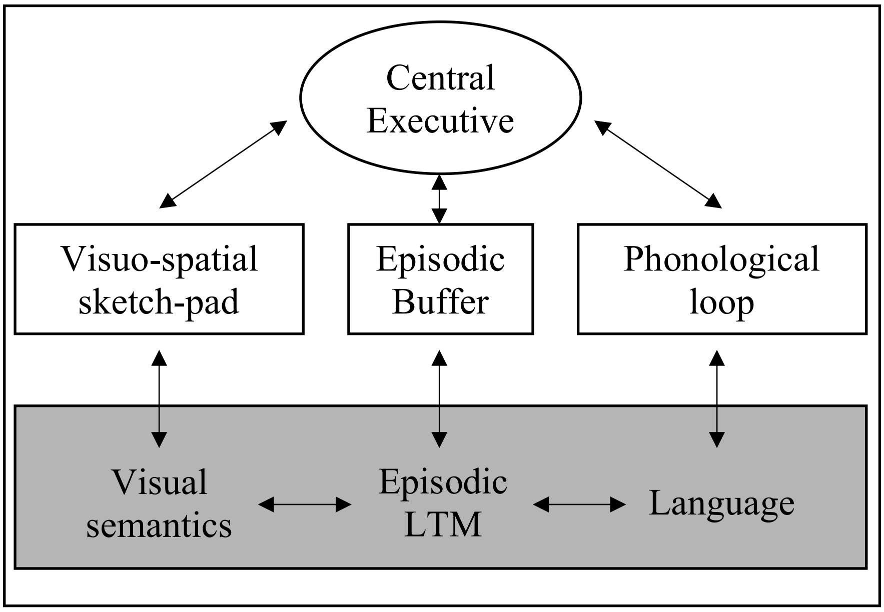

Figure 1. The multicomponent model of working memory. Adapted from “The episodic buffer: a new component of working memory?” by A. Baddeley, 2000, *Trends in Cognitive Sciences, 4*(11), p. 421.

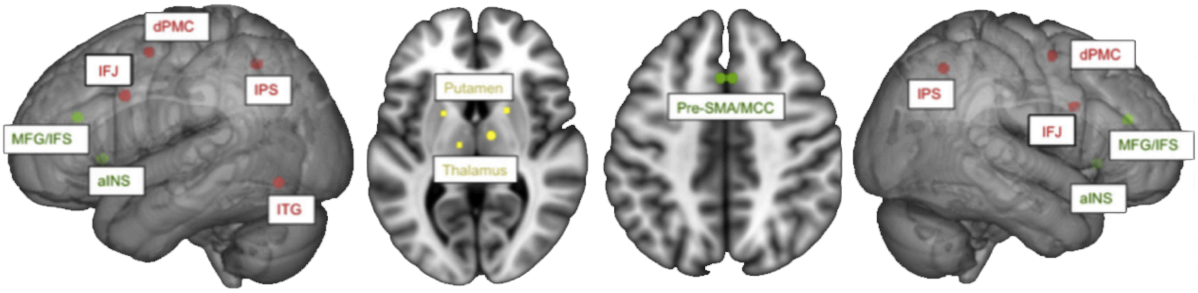

Figure 2. Regions of the extended multiple demand network. Adapted from “Definition and characterization of an extended multiple-demand network”, by J.A. Camilleri, V.I. Müller, P. Fox, A.R. Laird, F. Hoffstaedter, T. Kalenscher, S.B. Eickhoff, 2018, *NeuroImage, 165,* p. 144.

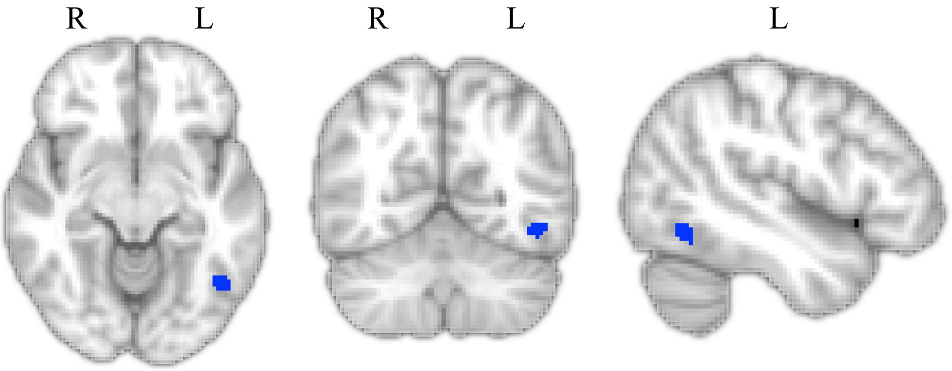

Figure 3. Left inferior temporal gyrus (dark blue) plotted onto the ICBM-152 template from the Montreal National Institute. From right to left: transversal view, frontal view, sagittal view. All in radiological view, therefore are right and left side transversed.

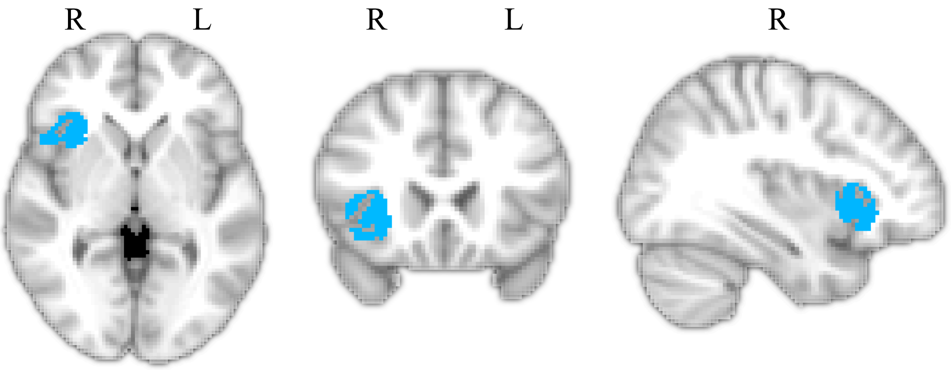

Figure 4. Right anterior insula (bright blue) plotted onto the ICBM-152 template from the Montreal National Institute. From right to left: transversal view, frontal view, sagittal view. All in radiological view, therefore are right and left side transversed.

Selbstständigkeitserklärung / Declaration of Authorship

Hiermit erkläre ich, dass ich die vorliegende Arbeit mit dem Titel

„Structural corelates of visuospatial and verbal working memory"

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I hereby declare that I have authored the thesis entitled

"Structural correlates of visuospatial and verbal working memory"

No other person's work has been used without due acknowledgement in this thesis. Where I have quoted from or adapted the work of others, the source is always given. This includes the sources of graphs and data.

Düsseldorf, 04.09.2018 L. Machalski

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