

Predicting working memory capacity based on glutamatergic concentration and its modulation of functional connectivity

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Competing interests

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Abstract

Working memory capacity, the amount of information one can hold online in mind, has a central role in cognition. Previous electrophysiological and imaging studies revealed the pivotal role of persistent activity within parietal and frontal regions as the neural foundations underpinning working memory capacity. The best candidate molecules determining persistent activity are the brain's major excitatory and inhibitory neurotransmitters, glutamate and gamma-aminobutyric acid (GABA), respectively. However, our knowledge of these neurophysiological determinants in forming working memory capacity is still poor. Using magnetic resonance spectroscopy, we examined the contribution of glutamate and GABA within the left intraparietal sulcus and the left inferior/middle frontal gyrus in tracking working memory capacity. A positive association was found between glutamate within the left intraparietal sulcus and working memory capacity. By utilising resting-state functional MRI, we identified a negative association between parieto-cingulate connectivity and working memory capacity. Individual variation in parieto-cingulate connectivity was explained by glutamatergic concentration in the intraparietal sulcus. Moreover, we found that parieto-cingulate connectivity mediated the relationship between intraparietal sulcus glutamate and working memory capacity. This set of findings reveals a novel mechanistic insight by which glutamatergic concentration within the intraparietal sulcus shapes WM capacity via parieto-cingulate connectivity.

Keywords: glutamate; working-memory; intraparietal sulcus; brain connectivity

Introduction

Working memory (henceforth, **WM**) represents our ability to maintain and manipulate information over a period of seconds (Baddeley, 1986). Individual differences in WM capacity are large and seem to be highly stable over time (Kane & Engle, 2002). WM is a central aspect of high-level cognition (Conway, Kane, & Engle, 2003; Süß, Oberauer, Wittmann, Wilhelm, & Schulze, 2002) and WM impairments were documented in several psychiatric and neurological disorders such as Down's syndrome, Williams syndrome, specific language impairment, and attentional deficits (Gathercole & Alloway, 2006; Luck & Vogel, 2013).

Given its widespread importance, the neural foundations of WM capacity were extensively studied using a wide range of methodologies which showed the pivotal role of frontal and parietal lobes. Early lesion studies demonstrated the contribution of the frontal cortex (Pribram, Mishkin, Rosvold, & Kaplan, 1952; Warren & Akert, 1964). Subsequent electrophysiological studies confirmed the role of frontal cortex in the monkey (Fuster & Alexander, 1971; Kubota & Niki, 1971), and a classic work extended this prior evidence by delineating how the frontal cortex encodes spatial information of remembered stimuli thus providing a neural code of spatial WM (Funahashi, Bruce, & Goldman-Rakic, 1989). Apart from the frontal cortex, the parietal cortex was involved in the storage of visuospatial information. In particular, functional magnetic resonance imaging (fMRI) and electroencephalography investigations demonstrated that parietal brain activity is sensitive to working memory load (Cowan et al., 2011; Dumontheil & Klingberg, 2011; Katsuki & Constantinidis, 2012; Linden et al., 2003; McNab & Klingberg, 2008; Vogel & Machizawa, 2004). More recent work attempted to decode stimulus identify from delay-period parietal activity but currently, there is no consistent support as decoding was successful in some studies but not in others (Bettencourt & Xu, 2016; Christophel, Hebart, & Haynes, 2012;

Emrich, Riggall, LaRocque, & Postle, 2013; Ester, Sprague, & Serences, 2015; Lee, Kravitz, & Baker, 2013; Linden, Oosterhof, Klein, & Downing, 2012; Riggall & Postle, 2012; Yu & Shim, 2017), and recent evidence rather suggest a general attentional role of the IPS in the context of WM (Majerus et al., 2016; Postle, 2015).

According to persistent activity models, WM maintenance ability is underpinned by persistent brain activity during information maintenance (Constantinidis & Klingberg, 2016). Indeed, the models of parietal and frontal persistent activity (Katsuki & Constantinidis, 2012) constitutes one of the most well-characterized neurofunctional profiles of WM capacity although it has been strongly questioned in the last few years (Masse, Yang, Song, Wang, & Freedman, 2019; Sreenivasan & D'Esposito, 2019) and other models have been proposed which rely on fast synaptic plasticity (Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015). Very recent accounts proposed that both persistent- and fast synaptic plasticity mechanisms can co-exist within a unified system in which neurons hold information in both activity and synapses (Manohar, Zokaei, Fallon, Vogels, & Husain, 2019). Since persistent activity is mediated by synaptic transmission involving the brain's major excitatory and inhibitory neurotransmitters (Shu, Hasenstaub, Badoual, Bal, & McCormick, 2003; Shu, Hasenstaub, & McCormick, 2003), an emerging question is whether the baseline concentrations of glutamate and GABA in these very regions can track individual variation in WM capacity. Importantly, recent studies demonstrated the role of glutamate and GABA in cortical excitation and inhibition in high-level cognition including mathematics, memory, and attention (Barron et al., 2016; Kathrin Cohen Kadosh, Beatrix Krause, Andrew J King, Jamie Near, & Roi Cohen Kadosh, 2015; Hone-Blanchet, Edden, & Fecteau, 2016; Kihara, Kondo, & Kawahara, 2016; Krause, Looi, Dresler, & Cohen Kadosh, 2018). A previous investigation failed to find an association between the WM and neurotransmitters within the left frontal and right parietal regions (K. Cohen Kadosh, B. Krause, A. J. King, J. Near, & R. Cohen Kadosh,

2015). However, apart from the right intraparietal sulcus, WM storage was documented in the left side in fMRI and electrophysiological studies, and the left intraparietal sulcus was also found to have a modality free contribution to WM (Cowan et al., 2011; Linden et al., 2003; Vogel & Machizawa, 2004). Therefore, the main aim of the present study was to examine whether glutamatergic and GABAergic concentrations within the left parietal (intraparietal sulcus; henceforth **IPS**) and frontal (inferior/middle frontal gyrus; henceforth **FG**) regions track individual variation in WM capacity. We combined a behavioural session (**Fig 1C**) assessing WM capacity with a scanning session involving magnetic resonance spectroscopy (henceforth, **MRS**) of the left IPS and FG only, that we defined apriori as a volume of interest while participants were in the scanner. During the scanning session, we quantified the concentration of glutamate and GABA in each region (**Fig 1A, B**). This procedure allowed us to identify the role of glutamatergic and GABAergic concentrations in tracking WM capacity and to establish its regional and neurotransmitter specificity. Furthermore, since glutamate and GABA are abundant in the brain and directly affect brain activity including regional blood-oxygen-level-dependent (BOLD) signal and brain connectivity in several networks including the default mode and the motor networks (DiNuzzo, Gili, Maraviglia, & Giove, 2011; Duncan et al., 2013; Frangou et al., 2019; Kapogiannis, Reiter, Willette, & Mattson, 2013; Logothetis, 2008; Staggs et al., 2014), we used resting-state functional magnetic resonance imaging (fMRI) in the same individuals to map the connectivity between the region that showed association with WM capacity and the rest of the brain as a function of WM capacity, and we examined how this resting-state connectivity was associated with neurotransmitters concentration and WM capacity.

Material and Methods

We recruited 22 healthy participants (16 males, mean age=26.05, standard deviation=6.5) who were informed that the study investigated the behavioural and neural mechanisms of

spatial memory. The completion of the structural, the neurochemical (MRS) and the neurofunctional (resting-state fMRI) acquisition lasted ~60min. The completion of the WM capacity testing, which was performed on a separate session outside the scanner, lasted ~15min. Participants received monetary compensation for their participation. The working memory capacity data of this cohort was previously used as part of a two-site neurostructural investigation (Zacharopoulos, Klingberg, & Kadosh, 2020). All participants provided written, informed consent and the study was approved by the University of Oxford's Medical Sciences Interdivisional Research Ethics Committee (MS-IDREC-C2_2015_016).

MR data acquisition and pre-processing

All MRI data were acquired at the Oxford Centre for Functional MRI of the Brain (FMRIB) on a 3T Siemens MAGNETOM Prisma MRI System equipped with a 32 channel receive-only head coil. Anatomical high-resolution T1-weighted scans were first acquired (MPRAGE sequence: TR=1900ms; TE=3.97ms; 192 slices; voxel size=1×1×1mm).

For MRS, spectra were measured with a semi-adiabatic localization by adiabatic selective refocusing (semi-LASER) sequence (TE=32 ms; TR=3.5 s; 32 averages) (Deelchand et al., 2015; Öz & Tkáč, 2011) with variable power RF pulses with optimized relaxation delays (VAPOR), water suppression and outer volume saturation. Unsuppressed water spectra acquired from the same volume of interest were used to remove residual eddy current effects and to reconstruct the phased array spectra with MRspa

(<https://www.cmrr.umn.edu/downloads/mrspa/>). Two 20mm³ voxels of interest were manually placed centred on the left intraparietal sulcus (IPS) and centred on the left inferior/middle frontal gyrus (FG) based on the individual's T1-weighted image while the

participant lay down in the MR scanner. Acquisition time per voxel of interest was 10-15 minutes including sequence planning and shimming and B0 shimming.

Neurochemicals were quantified with an LCmodel (Provencher, 2001) using a basis set of simulated spectra generated based on previously reported chemical shifts and coupling constants based on a VeSPA (versatile simulation, pulses, and analysis) simulation library (Soher, Semanchuk, Todd, Steinberg, & Young, 2011). Simulations were performed using the same RF pulses and sequence timings as in the 3T system described above. Absolute neurochemical concentrations were extracted from the spectra using a water signal as an internal reference.

As in previous studies, the exclusion criteria for data was the Cramér-Rao bounds (Emir, Tuite, & Öz, 2012). Neurotransmitters quantified with Cramér-Rao lower bounds (CRLB, the estimated error of the neurotransmitter quantification) >50% were classified as not detected. Additionally, we excluded cases with an SNR beyond 3 standard deviations (per voxel of interest, per neurotransmitter), and neurotransmitter or WM capacity score that fallen beyond 3 standard deviations from the group mean. This led to the exclusion of 2 cases for the GABA measure of the frontal gyrus. For each participant, we calculated 4 (brain region (frontal, parietal) * neurochemical (GABA, glutamate)) neurotransmitter concentrations all of which were calculated as the ratios between the absolute neurotransmitter concentrations divided by the absolute concentration of total creatine (creatin+phosphocreatine). The neurotransmitter concentrations were referenced to total creatine for (i) creatine is a commonly used as a reference and it is widely accepted as an internal reference standard, (ii) its signal shares the same imperfections (e.g., frequency drift, phase drift, and subject motion) as the signal of the GABA and glutamate as all concentrations are acquired simultaneously (Kathrin Cohen Kadosh et al., 2015).

Visuospatial WM capacity

WM capacity for each participant was assessed in a single session. Participants were asked to perform a trial session to ensure that they understood the instructions and be familiar with the experimental procedure and testing environment. Once this was done, the experimenter left and the participants completed the behavioural task in a soundproofed testing booth. Once the session was completed the participants informed the experimenter accordingly. The stimuli were presented on a computer screen, the responses were collected on a QWERTY keyboard, and the stimuli and the experimental procedure were implemented in MATLAB (Mathworks Inc., Natick, MA, USA) using Psychtoolbox (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997). During the main WM task (**Fig 1C**) participants were presented with three, four, five or six items followed by a delay and a probe phase where they were required to make a yes/no button press depending on whether the encoding stimuli had appeared at the location indicated by the probe stimulus. Participants completed 10 trials for each of the four conditions (i.e., three, four, five or six items). The WM capacity was measured using a standard formula (Cowan, 2001; Vogel, McCollough, & Machizawa, 2005) $K=S*(H - F)$, where K is the WM capacity, S is the array size, H is the observed hit rate and F is the false alarm rate. We calculated the K for all four array sizes and average them into a single score representing the WM capacity. We additionally present the mean (and standard deviation) of accuracy and reaction time in each of the four load conditions separately (see **Table 1**).

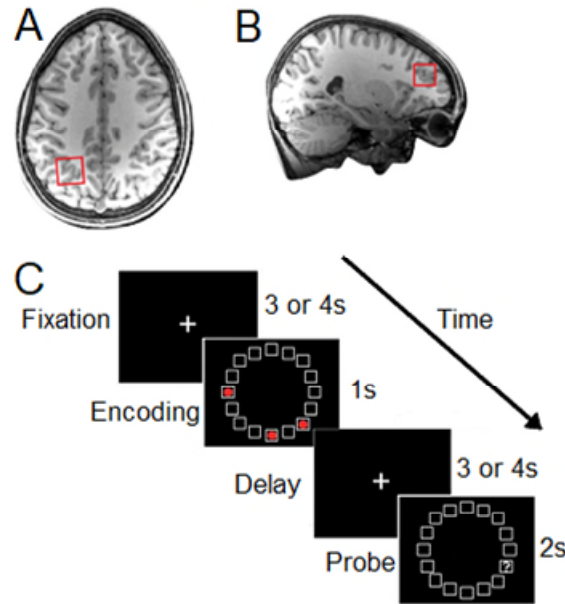


Fig 1. Positions of the two regions for the MRS displayed in a T1-weighted image for (A) IPS, (B) FG, are shown on axial and sagittal slices respectively. (C) Graphical representation of a single trial across the sequential trial events: i) fixation, (ii) encoding, (iii) delay, (iv) probe and response phases. Participants were asked to remember the location of 3 (red dots, as displayed here), 4, 5 or 6 stimuli.

Resting fMRI

Functional images were acquired with a multi-band acquisition sequence (Multi-band acceleration factor=6, TR=933ms, TE=33.40 ms, flip angle 64°, number of slices=72, voxel dimension=2×2×2mm, 380 volumes). Resting fMRI data were pre-processed and analysed using the CONN toolbox (www.nitrc.org/projects/conn, RRID:SCR_009550) (Whitfield-Gabrieli & Nieto-Castanon, 2012) in SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) using the default pre-processing pipeline “MNI-space direct normalization”. Functional volumes were motion-corrected, slice-timed corrected, segmented, normalized to a standardized (MNI) template, spatially smoothed with a Gaussian kernel (8-mm FWHM) and a pass filter (0.01Hz to Inf). Our a priori exclusion criteria were (i) the outlier identification step excluded more than 5% of the scans, and/or (ii) when the voxel-to-voxel correlation histogram was significantly non-zero ($r > .15$) led to 0%

exclusion of data. The IPS which was defined based on the Dorsal Attention network atlas which is featured within the CONN toolbox. We employed seed-to-voxel analyses and calculated the connectivity between the left IPS and the rest of the brain as a function of WM capacity score (described above) using an initial voxel-wise uncorrected threshold $P < .001$, and a cluster-level FDR corrected at $P < .05$, which are also the default values of the CONN toolbox.

Statistical Analyses

We examined the associations between the WM capacity and the concentration of glutamate and GABA in the IPS and FG. As the WM capacity score was not normally distributed in our sample (Kolmogorov-Smirnov statistic=.186, $P=0.047$, Shapiro-Wilk statistic=.901, $P=0.032$), we employed spearman correlations (Ibm, 2017). For mediation tests, we utilised the Sobel test ($z\text{-value} = a*b/\text{SQRT}(b^2*s_a^2 + a^2*s_b^2)$, where a = raw (unstandardized) regression coefficient for the association between independent variable and mediator, s_a = standard error of a , b = raw coefficient for the association between the mediator and the dependent variable (when the independent variable is also a predictor of the dependent variable), s_b = standard error of b (Sobel, 1982)). We also run the Goodman's version of the Sobel test $z\text{-value} = a*b/\text{SQRT}(b^2*s_a^2 + a^2*s_b^2 - s_a^2*s_b^2)$ (Goodman, 1960) from the mediation webpage by (Preacher & Leonardelli, 2001). We additionally assessed mediation using PROCESS, which estimates the indirect effect using bootstrapping methods (Hayes, 2017).

Results

Behavioural results

The descriptive statistics (mean and standard deviation) for accuracy and reaction time are displayed in **Table 1**. Lower accuracy and higher reaction time were observed with increasing load as expected.

Table 1. Mean and standard deviation of accuracy (%) and reaction time (ms) in each of the four load conditions separately.

	Accuracy		RT	
	M	SD	M	SD
Load 3	94	10	860	231
Load 4	93	7	921	233
Load 5	85	13	931	202
Load 6	78	19	1037	183

IPS glutamate positively predicts WM capacity

We first examined the association between WM capacity and IPS glutamate, IPS GABA, FG glutamate, and FG GABA. The IPS glutamate exhibited a positive association with WM capacity (**Fig 2A**, $r_s(20)=0.472$, $P=0.026$). None of the other three measures reached significance (**Fig 2B**, IPS GABA: $r_s(20)=0.053$, $P=0.813$; **Fig 2C**, FG glutamate: $r_s(20)=0.040$, $P=0.861$; **Fig 2D**, FG GABA: $r_s(18)=0.372$, $P=0.106$).

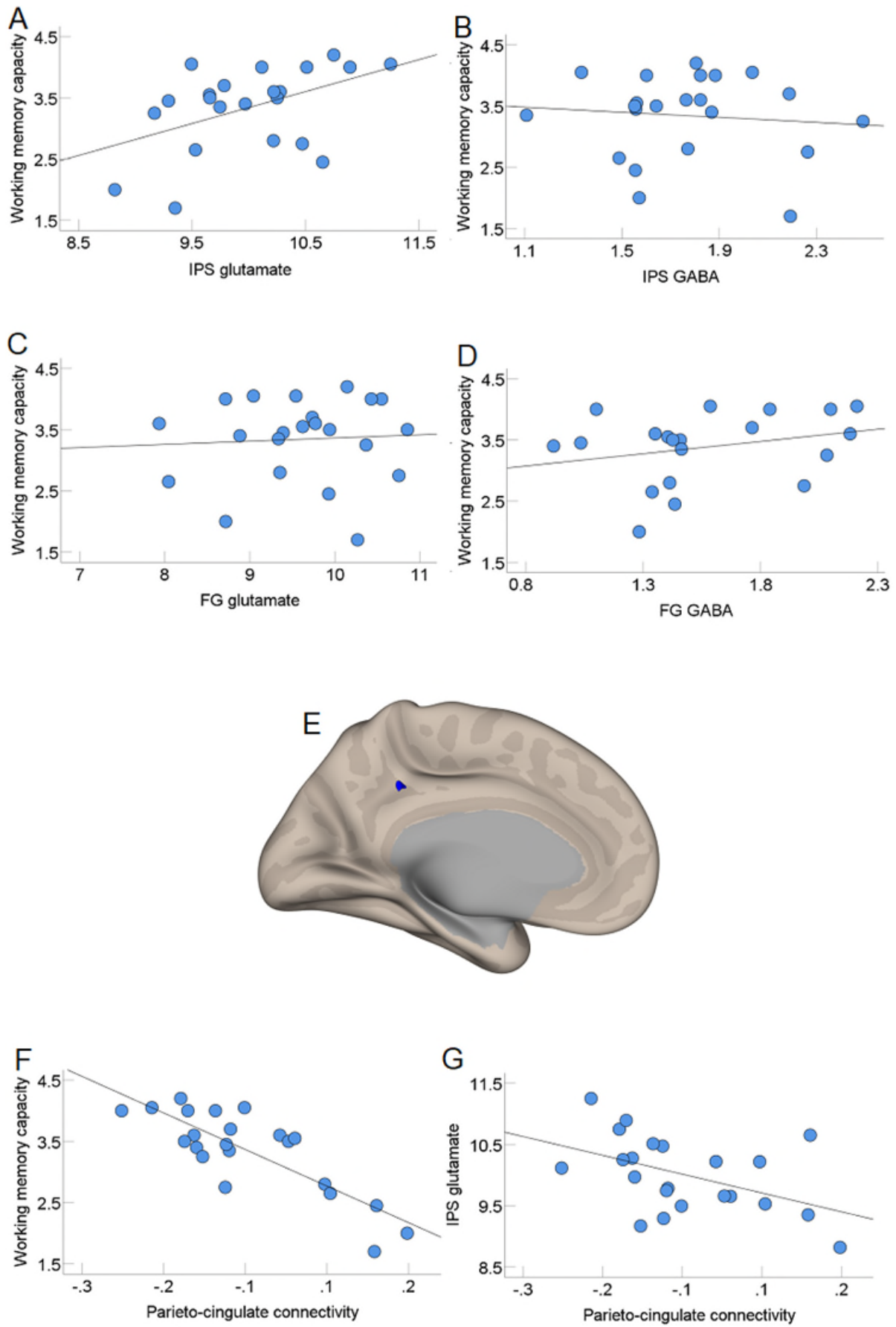


Fig 2. Scatterplots depicting the associations between individual variation in WM capacity (y-axis) and neurotransmitter concentrations in (A) IPS glutamate; (B) IPS GABA; (C) FG glutamate; and (D) FG GABA. Connectivity between the left IPS and (E) the posterior cingulate cortex (depicted in blue) was negatively associated with (F) WM capacity and (G) IPS glutamate concentration.

Subsequently, we examined whether glutamate's role was regionally specific to the IPS by regressing out the FG glutamatergic concentration from the IPS glutamatergic concentration. The correlation between the IPS glutamate unstandardized residuals and WM capacity was still significant ($r_s(20)=0.462$, $P=0.031$) highlighting that the glutamate's role on WM capacity is regionally specific to the IPS. To examine neurotransmitter specificity, we regressed out the IPS GABAergic concentration from the IPS glutamatergic concentration. This analysis revealed a significant correlation between the IPS glutamate unstandardized residuals and WM capacity ($r_s(20)=0.471$, $P=0.027$), suggesting that the IPS role on WM capacity was specific to glutamate than GABA. Taken these findings together, the strongest correlation between WM capacity and neurotransmitter concentration was found for glutamate within the IPS.

Parieto-cingulate connectivity is negatively associated with WM capacity

After elucidating the association between IPS glutamate concentration and WM capacity, we employed resting-state fMRI to investigate whether the connectivity between the left IPS and the rest of brain is related to WM capacity using a seed-to-voxel method (**Material and Methods** section). We identified a negative association between this left IPS and a cluster underlying posterior cingulate cortex/precuneus (**Fig 2E**, $x=14$, $y=-40$, $z=34$ $k=155$, $T(20)=3.85$, $pFDR=0.039$), and this connectivity was negatively associated to WM capacity (**Fig 2F**, $r_s(20)=-0.674$, $P=0.001$) and to IPS glutamate (**Fig 2G**, $r(20)=-0.470$, $P=0.027$).

We further examined whether IPS glutamate predicts WM capacity via parieto-cingulate connectivity which was indeed the case (Sobel test statistic=2.23, $SE=.19$, $P=0.026$, Goodman's version of the Sobel test statistic=2.25, $SE=0.19$, $P=0.024$). The same results

were obtained using Hayes's method where there was a significant indirect effect of IPS glutamate connectivity on WM capacity through parieto-cingulate connectivity (**Fig 3**, $b=0.40$, 90% CI [.06,.73]). Taken together, our results suggest that IPS glutamate affects WM capacity via parieto-cingulate connectivity.

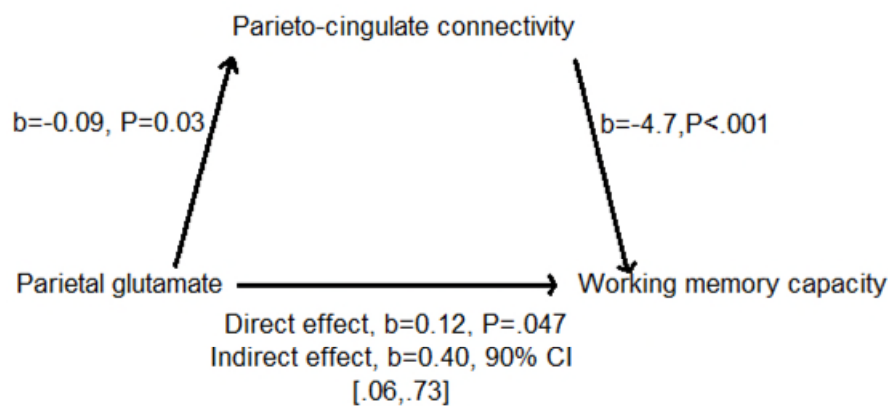


Fig 3. IPS glutamatergic concentration predicts WM capacity by the mediation of parieto-cingulate connectivity.

Discussion

In the present study, we examined the role of the brain's major excitatory and inhibitory neurotransmitters and relevant functional connectivity in tracking WM capacity in key frontal and parietal regions. We combined a computerised task assessing WM capacity with the quantification of glutamatergic and GABAergic concentrations using MRS, and functional connectivity using resting-state fMRI. These combinations allowed us to (i) find a positive relationship between IPS glutamate and WM capacity, (ii) obtained a negative relationship between parieto-cingulate connectivity and WM capacity, and (iii) reveal that this set of findings is explained by the mediation of parieto-cingulate connectivity in the relationship between IPS glutamate and WM capacity.

As discussed in the introduction, persistent activity within parietal and frontal regions is thought to be one of the putative neurophysiological mechanism underlying WM capacity.

The best candidate determinants of such persistent activity are the brain's major excitatory and inhibitory neurotransmitters within these frontal and parietal regions (Shu, Hasenstaub, Badoual, et al., 2003; Shu, Hasenstaub, & McCormick, 2003). Indeed, here we identified that the strongest correlation between WM capacity and neurotransmitter concentration was found for the glutamate concentration within the IPS. Previous fMRI and electroencephalography (Todd & Marois, 2004; Vogel & Machizawa, 2004) work highlighted the potential role of parietal brain activity in WM capacity. It is tempting to extend this prior work by suggesting a neurophysiological determinant of parietal persistent activity, namely the baseline concentration of parietal glutamate. However, this idea should be examined in future studies.

After establishing the association between IPS glutamate and WM capacity, we utilised resting-state fMRI to map the connectivity between the IPS and the rest of the brain as a function of WM capacity and revealed the importance of the connectivity between IPS and the posterior cingulate cortex. The posterior cingulate cortex was previously associated to cognitive load (Leech & Sharp, 2013) and individual variation in size of the posterior cingulate cortex was related to a decline in working memory performance (Kozlovskiy, Nikonova, Pyasik, & Velichkovsky, 2012). Concerning functional connectivity, the posterior cingulate cortex is indeed a highly connected region which participates in several resting-state networks including the default mode, the frontoparietal, the sensorimotor and the dorsal attention network (Leech & Sharp, 2013; Pearson, Heilbronner, Barack, Hayden, & Platt, 2011). Importantly, the IPS is a central node of the dorsal attention network (Corbetta, Patel, & Shulman, 2008). Our study extends these previous findings in several ways. First, we demonstrated that the connection between IPS and the posterior cingulate cortex is a strong predictor of WM capacity ($r_s(20)=-0.674$). In particular, individuals with positive IPS-posterior cingulate cortex connectivity exhibited low WM capacity, while individuals with negative IPS-posterior cingulate connectivity showed high WM capacity. Second, IPS-

posterior cingulate cortex connectivity was also negatively associated with IPS glutamate concentration. Namely, individuals with high IPS glutamate concentration exhibited negative IPS-posterior cingulate cortex connectivity, while individuals with low IPS glutamate concentration showed positive IPS-posterior cingulate cortex connectivity. Since our study was not designed to interrogate the direction of connectivity, it is difficult to conclude whether IPS affects posterior cingulate cortex or vice versa. Previous work demonstrated that lateral inhibition in the parietal cortex limits mnemonic capacity to a maximum of 2-7 items which is roughly the number of items used in the present study (Edin et al., 2009). Lateral inhibition refers to the mechanisms by which an excitatory neuron inhibits the action potential of neighbouring neurons. Here, we speculate that high negative connectivity between IPS and posterior cingulate cortex may be a proxy measure of lateral inhibition. Therefore we could tentatively speculate that high levels of parietal glutamate are associated with stronger lateral inhibition whereby IPS inhibits the posterior cingulate cortex. Furthermore, when taking into account the IPS-posterior cingulate cortex connectivity, as indicated in our mediation analysis, the IPS glutamatergic concentration no longer explained WM capacity. Taken together, this set of findings reveal a mechanism by which IPS glutamate concentration shapes WM capacity via resting parieto-cingulate connectivity.

Several studies provided evidence of a WM capacity improvement in response to working-memory training in both humans and animals (Edin et al., 2009; Klingberg, 2010; Tang, Qi, Riley, & Constantinidis, 2019). Several mechanisms underlying such training improvements have been proposed including changes in frontal and parietal brain activity, in frontoparietal connectivity, and in neurotransmitters particularly dopamine (Constantinidis & Klingberg, 2016; Klingberg, 2010). Building on this prior work, future investigations can probe the causal contribution of parietal glutamate concentration and WM capacity found here. One potential avenue is the combination of MRS with a learning and training study aiming at

increasing the levels of WM capacity. Indeed, glutamate and GABA neurotransmitter levels were previously associated with neuroplasticity in animal models (Dyke et al., 2017; Sun et al., 2010) which makes them excellent candidates in investigating plasticity mechanisms. A viable method to probe causality would involve a training investigation aiming at increasing the level of WM capacity combined with the corresponding pre- and post-training measurements of glutamate and GABA concentrations obtained with MRS. An increase in WM capacity that would be associated with post-pre measurements of parietal glutamate concentration but not with other neurotransmitter measures would indicate the causal contribution of parietal glutamate. Another future investigation for probing the causality could examine whether an increase in the excitability levels of the left parietal (vs. right parietal, or left/right frontal) cortex using transcranial stimulation, would lead to an increase in WM capacity. Importantly, such studies can additionally examine the extent to which the parieto-cingulate connectivity is altered in response to the training (i.e., became more negative).

A potential limitation of the current study concerns the exact role of neurotransmitters measured with MRS. This is because the MRS signal alone is not sensitive enough to distinguish between intracellular or extracellular neurotransmitter concentration or even a portion of these (Dyke et al., 2017). Therefore, even though the role of glutamate and GABA in cortical excitation and inhibition was documented in the prior work (Barron et al., 2016; Hone-Blanchet et al., 2016; Kim, Stephenson, Morris, & Jackson, 2014; Stagg et al., 2009; Terhune et al., 2015), making direct inferences of cortical excitability/inhibition based on the neurotransmitter concentrations should be done with caution. However, similar limitations of the exact origin of the observed neural signal measured via the MRI is shared with other more frequent neuroimaging modalities in humans (e.g., fMRI (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001), diffusion and structural MRI (Zatorre, Fields, & Johansen-Berg, 2012)

and do not alter the conclusions of the current study. Furthermore, our findings demonstrate the increasingly pressing need for a multi-modal imaging approach that would shed some light into the elusive mechanisms of glutamatergic excitation in the context of WM beyond the MRS signal. Another limitation concerns the neurocognitive specificity and in particular, the extent to which the association we found here is specific to WM rather than general cognitive ability. Lastly, even though our sample size is similar to the one from other individual variation MRS studies (N=14-29 (Kathrin Cohen Kadosh et al., 2015; Kihara et al., 2016; Lunghi, Emir, Morrone, & Bridge, 2015; Rae et al., 1998; Terhune et al., 2015; Valenzuela et al., 2000)), we need to acknowledge that it is relatively modest, and we appreciate that such a sample size may be suboptimal especially for examining complex regression and mediation analyses. However, it is important to highlight that these analyses were exploratory and a replication and extension of the current findings need to be investigated in future work.

In sum, by combining MRS and resting-state fMRI with behavioural testing the present research allowed the identification of a neurotransmitter marker for WM capacity, the baseline glutamate concentration within the left IPS. This marker was additionally related to parieto-cingulate connectivity which in turn mediated the relationship between parietal glutamatergic concentration and WM capacity. These findings highlight the benefit of multimodal neuroimaging to allow a better understanding of the interplay between different indices of neural activity and behaviour to provide a better mechanistic understanding of human behaviour.

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Contributions

G.Z., R.C.K. designed the experiment; G.Z. performed the experiments; G.Z. analysed the data, G.Z., R.C.K. wrote the paper.

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