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Neural Activity in the Fronto-Parietal Multiple Demand Network Robustly Predicts Individual Differences In Working Memory And Fluid Intelligence — Source link

Moataz Assem, Zachary Mineroff, Idan Blank, Ahmet Ademoglu ...+1 more authors

Institutions: Cognition and Brain Sciences Unit, Massachusetts Institute of Technology, Boğaziçi University, Harvard University

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Topics: Working memory and Executive functions

Activity in the Fronto-Parietal Multiple-demand Network is Robustly Associated with Individual Differences in Working Memory and Fluid Intelligence

Short title: MD activity correlates with working memory and IQ

Authors: Moataz Assem[1*], Idan Asher Blank[2,3], Zachary Mineroff[2], Ahmet Ademoglu[4], and Evelina Fedorenko[2,5,6*]

[1] MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK
[2] Brain & Cognitive Sciences Department, Massachusetts Institute of Technology, Cambridge MA, USA
[3] Department of Psychology, UCLA, Los Angeles CA, USA
[4] Institute of Biomedical Engineering, Bogazici University, Istanbul, Turkey
[5] McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge MA, USA
[6] Department of Psychiatry, Massachusetts General Hospital, Boston, USA

***corresponding authors**

Email: moataz.assem@mrc-cbu.cam.ac.uk (MA) and evelina9@mit.edu (EF)

Abstract

Numerous brain lesion and fMRI studies have linked individual differences in executive abilities and fluid intelligence to brain regions of the fronto-parietal “multiple-demand” (MD) network. Yet, fMRI studies have yielded conflicting evidence as to whether better executive abilities are associated with stronger or weaker MD activations and whether this relationship is restricted to the MD network. Here, in a large-sample (n=216) fMRI investigation, we found that stronger activity in MD regions – functionally defined in individual participants – was robustly associated with more accurate and faster responses on a spatial working memory task performed in the scanner, as well as fluid intelligence measured independently (n=114). In line with some prior claims about a relationship between language and fluid intelligence, we also found a weak association between activity in the brain regions of the left fronto-temporal language network during an independent passive reading task, and performance on the working memory task. However, controlling for the level of MD activity abolished this relationship, whereas the MD activity-behavior association remained highly reliable after controlling for the level of activity in the language network. Finally, we demonstrate how unreliable MD activity measures, coupled with small sample sizes, could falsely lead to the opposite, negative, association that has been reported in some prior studies. Taken together, these results align well with lesion studies demonstrating that a core component of individual differences variance in executive abilities and fluid intelligence is selectively and robustly positively associated with the level of activity in the MD network.

Keywords

Fronto-parietal; executive functions; fluid intelligence; individual differences; multiple-demand; language

Introduction

General cognitive abilities, such as fluid intelligence, and the tightly linked executive abilities, are among the best predictors of academic achievement and professional success (Gottfredson, 2002; Kuncel and Hezlett, 2010; Plomin and Deary, 2015). These abilities are thought to rely on a network of bilateral frontal and parietal brain regions. Damage to these regions, but not outside of them, is associated with disorganized executive behavior and significant loss of fluid intelligence (Duncan et al., 1995; Glascher et al., 2010; Roca et al., 2010; Warren et al., 2014; Woolgar et al., 2018, 2010). Similar frontal and parietal regions are active in brain imaging studies during diverse demanding tasks, including manipulations of working memory, fluid reasoning, selective attention, set shifting, response inhibition, and novel problem solving inter alia (Assem et al., 2019; Cole and Schneider, 2007; Dosenbach et al., 2006; Duncan, 2010, 2000; Duncan and Owen, 2000; Fedorenko et al., 2013; Geake and Hansen, 2005; Vakhtin et al., 2014). We refer to this set of brain regions as the “multiple-demand” (MD) network (following Duncan, 2013, 2010) given their sensitivity to multiple task demands. The MD network includes lateral and dorsomedial frontal areas, anterior insular areas, and areas along the intra-parietal sulcus (Assem et al., 2019; Fedorenko et al., 2013), and these areas form a functionally integrated system as evidenced by strong synchronization during naturalistic cognition (Assem et al., 2019; Blank et al., 2014; Paunov et al., 2019).

Prior fMRI studies have linked activity in the MD network with individual differences in executive abilities and fluid intelligence, but have left open the nature of this relationship. In particular, some have found that stronger MD activation is associated with worse performance on executive tasks and lower IQ (Basten et al., 2015; Deary et al., 2010; Dunst et al., 2014; Haier et al., 1988; Neubauer and Fink, 2009; Rypma et al., 2006; Rypma and Esposito, 2000; Santarnecchi et al., 2014; Stern et al., 2018). Such studies have typically advocated a “neural efficiency” explanation: smarter individuals can use neural resources more efficiently. Others, however, have found the opposite pattern, where stronger MD activation is associated with better executive task performance and higher IQ (Basten et al., 2013; Burgess et al., 2011; Choi et al., 2008; Cole et al., 2012; Gray et al., 2003; Lee et al., 2006; Tschentscher et al., 2017). In an attempt to reconcile these conflicting findings, some have suggested that the direction of the correlation may depend on task difficulty with “neural efficiency” (i.e., a negative association between MD activity and performance) observed in easier tasks, and positive associations observed during more complex tasks (for a review, see Neubauer and Fink, 2009).

Similarly, fMRI studies of inter-regional synchronization (typically, during rest; e.g. Fox et al., 2005) have not painted a consistent picture. Some have reported stronger synchronization among the MD brain regions in individuals with superior executive abilities and higher IQ (Cole et al., 2012), but others have reported weaker synchronization in such individuals (Santarnecchi et al., 2014; van den Heuvel et al., 2009).

Furthermore, a number of fMRI studies have linked individual differences in executive abilities and fluid intelligence with activity outside of the fronto-parietal MD network, including in occipito-temporal areas (Haier et al., 2003a; Park et al., 2010 but see Sani et al., 2019, and Assem et al., 2019, for evidence that these regions may belong to an extended MD network) and the default mode network (DMN) (Lipp et al., 2012; Smith et al., 2015; Sripada et al., 2019), and with the strength of synchronization among non-MD brain regions (Dubois et al., 2018; Hilger et al., 2017).

These apparently discrepant results could reflect the complexity of the brain-behavior relationship in the domain of executive abilities, with perhaps multiple underlying cognitive constructs and neural mechanisms contributing. However, a number of limitations plague previous studies that may instead explain away some of these discrepancies. *First*, many earlier studies have used small numbers of participants (as low as n=8) and/or transformed continuous behavioral measures into categorical variables (e.g., high- vs. low-performing participants). Both of these factors can produce inflated or spurious relationships (Haier et al., 1988; Lee et al., 2006; Rypma et al., 2006; Rypma and Esposito, 2000; Wager et al., 2005). *Second*, most studies have failed to assess the reliability of the relevant behavioral and/or brain measures (e.g., the strength of the BOLD response, or the strength of inter-regional synchronization) – a critical prerequisite for relating behavioral and brain individual variability (Dubois et al., 2018; Smith et al., 2015). Both behavioral and brain measures have to be stable within individuals over time (e.g., across multiple runs of a task, or across tasks) (Mahowald and Fedorenko, 2016). This is especially important for studies using BOLD estimates based on contrasts of task relative to fixation, or resting-state inter-region synchronization measures, which may fail to isolate MD activity from general state variables, like motivation, arousal, or caffeine intake (Basten et al., 2013; Cole et al., 2012; Dubois et al., 2018; Dunst et al., 2014; Gray et al., 2003; Rypma et al., 2006; Rypma and Esposito, 2000; Smith et al., 2015; Stern et al., 2018; Wager et al., 2005). *Third*, almost all previously mentioned studies have failed to take into consideration individual variability in the precise locations of the MD regions. This variability leads to losses in sensitivity and functional resolution (Brett et al., 2002; Nieto-Castañón and Fedorenko, 2012; Saxe et al., 2006), and it also affects the interpretation of inter-regional functional synchronization findings (Bijsterbosch et al., 2019, 2018). This problem is compounded by the proximity of MD areas to functionally distinct areas such as language-selective regions (Fedorenko et al., 2012), which show no response to any demanding task other than language processing (Fedorenko et al., 2011; Fedorenko and Varley, 2016; Monti et al., 2012). And *fourth*, many studies have failed to adequately assess the selectivity of the relationship between MD activity and behavior (Choi et al., 2008; Cole et al., 2012; Dubois and Adolphs, 2016; Gray et al., 2003; Rypma et al., 2006). This is important given that trait variables (e.g., brain vascularization) are known to affect neural responses (e.g., Ainslie and Duffin, 2009; Kazan et al., 2016), so to argue that the MD network's activity relates to individual differences in executive functions or fluid intelligence, it is important to demonstrate that activity in some other, control, brain region or network does not show a similar relationship.

To circumvent these limitations and rigorously test the relationship between MD activity and executive abilities and fluid intelligence, we conducted a large-scale fMRI study, where participants (n=216) performed a spatial working memory (WM) task that included a harder and an easier condition. We first established the reliability of the Hard>Easy (H>E) BOLD effect in the MD network (defined functionally in each participant individually (Fedorenko et al., 2013)), and then examined the relationship between the size of this effect and a) behavioral performance on the task (including in an independent run of data), and b) fluid intelligence (in a subset of participants, n=114). We further evaluated the selectivity of this MD-behavior relationship by examining fMRI responses in the left fronto-temporal language network while the same participants performed a language comprehension task (Fedorenko et al., 2010). This network serves as a good control because, on the one hand, the language network is robustly functionally distinct from the MD network (e.g., Blank et al., 2014; Mineroff et al., 2018; Fedorenko and Blank, submitted), but on the other hand, language has long been implicated in abstract and flexible thought (e.g., Bickerton, 1995; Carruthers, 2002; Dennett, 1997; cf. Fedorenko and Varley, 2016), including some studies that have linked damage to the regions of this network to performance on some fluid reasoning tasks (e.g., Baldo et al., 2010; cf. Woolgar et al., 2018).

To foreshadow our results, we found that stronger (rather than weaker) MD responses were associated with better performance on the spatial WM task as well as higher fluid intelligence scores. We also found a weak association between the strength of activity in another large-scale network – the language network – and WM task performance. However, this relationship was eliminated once the level of MD activity was taken into account. Finally, we demonstrate how unreliable MD activity measures, coupled with small sample sizes, could lead to the opposite (negative) association between MD activity level and behavior as has been reported in the literature. These results align well with findings from lesion studies that have suggested that a key proportion of variance in executive abilities and fluid intelligence is strongly and selectively associated with frontal and parietal MD brain regions.

Materials and Methods

Participants

216 right-handed participants (age 23.6 ± 6.4), 136 males; 190 right handed, 13 left handed, 8 ambidextrous, 5 with missing handedness data) with normal or corrected-to-normal vision, students at Massachusetts Institute of Technology (MIT) and members of the surrounding community, participated for payment. All participants gave informed consent in accordance with the requirements of the Committee On the Use of Humans as Experimental Subjects (COUHES) at MIT.

Experimental Paradigms

Participants performed a spatial working memory task in a blocked design (**Fig. 1**). Each trial lasted 8 seconds: within a 3x4 grid, a set of locations lit up in blue, one at a time for a total of 4 (easy condition) or two at a time for a total of 8 (hard condition). Participants were asked to keep track of the locations. At the end of each trial, they were shown two grids with some locations lit up and asked to choose the grid that showed the correct, previously seen locations by pressing one of two buttons. They received feedback on whether they answered correctly. Each participant performed two runs, with each run consisting of six 32-second easy condition blocks, six 32-second hard condition blocks, and four 16-second fixation blocks, for a total duration of 448s (7min 28s). Condition order was counterbalanced across runs.

In addition to the spatial working memory task, all participants performed a language localizer task (Fedorenko et al., 2010), used here to test the selectivity of the relationship between the MD network's activity and behavior. The majority of the participants (n=182, 84.3%) passively read sentences and lists of pronounceable nonwords in a blocked design (see Table 1). The Sentences>Nonwords (S>N) contrast targets brain regions sensitive to high-level linguistic processing (Fedorenko et al., 2011, 2010). Each trial started with 100ms pre-trial fixation, followed by a 12-word-long sentence or a list of 12 nonwords presented on the screen one word/nonword at a time at the rate of 450ms per word/nonword. Then, a line drawing of a hand pressing a button appeared for 400ms, and participants were instructed to press a button whenever they saw the icon, and finally a blank screen was shown for 100ms, for a total trial duration of 6s. The button-press task was included to help participants stay alert and focused. Each block consisted of 3 trials and lasted 18s. Each participant performed two runs, with each run consisting of sixteen experimental blocks (eight per condition), and five fixation blocks (14s each), for a total duration of 358s (5min 58s). Condition order was counterbalanced across runs. The remaining 21 participants performed similar versions of the language localizer with minor differences in the timing and procedure, with one participant performing an auditory version of the localizer (see Table 1 for exact timings and procedures; we have previously established that the localizer contrast is robust to such differences (Fedorenko et al., 2010; Scott et al., 2016).

	Version			
	A	**B**	**C**	**D**
Number of participants	182	12	1	8
Task (Passive Reading/Listening / Memory)	PR	M	PL	M
Words / nonwords per trial	12	12	variable	12
Trial duration (ms)	6,000	6000	18000	6000
Fixation	100	300	0	300
Presentation of each word / nonword	450	350	variable	350
Probe (M) + button press (M/PR)	400	1000	--	1000
Fixation	100	500	0	500
Trials per block	3	3	1	3
Block duration (s)	18	18	18	18
Blocks per condition (per run)	8	8	8	6
Conditions	Sentences Nonwords	Sentences Nonwords	Intact speech Degraded speech	Sentences Nonwords Word-lists*
Fixation block duration (s)	14	18	14	18
Number of fixation blocks per run	5	5	5	4
Total run time (s)	358	378	358	396
Number of runs	2	2	2	2-3

Table 1. Details of the design, materials, and procedure for the different variants of the language localizer task. *indicates conditions not used in this study

Finally, most participants completed one or more additional experiments for unrelated studies. The entire scanning session lasted approximately 2 hours.

A subset of 114 participants performed the non-verbal component of KBIT (Kaufman and Kaufman, 2013) after the scanning session. The test consists of 46 items (of increasing difficulty) and includes both meaningful stimuli (people and objects) and abstract ones (designs and symbols). All items require understanding the relationships among the stimuli and have a multiple-choice format. If a participant answers 4 questions in a row incorrectly, the test is terminated, and the remaining items are marked as incorrect. The test is scored following the formal guidelines to calculate each participant's IQ score.

FMRI data acquisition

Structural and functional data were collected on the whole-body 3 Tesla Siemens Trio scanner with a 32-channel head coil at the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research at MIT. T1-weighted structural images were collected in 128 axial slices with 1mm isotropic voxels (TR=2,530ms, TE=3.48ms). Functional, blood oxygenation level dependent (BOLD) data were acquired using an EPI sequence (with a 90° flip angle and using GRAPPA with an acceleration factor of 2), with the following acquisition parameters: thirty-one 4mm thick near-axial slices, acquired in an interleaved order with a 10% distance factor; 2.1mm x 2.1mm in-plane resolution; field of view of 200mm in the phase encoding anterior to posterior (A > P) direction; matrix size of 96mm x 96mm; TR of 2,000ms; and TE of 30ms. Prospective acquisition correction (Thesen et al., 2000) was used to adjust the positions of the gradients based on the participant's motion one TR back. The first 10s of each run were excluded to allow for steady-state magnetization.

FMRI data preprocessing and first-level analysis

FMRI data were analyzed using SPM5 and custom MATLAB scripts. (Note that first-level analyses have not changed much in later versions of SPM; we used an older version of the software here due to the use of these data in other projects spanning many years and hundreds of subjects; critical second-level analyses were performed using custom MATLAB scripts). Each subject's data were motion corrected and then normalized into a common brain space (the Montreal Neurological Institute (MNI) template) and resampled into 2mm isotropic voxels. The data were then smoothed with a 4mm Gaussian filter and high-pass filtered (at 200s). The task effects in both the spatial WM task and in the language localizer task were estimated using a General Linear Model (GLM) in which each experimental condition was modeled with a separate boxcar regressor (with boxcars corresponding to blocks). For the working memory task, each run was modelled by one regressor for the easy blocks and one regressor for the hard blocks; similarly for the language task, each run was modelled by one regressor for sentence blocks and one regressor for non-word blocks. Regressors were convolved with the canonical hemodynamic response function (HRF). Fixation blocks in both tasks were not modeled and considered as part of the implicit baseline.

MD fROIs definition and response estimation

To define the MD and language (see below) functional regions of interest (fROIs), we used the Group-constrained Subject-Specific (GSS) approach (Fedorenko et al., 2010). In particular, fROIs were constrained to fall within a set of "masks", areas that corresponded to the expected gross locations of activation for the relevant contrast. For the MD fROIs, following Fedorenko et al. (Fedorenko et al., 2013) and Blank et al. (Blank et al., 2014), we used eighteen anatomical masks (Tzourio-Mazoyer et al., 2002) across the two hemispheres. These masks covered the portions of the frontal and parietal cortices where MD activity has been previously reported, including bilateral opercular inferior frontal gyrus (L/R IFGop), middle frontal gyrus (L/R MFG), orbital MFG (L/R MFGorb), insular cortex (L/R Insula), precentral gyrus (L/R PrecG), supplementary and presupplementary motor areas (L/R SMA), inferior parietal cortex (L/R ParInf), superior parietal cortex (L/R ParSup), and anterior cingulate cortex (L/R ACC) (**Fig. 2a)**. (It is worth noting, however, that a whole-brain GSS analysis (Fedorenko et al., 2010) performed on the Hard>Easy spatial WM activation maps of n=197 participants yields a set of functional masks that largely overlap with these anatomical parcels (e.g., Diachek et al., 2019). Within each mask, we selected the top 10% (as well as the top 20% and 30% for validation analyses, as described below) of most responsive voxels in each individual participant based on the *t*-values for the H>E spatial WM contrast. This top n% approach ensures that each fROI can be defined in every participant, and that the fROI sizes are identical across participants.

To estimate the fROIs' responses to the Hard and Easy conditions, we used an across-run cross-validation procedure (Nieto-Castañón and Fedorenko, 2012) to ensure that the data used to identify the fROIs are independent from the data used to estimate their response magnitudes (Kriegeskorte et al., 2009). To do this, the first run was used to define the fROIs and the second run to estimate the responses. This procedure was then repeated using the second run to define the fROIs and the first run to estimate the responses. Finally, the responses were averaged across the left-out runs to derive a single response magnitude estimate for each participant in each fROI for each condition. Finally, these estimates were averaged across the 18 fROIs of the MD network to derive one value per condition for each participant (see **Fig. 2c** for evidence of strong inter-region correlations in effect sizes, replicating Mineroff et al., 2018). (An alternative approach could have been to examine fROI *volumes* – the number of MD-responsive voxels at a fixed significance threshold – instead of effect sizes. However, first, effect sizes and region volumes are strongly correlated; and second, effect sizes tend to be more stable within participants than region volumes (Mahowald and Fedorenko, 2016)).

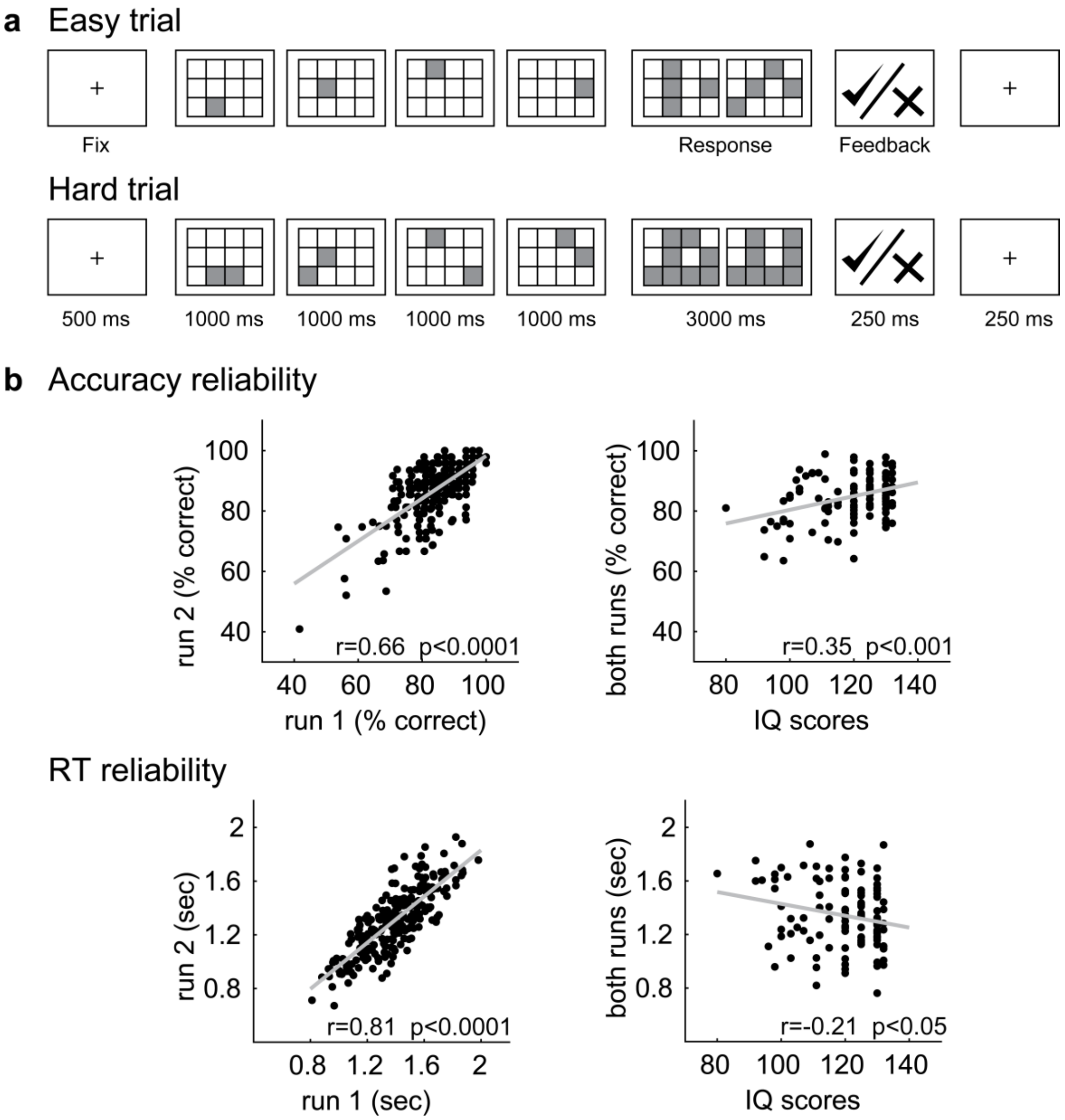
Language fROIs definition and response estimation

To define the language fROIs, we used a set of six functional masks that were generated based on a group-level representation of data for the Sentences>Nonwords contrast from a large set (n=220) of participants (e.g., Paunov et al., 2019). These masks included three regions in the left frontal cortex: two located in the inferior frontal gyrus, and one located in the middle frontal gyrus; and three regions in the left temporal and parietal cortices spanning the entire extent of the lateral temporal lobe and going posteriorly to the angular gyrus. Within each masks, we selected the top 10% of most responsive voxels in each individual participant based on the *t*-values for the Sentences>Nonwords contrast. To estimate the fROIs' responses to the Sentences and Nonwords conditions, we used the across-run cross-validation procedure described above.

Results

Reliability of behavioral measures

Behavioral performance on the spatial WM task was as expected: individuals were more accurate and faster on the easy trials (accuracy=92.22% ± 7.88%; RT=1.20s ± 0.23s) than the hard trials (accuracy=77.47% ± 11.10%, $t_{(215)}$=-23.23, *p*<0.0001, Cohen's *d*=1.53 (effect sizes are based on the two-tailed independent samples *t*-test); RT=1.49s ± 0.25s, $t_{(215)}$=-26.14, *p*<0.0001, Cohen's *d*=-1.23). Behavioral measures were stable within individuals across runs for overall (averaging across the Hard and Easy conditions) accuracies (*r*=0.66, *p*<0.0001) and RTs (*r*=0.81, *p*<0.0001). In contrast, difference scores (Hard > Easy) were less stable for both accuracies (*r*=0.26, *p*<0.0001) and RTs (*r*=0.46, *p*<0.0001) (**Fig. 1**). To further validate overall scores as a reliable individual measure, we tested their correlation with IQ scores, a well-established stable measure, in the subset of subjects (n=114) that performed the IQ KBIT test. Indeed, IQ scores correlated with overall but not difference accuracy scores (*r*(IQ vs. overall)=0.35 vs. r(IQ vs. H>E)=0.0033) while the correlations were similar for RTs (*r*(IQ vs. overall)=-0.21 vs. *r*(IQ vs. H>E)=0.22). Thus, in the critical brain-behavior analyses below, we used overall accuracies and RTs rather than the H>E measures, because the former are more stable within individuals as demonstrated by their high correlation across runs and correlation with the well-established stable IQ measure. Furthermore, the H>E behavioral measures might contain a non-linearity, such that smaller between-condition differences are observed in both high performers (when performance is close to ceiling) and low performers (when performance is close to chance).



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324 **Figure 1.** (a) Sample trials of the in-scanner spatial WM task and (b) reliability of its
325 behavioral measures across runs (n=216) and with an independent measure of IQ score
326 (n=114).

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MD network activity and behavior

As expected (Fedorenko et al., 2013), each of the eighteen MD fROIs individually, as well as the average across fROIs, showed a highly robust positive H>E effect across participants separately in each run ($ts_{(216)}$>11.54, *p*s<0.0001, Cohen's *d*=0.79-1.54). Individual differences in the MD H>E effect sizes were also stable across runs for each MD fROI individually (*r*s=0.60–0.80) and when averaging across fROIs (*r*=0.74, *p*<0.0001; **Fig. 2d**). We used the H>E contrast as it was more stable than task>fixation contrasts (H>fix *r*=0.65 and E>fix *r*=0.31). This greater stability of the H>E contrast plausibly reflects the fact that it factors out variability due to state differences, thus honing in on the relevant variability, related to the level of the MD network's activity. For each participant, we averaged the H>E effect size across the 18 MD fROIs to derive a single measure because the H>E effect sizes were strongly correlated across the 18 regions (*r*s=0.45-0.88; **Fig. 2c**), replicating Mineroff et al., 2018, and in line with general evidence of the MD brain regions forming a tightly functionally integrated system (Assem et al., 2019; Blank et al., 2014; see also Paunov et al., 2019).

To ensure that the stability of the MD H>E effect size did not depend on the particular details of the fROI definition (i.e., top 10% of most responsive voxels within the masks), we also extracted the effect sizes from the fROIs defined as the top 20% and top 30% of most responsive voxels. The extracted H>E effect sizes were almost perfectly correlated with those extracted from the top 10% fROIs (20% vs 10%, r=0.99, p<0.0001; 30% vs 10%, r=0.98, p<0.0001). Thus, we proceed to use the H>E effect sizes extracted from the original (10%) fROIs.

For each participant, we used behavioral measures from the spatial WM task (overall accuracies and RTs), and one brain activation measure (H>E effect sizes averaged across the 18 MD ROIs). The critical analyses revealed that larger MD H>E effect sizes were associated with more accurate (r=0.44, p<0.0001) and faster (r=-0.29, p<0.0001; **Fig. 2e**) performance. To further test the predictive power of MD H>E effect sizes, we cross-compared brain-behavior relationships across runs (Dubois and Adolphs, 2016) and found that MD H>E effect sizes in run 1 correlated with both accuracies (r=0.34, p<0.0001) and RTs (r=-0.22, p<0.0001) in run 2, and MD H>E effect sizes in run 2 correlated with accuracies (r=0.40, p<0.0001) and RTs (r=-0.27, p<0.0001) in Run 1.

Next, to test the generalizability of the relationship between MD activation and behavior, we asked whether MD H>E effect sizes explain variance in fluid intelligence, as measured with the Kaufman Brief Intelligence Test (KBIT) (Kaufman and Kaufman, 2013) in a subset of participants (n=114). Indeed, larger MD H>E effect sizes were associated with higher intelligence quotient (IQ) scores (r=0.34, p<0.0002, normalized $R^2(R^2_{\text{H>E vs IQ}}/R^2_{\text{H>E reliability}})$=21%; **Fig. 2e**). This relationship was still significant after controlling for WM accuracy using a partial correlation analysis (r=0.26, p=0.0061), suggesting that MD activity explains unique variance captured by the fluid intelligence test over and above any shared working memory component between the test and the task.

These results thus support a positive association between MD activity and fluid cognitive abilities. In the next section we assess the selectivity of this MD-behavior relationship.

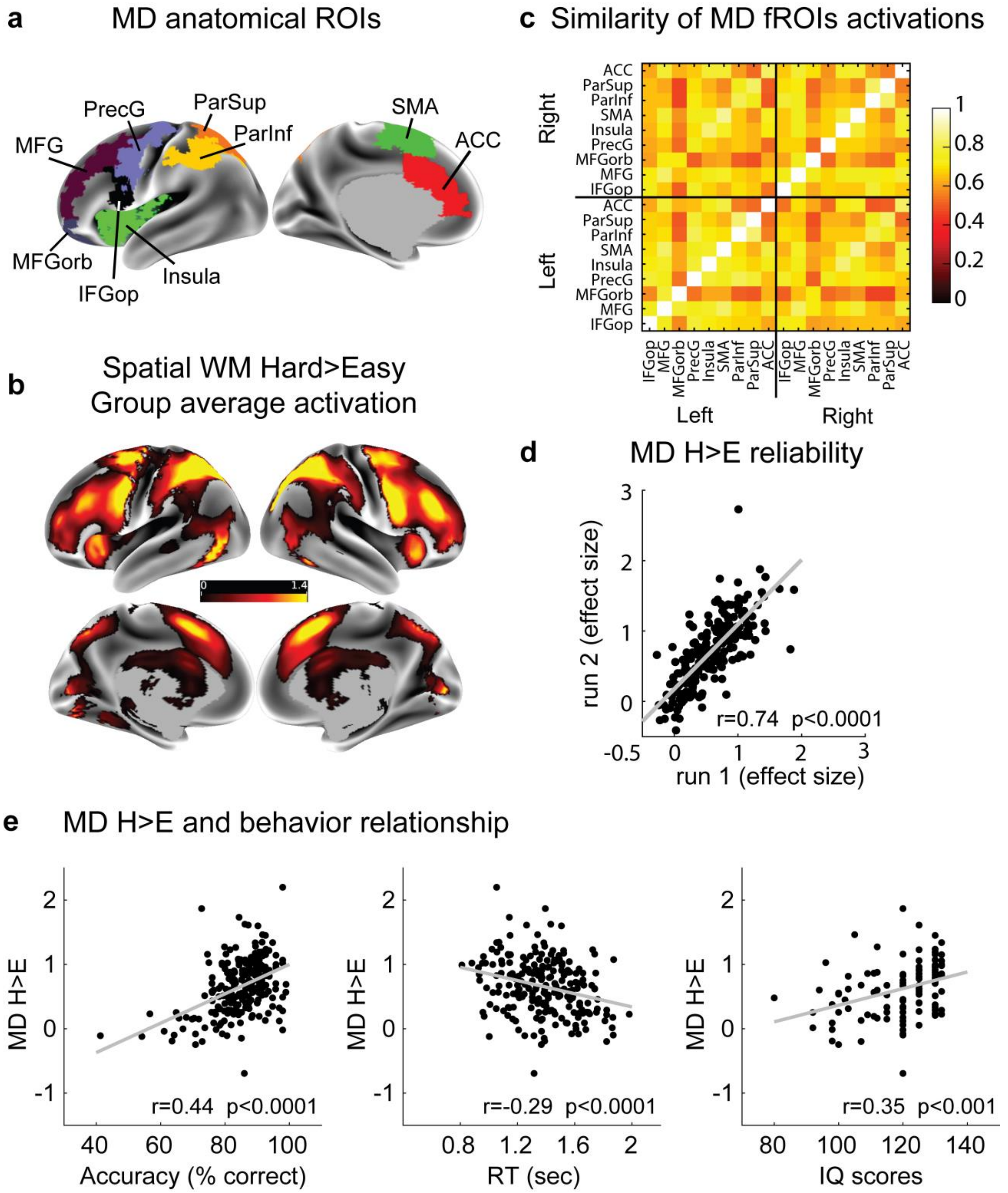

Figure 2. MD activity and behavior. (a) Anatomical masks used to constrain individual-specific functional activations. **(b)** Unthresholded group average activation

map (beta estimates) for the spatial WM Hard>Easy (H>E) contrast. **(c)** Pearson correlation values between MD regions for the H>E contrast, computed across individuals **(d)** Stability of MD H>E effect sizes across runs (n=216). **(e)** MD H>E effect sizes and behavior relationship: Larger MD H>E effect sizes are associated with better accuracy (*left*) and faster RTs (*middle*) in the spatial WM task (n = 216), as well as higher IQ scores (n = 114) (*right*) as measured by an independent test (KBIT).

Language network activity and behavior

Does the strength of brain activity outside of the MD network explain variance in executive abilities? We tested the selectivity of the MD-behavior relationship by examining another large-scale network implicated in high-level cognition: the fronto-temporal language-selective network in the left hemisphere (Fedorenko et al., 2011).

We extracted the language network's activity during a reading task (Fedorenko et al., 2010) (Sentences>Nonwords (S>N) contrast; **Fig. 3a**). Similar to MD H>E effect sizes, language S>N effect sizes were highly stable across runs for each language fROI individually and averaging across fROIs (r=0.83, p<0.0001; **Fig. 3b**), in line with prior work (Mahowald and Fedorenko, 2016).

Larger language S>N effect sizes were weakly associated with more accurate (r=0.18, p<0.01) but not faster (r=-0.08, p=0.24) performance on the spatial WM task **(Fig. 3c**). We also observed a weak trend for a relationship between S>N effect sizes and IQ scores (r=0.16, p=0.09) (**Fig. 3c**). Critically, however, controlling for the size of the MD H>E effects, in a partial correlation analysis, abolished the associations between language S>N effect sizes and the behavioral measures (spatial WM accuracies: r=0.11, p=0.10; IQ scores: r=0.14, p=0.14; **Fig. 3d**). In contrast, controlling for the size of the language S>N effects did not affect the relationship between MD H>E effect sizes and the behavioral measures (spatial WM accuracies: r=0.42 cf. r=0.44; spatial WM RTs: r=-0.27 cf. r=-0.29; IQ scores: r=0.34 cf. r=0.35; all ps<0.001).

In line with findings from brain lesion studies, these results confirm the selective relationship between the MD network and executive functions / fluid intelligence.

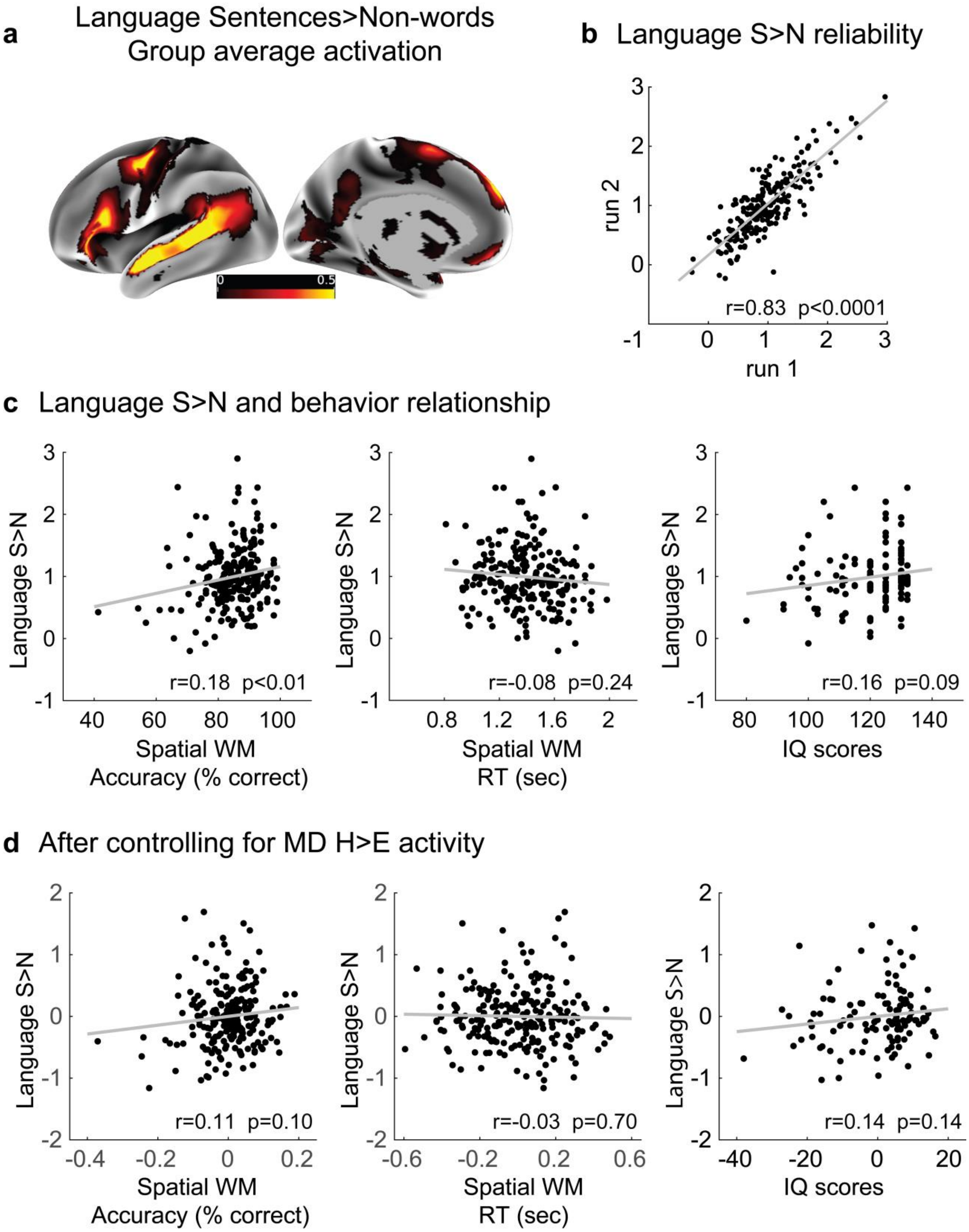
a
Language Sentences>Non-words
Group average activation
0
0.5
b Language S>N reliability
run 2
run 1
r=0.83 p<0.0001
3
2
1
0
-1
c Language S>N and behavior relationship
Language S>N
r=0.18 p<0.01
Spatial WM
Accuracy (% correct)
40
60
80
100
r=-0.08 p=0.24
Spatial WM
RT (sec)
0.8
1.2
1.6
2
r=0.16 p=0.09
IQ scores
80
100
120
140
d After controlling for MD H>E activity
r=0.11 p=0.10
-0.4
-0.2
0.2
r=-0.03 p=0.70
-0.6
0.6
r=0.14 p=0.14
-40
-20
20
-2

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Figure 3. Language network activity and behavior. (a) Unthresholded group average activation map (betas) for the language Sentences>Nonwords (S>N) contrast. **(b)** Stability of language S>N effect sizes across runs (n=216). **(c)** Language S>N effect sizes and behavior relationship: Larger language S>N effect sizes are weakly associated with better accuracy in the spatial WM task (*left*) and higher IQ scores (*right*), but not RTs in the WM task (*middle*). **(d)** Language S>N effect sizes and behavior relationship, controlling for MD H>E effect sizes: The weak relationships between language S>N effect sizes and behavior observed in (c) are now abolished.

Effect of sample size and reliability of the neural measure on brain-behavior associations

In a further attempt to explain discrepancies in the prior literature (e.g., some studies finding that stronger MD activity is associated with better executive abilities, but other studies finding the opposite pattern, as discussed in the Introduction), we examined the effects of sample size and reliability of the fMRI effect sizes on the brain-behavior relationships (Gelman and Carlin, 2014). We used two indices of MD activity that differed in their reliability – (1) MD H>E effect size used in the main analysis above (a highly reliable measure, with the across-runs correlation of r=0.74) and (2) MD E>Fix effect size (a less reliable measure, with the across-runs correlation of r=0.31) – and examined their relationship to IQ scores.

Samples of different sizes (ranging from 10 to 110, in increments of 10) were randomly selected from our set of 114 participants. For each sample, we computed a correlation between each of the two activity measures and IQ scores. This process was repeated 1,000 times per sample size. The resulting correlations were then examined for their sign, size, and significance. The results, shown in **Fig. 4 (left)**, clearly demonstrate that a combination of small samples and brain activity measures of low reliability (e.g., MD E>fix effect size), like those used in many earlier studies, can produce a significant ($p<0.05$) correlation of the opposite sign to that observed in a larger population (red dots with a negative correlation). This problem is diminished, but not eliminated, when a reliable neural measure like the MD H>E effect size is used (**Fig. 4, right**). The results also demonstrate that inflated correlations that are often observed in small samples are not eliminated even when a reliable activity measure is used.

The results from this analysis also challenge the claim of a negative association between MD activity and performance observed in easier tasks. As demonstrated above, at least in this paradigm, brain activity during a relatively easy executive task was not reliable within individuals across runs. This low reliability could yield correlations of opposite sign. However, even with large sample sizes, the MD E>fix effect size shows a weak positive, not negative, association with IQ scores (**Fig. 4, left)**.

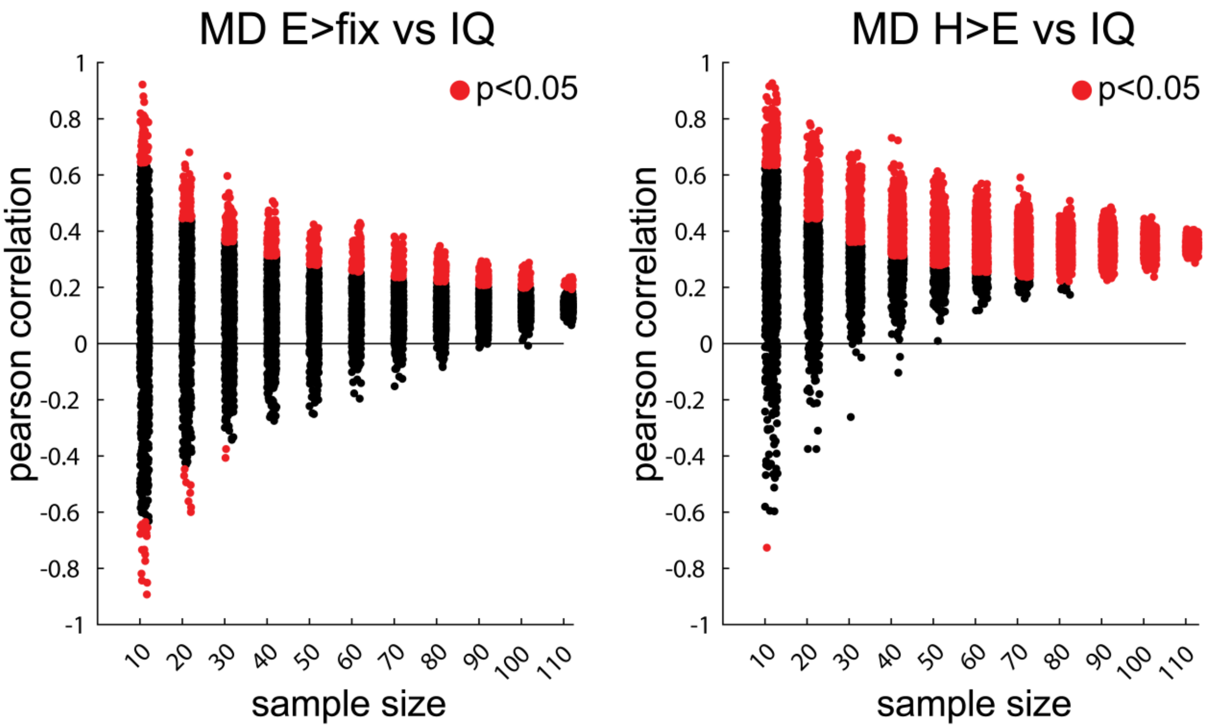

Figure 4. Effects of sample size and the reliability of the brain measure on brain-behavior relationships. On the x-axis in both panels, we show correlations (1,000 per sample) obtained for samples of different sizes. In the left panel, we use a brain activity measure of low reliability (MD E>Fix effect size), and in the right panel, we use a highly reliable brain activity measure (MD H>E effect size). Correlations significant at the p<0.05 level are marked in red.

Discussion

In a large set of participants, we examined the relationship between activity in the fronto-parietal “multiple-demand (MD)” network (Duncan, 2013, 2010), on the one hand, and executive abilities and fluid intelligence, on the other. The brain regions of interest were defined in individual participants using a functional localizer task (e.g. Fedorenko et al., 2013). We observed a robust positive association between the strength of activation in the MD network and performance on a spatial working memory (WM) task in the scanner, as well as IQ measured independently. We also examined the specificity of this relationship by considering another network important for high-level cognition – the fronto-temporal language-selective network (Fedorenko et al., 2011). Although the strength of activation in this network showed a weak positive association with some of the behavioral measures, these relationships were eliminated once the level of the MD network’s activity was taken into account (controlling for the level of the language network’s activity did not affect the MD-behavior relationships). Finally, we showed how small sample sizes and/or the use of brain activity measures of low reliability, as used in many earlier studies (Dunst et al., 2014; Haier et al., 1988; Lipp et al., 2012; Rypma et al., 2006), could produce inflated and/or the opposite-sign correlations between brain and behavior. To our knowledge, our relatively large sample size, coupled with the participant-specific functional localization approach to defining the regions of interest (Nieto-Castañón and Fedorenko, 2012; Saxe et al., 2006), provides the strongest evidence to date for the positive and selective association between the MD network’s activity and behavioral measures of executive abilities and fluid intelligence. This evidence aligns well with findings from lesion studies that have also reported a selective relationship between fronto-parietal regions and fluid cognitive abilities (Duncan et al., 1995; Glascher et al., 2010; Roca et al., 2010; Warren et al., 2014; Woolgar et al., 2018, 2010).

Some limitations of our study are worth noting. First, some have previously tried to explain the discrepancies in the MD-behavior literature by alluding to differences in the age of participants across studies (Reuter-Lorenz et al., 2000; Rypma and Esposito, 2000), arguing that the MD-behavior relationship may change across the lifespan. The age range in our sample (25^{th}-75^{th} percentile = 20-25) is too narrow to evaluate this hypothesis rigorously. The studies that had motivated this hypothesis a) used small sample sizes (e.g. Rypma and Esposito, 2000), b) used task>fixation measures of neural activity that are likely to be unreliable, and c) did not take into account inter-individual variability in the locations of the MD regions, which may be especially important given the increased variability in the functional architecture of older adults (Geerligs et al., 2017).

Second, our study used MD activity estimates during a single task. An estimate derived from multiple MD tasks may more accurately capture the variability in the MD network's engagement across individuals. Similarly, our measure of fluid intelligence was derived from a single IQ test (KBIT; Kaufman and Kaufman, 2013). A measure of fluid intelligence based on a diverse battery of executive function tasks may be more reliable. Nevertheless, we note that in our study (a) the size of the correlation we observed (r=~0.35) is within the range of correlations reported in recent studies that have used a multi-task-based estimate of fluid intelligence (Dubois et al., 2018; Sripada et al., 2019), (b) the relation between MD-IQ survived after controlling for the correlation between IQ and WM performance, highlighting the unique behavioral variance captured by the KBIT test over and above the WM task.

Third, we estimated MD activity using a blocked design experiment, thus averaging across multiple steps of a cognitive process (in our case, encoding of information into working memory, maintaining it over time, and finally, retrieving it from working memory at the decision-making step). Temporally finer-grained MD activity estimates at particular steps in the task may more precisely narrow in on the core neural computations that relate to executive abilities / fluid intelligence. For instance, a recent event-related study demonstrated robust MD activity at each of the stages above (Soreq et al., 2019). A general challenge with this approach is that individual-level estimates from event-related designs are likely to be more noisy / less reliable, although with sufficient data per participant, this limitation could be overcome. An early study (Gray et al., 2003) with 60 participants found a significant difference between higher and lower IQ subjects in MD activity when it was estimated from individual lure trials (in a n-back task) but not when MD activity was estimated across an entire block of trials. In our study, we demonstrate that MD activity estimated from a block of trials carries meaningful variance about individual differences in fluid intelligence. Stronger MD activation during more difficult tasks is thought to reflect the increased demand on integrating different kinds of information needed to solve the task at hand (Assem et al., 2019; Duncan, 2013; Tschentscher et al., 2017). Thus, stronger MD activity across a block could plausibly reflect less frequent lapses of “attentional focus” – needed for the correct binding of information to solve the task at hand – and thus better behavioral performance.

Studies of brain lesions have demonstrated repeatedly that there is no relation between lesions in the language network and executive abilities (Fedorenko and Varley, 2016; Woolgar et al., 2018; cf. Baldo et al., 2010). Our study, to our knowledge, is the first to investigate the relationship between brain activity in the language network and behavior employing a large sample size and individual-subject fROIs. In line with lesion findings, we show that controlling for MD activity abolishes any relationship between activity in the language network and spatial WM performance. The weak language-behavior association observed prior to controlling for MD activity is plausibly related to a trait factor like vascularization, or a state factor like arousal.

As we have briefly alluded to in the introduction, several studies have linked executive abilities and fluid intelligence to other brain measures, both structural and functional, including outside the boundaries of the MD network. For example, a recent large-scale study using the UK Biobank dataset (n=~30,000) reported that total brain volume, as well as multiple global measures of grey and white matter macro- and microstructure (especially, in older participants), explained substantial variance in fluid intelligence (Cox et al., 2019). Another large-scale study used the Human Connectome Project dataset (n=920) to show that the strength of functional dissociation between the MD network and the default mode network (DMN) (Power et al., 2011) during an n-back working memory task explains substantial variance (~25%) in IQ scores (Sripada et al., 2019), similar to the current study, although the same measure extracted from two other executive tasks (also in the HCP dataset) explained only ~10% of variance in IQ scores. It is not known whether or how these, or other measures that have been put forward in the prior literature as candidate predictors of variation in fluid intelligence, correlate with the measure used in the current study (i.e., the relative increase in the MD activity for a more difficult compared to an easier version of an executive task). Further studies that assess the reliability of those diverse brain measures, extracted with analysis pipelines that respect individual variability in structure (Masouleh et al., 2019) and function (Coalson et al., 2018; Nieto-Castañón and Fedorenko, 2012), and direct comparisons among those measures can help clarify their unique and shared contributions to explaining variability in executive abilities and intelligence. Given the complexity of human reasoning abilities, multiple brain processes likely contribute, but we suggest that the MD network is a key player governing individual differences in fluid intelligence and executive abilities, in line with the fact that damage to MD structures selectively and robustly predicts intelligence losses.

To conclude, against a backdrop of contradictory prior findings, we demonstrate a robust positive and selective association between the MD network's activity level, on the one hand, and executive abilities and fluid intelligence, on the other. Our analyses also help resolve some of the prior contradictions in the literature. Given its high reliability, the MD activity measure used here, and measures obtained from similarly strong manipulations of cognitive demand, can be used as a neural marker to further probe variability in executive abilities both in the typical population and among individuals with cognitive and psychiatric disorders. This marker can also serve as a promising neural bridge (Braver et al., 2010) between behavioral variability and genetic variability associated with differences in fluid intelligence (Deary et al., 2006; Plomin and Spinath, 2004).

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Declarations of interest

None

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