

Working memory capacity and the functional connectome - insights from resting-state fMRI and voxelwise centrality mapping

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Abstract The functional connectome represents a comprehensive network map of functional connectivity throughout the human brain. To date, the relationship between the organization of functional connectivity and cognitive performance measures is still poorly understood. In the present study we use resting-state functional magnetic resonance imaging (fMRI) data to explore the link between the functional connectome and working memory capacity in an individual differences design. Working memory capacity, which refers to the maximum amount of context information that an individual can retain in the absence of external stimulation, was assessed outside the MRI scanner and estimated based on behavioral data from a change detection task. Resting-state time series were analyzed by means of voxelwise degree and eigenvector centrality mapping, which are data-driven network analytic approaches for the characterization of functional connectivity. We found working memory capacity to be

inversely correlated with both centrality in the right intraparietal sulcus. Exploratory analyses revealed that this relationship was putatively driven by an increase in negative connectivity strength of the structure. This resting-state connectivity finding fits previous task based activation studies that have shown that this area responds to manipulations of working memory load.

Keywords Working memory · Resting-state fMRI · Connectome · Intraparietal sulcus · Working · memory capacity, cognitive ability

Introduction

The ability to retain and to manipulate information, even in the absence of external stimulation, is a key prerequisite for goal-directed and purposeful interaction with the environment. The mental faculty underlying this ability has been labeled working memory (Baddeley and Hitch 1974; Goldman-Rakic 1995) and is one of the most central concepts in cognitive psychology and the cognitive neurosciences, most likely because of its relevance for clinical phenotypes (Lee and Park 2005), intelligence (Conway et al. 2003) and academic success (Alloway and Alloway 2010). A distributed set of brain regions supports working memory processes with lateral prefrontal cortex (PFC) being the most prominent (Owen et al. 2005). Lateral PFC shows sustained activity during the retention of information in working memory. It is debated however, if lateral PFC stores information itself (Sreenivasan et al. 2014; Riley and Constantinidis 2016). Current systems neuroscience accounts content that lateral PFC provides attentional control signals that exert control over extrastriate areas that hold representations of the retained information online (Smith

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and Jonides 1999; Petrides 2000; D’Esposito et al. 2000; Awh and Jonides 2001; Lee and D’Esposito 2012; Riggall and Postle 2012; Scolarì et al. 2015; Lorenc et al. 2015). This segregation of the working memory network into storage and control structures is in line with cognitive working memory accounts that postulate a control system that monitors modality specific storage units (Baddeley 1986; Cowan 1999).

A neural correlate for the storage unit for visuospatial information has been localized in posterior parietal regions, along the dorsal visual stream (Mishkin et al. 1983): Here, neural activity is sensitive to the amount of information retained: Evidence from electroencephalographic recordings (Vogel and Machizawa 2004; Vogel et al. 2005) and functional magnetic resonance imaging (Todd and Marois 2004, 2005) shows a linear (positive) relationship between activity and working memory load until the individual’s capacity limit is reached, and an asymptotic plateau afterwards. The neural source of these signals has been localized along the intraparietal sulcus, with stronger activation in the right hemisphere (McNab and Klingberg 2008).

An imminent aspect of this neural framework for working memory is the idea that all implicated regions exchange information during working memory performance. And indeed, the analysis of task-related functional connectivity (Palva et al. 2010; Nee and Brown 2013) indicates that the distributed neural sites activated by working memory tasks form a functionally connected network. It is assumed that characteristics of this network relate to performance on working memory task and can be diagnostic for individual differences in the normal range but also in clinical conditions (Repovš and Barch 2012).

The field of connectomics is currently emerging as the science of brain networks. Besides seed-based analysis of single brain connections and multivariate statistical composition of connectivity data, the field draws from the corpus of mathematical graph theory to characterize connectivity on the whole brain level (van den Heuvel and Hulshoff Pol 2010; Bassett and Bullmore 2009). In order to study the functional connectome, cognitive neuroscience studies have extensively capitalized on resting-state functional magnetic resonance imaging (rs-fMRI) data (Smith et al. 2013; Vaidya and Gordon 2013). In typical rs-fMRI experiments, participants do not engage in a specific task while functional images are acquired (van den Heuvel and Hulshoff Pol 2010). Despite the unconstrained nature of the resting-state, there is a high degree of stability in the organization of functional connectivity (Shehzad et al. 2009; Braun et al. 2012; Cao et al. 2014) suggesting trait-like properties of the functional connectome at rest (Markett et al. 2013).

While working memory can be understood as a collection of processes that support encoding, maintenance, and retrieval of information in support of current task goals and therefore has a strong state component (D’Esposito and Postle 2015),

working memory capacity on the contrary is thought to have stable trait-like properties. Working memory capacity refers to the maximal amount of information an individual can retain over a short interval in the absence of external stimulation (Owen et al. 2005) and is surprisingly limited (Cowan 2001), given its tremendous impact on general cognitive ability (*g*, intelligence) (Conway et al. 2003). Working memory capacity cannot be directly observed but can only be inferred across a set of instances. In the visual modality, this can be accomplished by the change-detection task that involves the short-term retention of a variable number of visual objects (Luck and Vogel 1997).

In the present study we seek to characterize neural correlates of working memory capacity as a cognitive trait with network properties of the resting brain. To this end, we apply two types of centrality mapping to resting-state data. During centrality mapping, a weight is assigned to each voxel based on its connectivity pattern with all other voxels (Lohmann et al. 2010). We calculated degree centrality (DC) which is a voxel-wise summary measure of connectivity strength. DC mapping exclusively aims at “first step connectivity”, i.e. at connectivity strength between a given voxel and all other voxels. We therefore complemented our analysis by eigenvector centrality (EC) mapping which additionally takes connectivity pattern beyond the first step into account. During EC mapping, centrality scores are weighted by the centrality of connected voxels. Thus, higher values do not only indicate more connections, but also more connections to well-connected voxels. As data-driven and model-free approaches, centrality mapping techniques do not require the selection of regions or networks of interest as nodes for network analysis and are an ideal method for the study of connectivity throughout the entire functional connectome. Besides from this exploratory whole-brain approach, we focus on the intraparietal sulcus region as this area has been implicated in visuo-spatial working memory capacity in previous reports (McNab and Klingberg 2008).

Methods

Subjects

The study protocol was approved by the ethics committee of the University Clinics Bonn and was in accordance with the Declaration of Helsinki. A total of $N = 78$ healthy, right-handed volunteers ($n = 39$ males, $n = 39$ females, mean age $M = 23.32$ years, $SD = 3.71$) participated in the study after providing informed written consent. All participants were free of past or present psychiatric disorders, neurological disorders or past head injuries as assessed by a screening questionnaire.

Behavioral testing

Working memory capacity was assessed outside the MRI scanner immediately after image acquisition by a change detection task (Luck and Vogel 1997). A total of 128 trials were administered in 4 blocks (hence 32 trials in each block). The stimulus sequence of a representative trial is depicted in Fig. 1. Each trial started with a centrally presented fixation cross (500 ms). Subsequently, a variable number of colored squares ($.08^\circ$) lit up on randomly chosen positions around central fixation (about 3.3° away). Squares were either black, blue, green, purple, red, white or yellow, and no squares of the same color were presented on a given trial. The brief presentation of 100 ms ensured that participants were not able to rely on eye-movements or meta-mnemonic strategies to memorize the squares' colors. The number of squares was increased block wise from three to six (block 1 = three squares, block 2 = four squares, block 3 = five squares and block 4 = six squares). After stimulus presentation and a stimulation free retention interval of 1000 ms a probe array appeared. This array was either identical to the memory array (catch trial) or different with respect to the color of one square (change trial). Figure 1 depicts a change trial. Both trial types occurred equally often (16 catch and 16 change trials) and participants were instructed to indicate by button press on a keyboard whether a change had occurred or not. Trials were spaced by an intertrial interval of 1000 ms. Participants were allowed to take breaks between blocks. Participants chose to rest for $M = 6.7$ s between blocks on average ($SD = 8.9$). The length of breaks was not correlated with the main performance measure ($r = -.049$, n.s.). Individuals' working memory capacity was quantified by a formula originally proposed by Pashler (1988) for whole-display change detection paradigms: For each block, the maximal capacity was estimated by $K = ((HR - FR) / (1 - FR)) * N$, where K is the individuals working memory capacity on this block, HR and FR the hit and false alarm rates and N the number of squares in the array. As the main dependent measure, the highest individual capacity estimate across blocks was selected and set as individuals' overall working memory capacity (Markett et al. 2010). This measure captures working memory capacity best because the change detection task is a classical power test with little between-participant variation

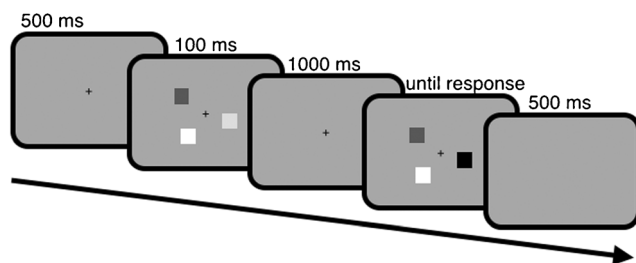


Fig. 1 Representative trial from the working memory task. Depicted is a trial with three items in the target array

before and a performance plateau after the individual capacity limit is reached.

Imaging protocol

From each participant, 245 T2*-weighted volumes were obtained on a Siemens Avanto 1.5 T scanner (Siemens, Erlangen, Germany) at the Life & Brain Center in a single 12-min session. Each volume consisted of 38 slices (thickness: 3 mm, interslice gap: 1 mm, in plane resolution: 3 mm \times 3 mm) scanned in interleaved order (TR: 3.04 s, TE: 45 ms, Flip Angle: 90°, Field of View: 192 mm). Participants were instructed to lie as still as possible with their eyes closed and without thinking about anything in particular and without falling asleep. All participants confirmed immediately after image acquisition via the MRI intercom that they managed to stay awake throughout the scanning session. After the functional scan, a high resolution structural T1-weighted image with 160 sagittal slices with 1 mm thickness was acquired from each participant using a Magnetization Prepared Rapid Gradient Echo (MP-RAGE) sequence (Field of View: 256 mm, in plane resolution: 1 mm \times 1 mm). Foam padding was used to constrain head movements during image acquisition.

Preprocessing

Preprocessing of the functional MRI data was carried out using SPM8 (www.fil.ion.ucl.ac.uk/spm) and the data processing assistant for resting state fMRI (DPARF, Yan and Zang 2010) as in a previous study using voxelwise centrality mapping (Markett et al. 2015). Preprocessing contained the following steps: (1) removal of the first ten volumes (2) slice timing (3) realignment (4) controlling for twelve voxel-specific movement parameters and the head motion scrubbing regressors (Power et al. 2012; DPARF default settings), as well as whole brain, white matter and cerebrospinal fluid signals by means of linear regression (5) bandpass filtering (.01–.08 Hz) (6) coregistration with the high resolution structural scan (7) spatial normalization using the T1-unified segmentations of the structural image and (8) spatial smoothing with a Gaussian kernel with a full width of 6 mm at half maximum. Identification of bad time points for head motion scrubbing (“motion censoring”) was based on the DPARF default setting: Time points with a framewise displacement >0.5 as well as time points immediately preceding (one time point) and succeeding (two time points) these time points were flagged as bad. Scrubbing was performed by means of linear regression to avoid individual differences in the amount of time points for connectivity analyses. Three participants were excluded from further analyses because of excessive head movement ($>3^\circ$ rotation or >3 mm translation).

Even though motion scrubbing and bandpass filtering are recommended and commonly applied in resting-state fMRI

studies, the two preprocessing steps are not without criticism (Carp 2013; Niazy et al. 2011; Kalcher et al. 2014). We therefore tested whether the main results reported in the results section depended on these two preprocessing steps. Omitting scrubbing from the preprocessing pipeline did not change the results. Omitting bandpass filtering and only applying a high pass filter of .01 Hz however, affected the results in a way that no significant results were obtained. The here reported associations hold only for the lower frequency band of resting-state time series.

Graph formation and network analysis: The functional connectome was modeled as a weighted undirected graph with each voxel in the cerebrum as a node and functional connectivity between each pair of voxels as an edge. Edge weights representing connectivity strength were defined as linear correlations between blood oxygen level dependent (BOLD) time-series of each pair of voxels. We denote the corresponding adjacency matrix by R , which is a symmetric N -by- N matrix, where N is the number of voxels. DC is defined as the row-wise sum of all entries in the adjacency matrix. EC is defined as the normalized positive eigenvector belonging to the largest eigenvalue of the adjacency matrix. Due to the Perron-Frobenius theorem the existence and uniqueness of such an eigenvector is ensured for (irreducible) matrices with non-negative entries. While the assumption of irreducibility is valid here, correlations might be negative. Hence a transformation R into a non-negative connectivity measure is required. This is done in our case by linear scaling to the unit interval (Lohmann et al. 2010; Wink et al. 2012), i.e. we define the N -by- N connectivity matrix C by $C_{ij} = (1 + R_{ij}) / 2$. No further thresholding was applied.

The main issue of performing centrality mapping is assembling and storing the matrix C and R , because of the enormous number of correlations. This obstacle can be overcome by using a so-called matrix factorization approach proposed by Wink et al. (2012): the correlation matrix R is rewritten as a product $R = QQ^t$, where Q is an N -by- T matrix and Q^t its transposed matrix. Here T is the length of the time series which is several orders smaller than N . Note that Q represents the normalized time series, i.e. the i ’th row of Q corresponds to the time series of the i ’th voxel with zero mean and unit variance. Based on this factorization ECM was carried out in Matlab with the power-iteration algorithm applied to C as proposed by Wink et al. (2012). The only storage requirement for this algorithm is the N -by- T matrix Q (instead of the N -by- N matrix R) and the vector-matrix-multiplication (as the core operation in the power-iteration algorithm) is rendered efficiently. For DC mapping, row-wise sums of C were computed. Because only first-step connections are required for the calculation of DC, the only computational requirement for DC mapping was assembling but not storing R and

C which rendered DC computation also efficient. Prior to statistical analysis, all centrality maps were transformed into a Gaussian distribution (Van Albada and Robinson 2007).

Statistical analyses

We relied on parametric statistical testing for all analyses because a Shapiro-Wilk test indicated that the individual working memory capacity estimates followed a normal distribution ($p = .489$). Possible sex differences were assessed by a t-test and a possible relationship with age was explored using linear correlation analysis.

Association between working memory capacity and centrality maps were tested by multiple linear regression models in SPM8 with working memory capacity as covariate of interest and age, sex, and the number of scrubbed time points as nuisance regressors. The family-wise error in the resulting statistical parametric map was corrected at the cluster level ($p < .05$), after applying an initial statistical threshold of $p < .001$, uncorrected.

The calculation of centrality values included a linear scaling factor to circumvent the problem that arises from negative edge weights (Wink et al. 2012). This, however, complicates the interpretation of individual differences. Lower centrality values can either result from weaker positive connections or from stronger negative connections. Higher centrality values on the other hand can result from stronger positive or less pronounced negative connections. We therefore complemented our main analysis by an exploratory analysis where the sum of all positive and all negative connections was calculated separately from the R matrix and then correlated with working memory capacity. Because of its exploratory nature, this analysis was constrained to clusters that showed significant associations between centrality estimates and working memory capacity in the main analysis. Please note that this approach is similar to the analysis of “first step connectivity” proposed by Geib et al. (2015).

Results

Age, gender and performance in working memory

Women and men did not differ in their working memory capacity ($t(73) = .342, p = .733$) and there was no correlation between working memory capacity and participants’ age ($r = -.089, p = .499$).

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Figure 2 depicts participants’ mean working memory capacity depending on working memory load, i.e. number of items in

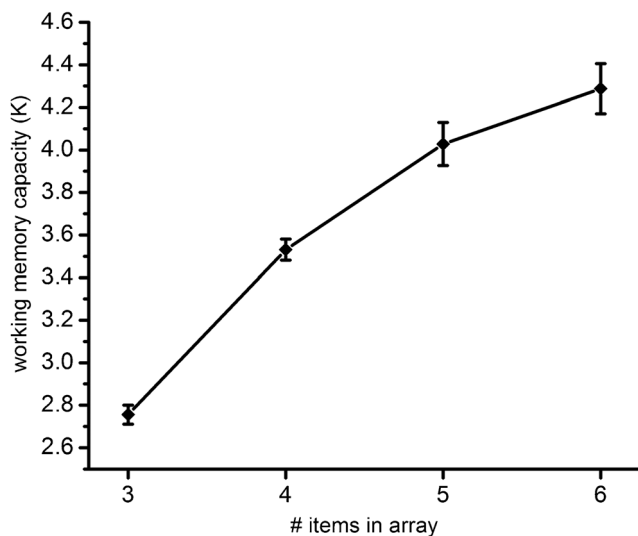
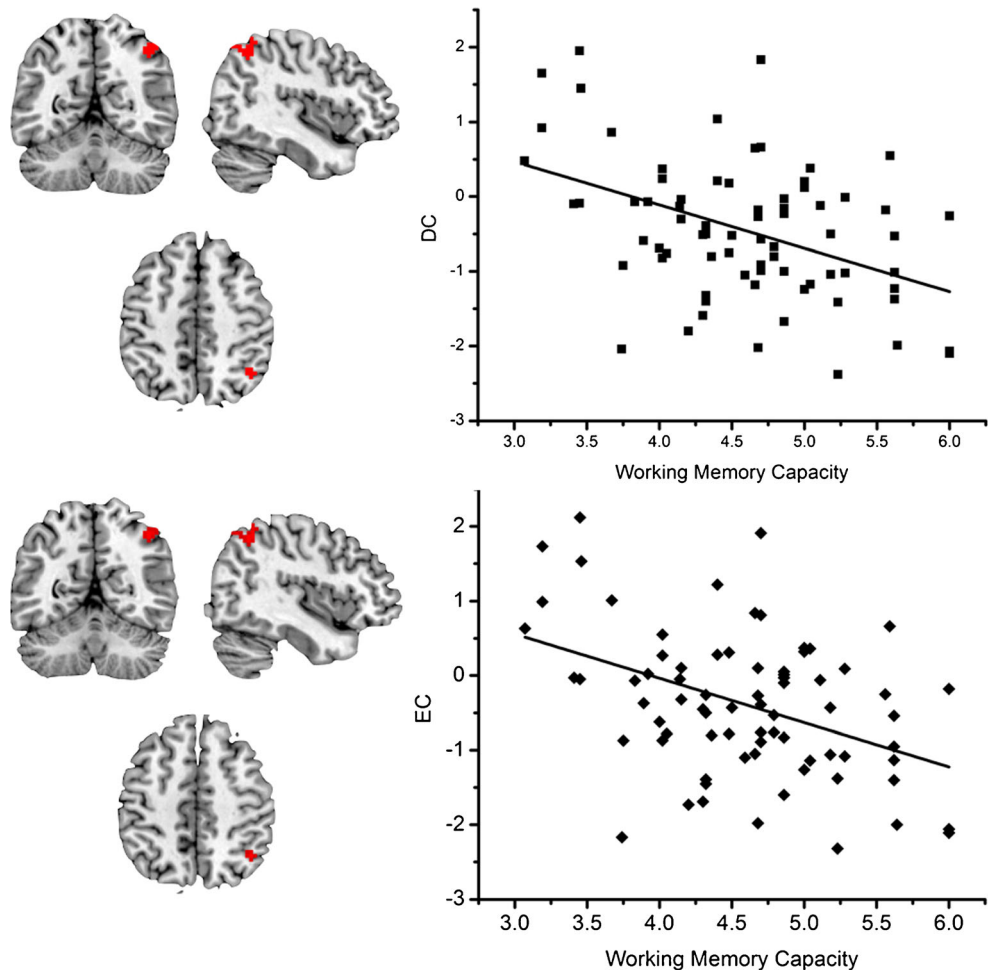


Fig. 2 Mean working memory capacity depending on working memory load across participants as estimated with the Pashler-K formula

the memory array. In accordance to previous reports, mean maximal working memory capacity equaled about four items

Fig. 3 A cluster in the right intraparietal sulcus ($x = 42$, $y = -57$, $z = 48$) shows an inverse relationship with working memory capacity (Top panel for DC, bottom panel for EC). The scatterplot on the top shows extracted mean DC values from the cluster, plotted against working memory capacity. The scatterplot on the bottom shows results for EC correspondingly



(Cowan 2001; Vogel and Machizawa 2004). Fig. 3 shows the results from the whole brain individual differences analysis on the relationship between working memory capacity (kmax) and the centrality maps. A negative relationship between centrality and WMC was observed for both DC (top panels) and EC (bottom panels). Both analyses revealed almost identical clusters in cortical areas along the right intraparietal sulcus including the inferior and superior parietal lobules (DC: peak voxel at $x = 42$, $y = -57$, $z = 48$, cluster size $k = 46$ voxels, $t(70) = 3.76$, $p = .027$, FWE-corrected; EC: peak voxel at $x = 42$, $y = -57$, $z = 48$, cluster size $k = 45$ voxels, $t(70) = 3.947$, $p = .022$, FWE-corrected). The reverse contrasts did not yield any results. Because the right intraparietal sulcus area has previously been found to be sensitive to working memory load in a task-activation fMRI study using the change detection task (McNab and Klingberg 2008), we complemented the whole brain analysis by a region of interest analysis (ROI) with a spherical ROI (10 mm radius) around the peak activation coordinate ($x = 48$, $y = -66$, $z = 48$) reported in the McNab and Klingberg (2008) paper. The rationale was to examine whether the present resting-state finding includes the precise anatomical location of previously

reported activation changes in the intraparietal sulcus. The statistical threshold for this ROI analysis was set to $p < .05$, corrected for the family wise error rate, as implemented in SPM's small volume correction. The additional ROI analysis confirmed that the cluster observed in the data-driven whole brain analyses corresponds to the previously reported location (DC: $t(70) = 3.76$, $p = .018$, family-wise error corrected at the ROI level; EC: $t(70) = 3.73$, $p = .021$, family-wise error corrected at the ROI level).

In a last step, we correlated working memory capacity with the sum of positive and negative functional connectivities from the cluster in the intraparietal sulcus separately (see methods). The brain-wide sum of all positive connectivities did not correlate with working memory capacity ($r = .096$, $p = .410$) while the brain-wide sum of all negative connectivities was intercorrelated with working memory capacity ($r = -.256$, $p = .027$). The negative sign of the correlation coefficient indicates stronger negative connections of the intraparietal sulcus in high capacity individuals.

Discussion

The present study's objective was to elucidate the relationship between resting-state connectivity and working memory capacity by combining centrality mapping on the voxel-level and behavioral performance on a visual change detection task. We observed an inverse relationship between degree and eigenvector centrality in a cluster alongside the right intraparietal sulcus and the maximum number of items participants could retain in working memory. Degree centrality is a summary measure of direct functional connectivity of a given brain region while eigenvector centrality introduces an additional weighting of the centrality estimates by taking connectivity profiles of other brain regions into account. Given the high degree of similarity in the results from either method and the considerable conceptual overlap between the two measures, we conclude that it is particularly the first step connectivity of the right intraparietal sulcus that is linked to working memory capacity.

The negative relationship between centrality estimates and working memory capacity suggests that the intraparietal sulcus is less centrally embedded into the whole brain functional connectome in individuals with higher working memory capacity. This, however, was not confirmed in additional analyses. Because of the linear scaling factor that was applied to account for negative edge-weights (Wink et al. 2012), lower centrality estimates do not necessarily reflect weaker positive connectivity but can also result from more pronounced negative connectivity. We found that negative but not positive connectivity strength of the intraparietal sulcus was linked to working memory capacity. This suggests that the reduced centrality estimates in high capacity individuals resulted from more pronounced negative connectivity of the intraparietal

sulcus. The intraparietal sulcus is a nexus within the frontoparietal attention network but shows a strong negative coupling with task-negative regions at rest (Fox et al. 2005; Fox et al. 2009). Weaker anti-phasic relationships between task-positive and negative networks at rest have been linked to higher behavioral variability and thus poorer performance during cognitive tasks (Kelly et al. 2008). The current finding could reflect a similar relationship. Increases in negative connectivity strength of the intraparietal sulcus in high capacity individuals could thus also stem from more efficient inhibition of task-irrelevant processing which has been shown to interrupt working memory and control processing (Vogel et al. 2005; Weissman et al. 2006).

Previous work has highlighted the posterior parietal cortex and particularly the intraparietal sulcus as key neural correlates of performance in the change detection working memory task. This is important to note since the present study focussed on a graph theoretical analysis of resting-state fMRI data. Even though graph theoretical approaches to functional connectivity data are widely used and well-evaluated means for the data-driven exploration of large connectivity datasets (Keilholz et al. 2010), its high level of abstraction raises questions on the underlying physiology (De Vico Fallani et al. 2014). Evidence from complementary approaches has shown that the intraparietal sulcus seems to scale its activity during the retention of visuospatial information with memory load. Event related potentials in electrophysiological activity over parietal sites show an increasing negativation that depends on the number of items retained and BOLD activity in the intraparietal sulcus increases linearly with increasing working memory load (Vogel et al., 2004; Todd and Marois 2004). The present study's cluster lies at the exact same location as a load sensitive cluster reported previously (McNab and Klingberg 2008). It thus appears that the association between the intraparietal sulcus and working memory capacity extends into the stimulation-free resting state. Newer evidence suggests that the intraparietal sulcus encodes the precision of working memory representations (Weber et al. 2016) and shows increased functional connectivity with lateral PFC during the manipulation of memory representations (Bray et al. 2015). This connectivity is presumably supported by structural white matter tracts that connect posterior parietal and prefrontal sites either directly or indirectly via the thalamus and the basal ganglia. Working memory maintenance correlates particularly with structural connectivity strength of the direct pathway (Ekman et al. 2016). This finding was obtained by a graph theoretical investigation and validated by probabilistic tractography. Our version of change detection task emphasized working memory maintenance which raises the question how the present finding relates to structural connectivity. Future studies may want to combine resting-state functional with structural connectivity assessments to characterize the brain network that underlies working memory and individual

differences in working memory functions in more depths. This should be combined with the examination of task-evoked network changes during working memory. First studies have looked at network-specific and brain-wide connectivity changes during working memory tasks (Cohen et al. 2014; Cohen and D'Esposito 2016). Such approaches will help to clarify the relationship between activity and connectivity, at rest and during task performance. Furthermore, it is of utmost importance to characterize connectivity changes with complementary methods. Palva et al. (2010) have used magnetencephalographic recordings to study brain wide phase synchrony in different frequency bands. Of note, they also identified the intraparietal sulcus as the connectivity hub with the highest involvement in individual differences in working memory capacity. New approaches have been proposed to combine hemodynamic and electrophysiological recordings for the formation of brain-wide network graphs (Yu et al. 2016). Such approaches will help to clarify the physiological basis of graph-theoretical measures. Together with other approaches to resting-state fMRI such as independent component analysis (Beckmann et al. 2005; Seeley et al. 2007; Bey et al. 2015; Smith et al. 2015) and resting-state data of higher quality such as data taken from the Human Connectome Project (Van Essen et al. 2013), they have the potential to eventually clarify the relationship between functional connectivity and higher cognition.

Even though areas alongside the intraparietal sulcus show sustained activity during retention intervals of working memory tasks, the identity of memorized items is not decodable from this activity: These areas seem to encode trial-specific information related to task instructions while stimulus identity is encoded by non-sustained activity in low-level sensory areas (Riggall and Postle 2012). Given the intraparietal sulcus does not store information itself, the present finding should be better interpreted as a resting-state correlate of a working memory related control processes rather than a correlate of item storage capability at baseline. This, however, would rise the question why prefrontal control areas do not show a similar relationship. While the prefrontal cortex shows sustained activity during working memory retention (Curtis and D'Esposito 2003), its activity levels do not correlate with working memory load in the change detection task (Todd and Marois 2004). It is conceivable that the present association between working memory capacity and the intraparietal connectivity at rest reflect between-participant efficiency by which this region can be recruited during task processing.

Working memory capacity relates positively to general cognitive ability, even to an extent that some authors consider the two constructs isomorphic (Kyllonen and Christal 1990). A prominent theory on the neurobiological foundations of cognitive ability highlights the integration of frontal and parietal sites as a neural substrate of human intelligence differences (Jung and Haier 2007). In the resting state, the

intraparietal sulcus is the central hub of the fronto-parietal network (Fox et al. 2005). This network has already been linked to general cognitive ability (Colom et al. 2010). Furthermore, frontal and parietal regions have recently been implicated in a multivariate pattern of brain connectivity that relates to a wide range of behavioral and demographic variables, including general cognitive ability (Smith et al. 2015). Given the high importance of general intelligence for academic success, health, and longevity (e.g. Gottfredson and Deary 2004), it is not only of high importance to understand the basis of intelligence, it is also imperative to derive training routines and to obtain measures to monitor training success. The fast centrality mapping approach applied here provides a fast and efficient means to assess the organization of large scale functional connectivity across the entire brain network. It would be valuable to explore the robustness of our present finding across different populations and its plasticity to cognitive training programs.

Compliance with ethical standards

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Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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