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Multiple Demand (MD) system's activity predicts individual differences in working memory and fluid intelligence

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Abstract

Executive abilities are supported by the fronto-parietal Multiple Demand (MD) network, yet attempts to link individual behavioral variability to MD activity have yielded contradictory findings. In a large-scale fMRI study (n=140), higher MD responses were strongly associated with better performance on a working memory task and higher IQ. These results pave the way for using individual fMRI measures to link genetic and behavioral variation in health and disease.

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Main text

Individuals vary in their executive abilities, which include attention, working memory, inhibitory control, error monitoring, and problem solving, and – in tandem – allow for flexible thought and behavior, the hallmark of our species. Understanding the underlying sources of this inter-individual variation will pave the way for personalized medical diagnosis and treatment, provide an *intermediate link* between behavioral and genetic variability, as well as yield a deeper understanding of basic cognitive and neural architecture[1,2]. We therefore here examine the relationship between behavioral variability in executive abilities and neural variability.

A bilateral network of frontal and parietal domain-general brain regions – the multiple demand (MD) system – has been strongly linked to executive functions[3,4]. This network is active during diverse goal-directed behaviors[5–7], and its damage – as a result of stroke, degeneration, or head injury – leads to poorer executive abilities and lower fluid intelligence[8–10]. Furthermore, aberrant functioning of this network, as measured with fMRI, has been reported in a variety of cognitive and psychiatric disorders[11]. Critically though, the potential usefulness of neural measures of MD activity depends on our ability to link such activity to behavior. Yet previous attempts to do so have yielded contradictory findings: some studies report stronger MD responses associated with worse behavioral performance[12] and lower IQ[13,14], others – with better performance[15,16] and higher IQ[15,17].

These discrepancies may be due to a number of shortcomings that characterize many prior studies that have probed the relationship between MD neural responses and behavioral measures, including (1) small numbers of participants and/or the transformation of continuous behavioral measures into categorical variables (e.g., high- vs. low-performing participants), both of which can produce inflated or spurious relationships[12,14,16,17], (2) use of BOLD estimates based

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on contrasts of task relative to fixation, which may fail to isolate MD activity from general state (e.g., motivation, sleepiness, caffeine intake) or trait (e.g., brain vascularization) variables[12,14,15], (3) failure to take into consideration inter-individual variability in the locations of MD regions thus losing sensitivity and functional resolution[18], and (4) failure to establish, or even assess, the *selectivity* of the relationship between MD activity specifically (cf. any other neural measure) and behavior[1,14].

To circumvent these limitations and rigorously test the relationship between MD activity and behavior, we conducted a large-scale fMRI study, where participants (n=140) performed a spatial working memory (WM) task that included a harder and an easier condition (**Fig. 1**). We then examined the relationship between the size of the Hard>Easy (H>E) BOLD effect across the MD network (defined functionally in each participant individually[6]; **Fig. 2**), and a) behavioral performance on the task (including in an independent run of data), as well as b) a measure of fluid intelligence (in a subset, n=61). We further evaluated the specificity of this brain-behavior relationship by examining neural activity in another large-scale brain network.

Behavioral performance on the spatial WM task was as expected: individuals were more accurate and faster on the easy trials (accuracy=92.86%; RT=1.19s) than the hard trials (accuracy=78.11%, $t_{(139)}$=-18.64, p<0.0001; RT=1.51s, $t_{(139)}$=23.45, p<0.0001). Similarly, as expected[6], each of the eighteen MD functional regions of interest (fROIs) showed a highly reliable Hard>Easy effect across participants ($ts_{(139)}$>11.5, ps<0.0001).

For each participant, we computed two behavioral measures (overall accuracies and RTs, averaging across the Hard and Easy conditions), and one neural measure (the size of the H>E effect averaged across the 18 MD fROIs). All three measures were highly stable within individuals as evidenced by high correlations across the two runs of the task (**Supp. Part 1 and**

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Supp. Fig. 1-2). We used the Hard>Easy effect size for our neural measure (cf. task>fixation) in order to factor out variability due to state/trait differences and thus to hone in on the variability in the MD system's activity given its functional signature of sensitivity to difficulty[6]. The reason for averaging neural responses across MD regions is that the MD network has been shown to be a highly functionally integrated system: the MD regions' time-courses show strong correlations during both rest and task performance[19–22]. In line with these prior findings, the Hard>Easy effect sizes were strongly correlated across the 18 regions in the current dataset (**Supp. Fig. 3**).

The critical analyses revealed that larger MD Hard>Easy responses were associated with better behavioral performance as reflected in both higher accuracies (r=0.33, p<0.001) and fasters RTs (r=-0.23, p<0.01; **Fig. 3**). To further test the predictive power of the MD Hard>Easy index, we cross-compared BOLD-behavior relationships across runs[1] and found that the MD Hard>Easy effect size in Run 2 successfully predicted both accuracies (r=0.29, p<0.001) and RTs (r=-0.21, p=0.01) in Run 1, and MD H>E effects size in Run 1 predicted accuracies (r=0.25, p=0.003) and RTs (r=-0.21, p=0.01) in Run 2 (**Supp. Fig. 4**).

Next, to test the generalizability of the relationship between MD activity and behavior, we asked whether the H>E MD index could explain variance in fluid intelligence, as measured with the Kaufman Brief Intelligence Test (KBIT)[23] in a subset of participants. Indeed, larger MD H>E responses were associated with higher intelligence quotient (IQ) scores (r=0.32, p=0.01) (**Fig. 3**). It is worth noting that the strength of the BOLD responses to the Hard or Easy condition relative to the fixation baseline did not correlate with IQ (H>fix: r=0.17, p=0.2; E>fix: r=0.01, p=0.9).

Finally, to test whether the brain-behavior relationship we observed was selective to the MD network, we considered another large-scale neural network: the fronto-temporal left-

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hemisphere language network[24] (**Supp. Part 2**). The size of the Sentences>Nonwords (S>N) effect, used to define the language regions[25], only weakly correlated with the spatial WM accuracies (r=0.19, p=0.02), and not RTs (r=-0.10, p=0.25). We did find an unexpected[26] correlation with IQ (r=0.30, p=0.02) (**Supp. Fig. 5).** However, MD H>E and language S>N responses showed only a weak and non-significant relationship (r=0.12, p=0.14) suggesting that neural activity in the two networks explain largely non-overlapping variance in the IQ scores.

To conclude, across a large set of participants, we observed a robust relationship between neural activity in the domain-general fronto-parietal MD network and behavioral performance on a working memory task performed in the scanner, as well as an independent measure of fluid intelligence. This relationship was, to some degree, selective to the MD network: neural activity in the fronto-temporal language network did not reliably predict WM performance.

A stronger up-regulation of the MD activity with increases in task difficulty (as indexed by larger Hard>Easy effect sizes) – a functional signature of this network[5,6]– was associated with better behavioral performance and overall higher intelligence. Although these results will be important to generalize to other executive tasks in similarly large samples, the size of the Hard>Easy effect in the MD network appears to be a promising functionally meaningful phenotypic marker that can be used to further probe variability in executive abilities in the healthy population and neurological and psychiatric disorders, as well as to bridge behavioral variability to variability in genes that have been linked to brain development and function.

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Online Methods

Participants

140 right-handed participants (age 22.8 ± 5.4, 47 males) 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 at MIT.

Experimental Design

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 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 four 32-second easy condition blocks, four 32-second hard blocks, and four 16-second fixation blocks. Condition order was counterbalanced across runs. In addition to the spatial working memory task, each participant performed a language localizer task[25] (**Supp. Part 2**), used here for a selectivity-assessment analysis, and one or more unrelated experiments. The entire scanning session lasted approximately 2 hours.

A subset of 61 participants performed the non-verbal component of KBIT[23] after the scanning session. The test consists of 46 items (of increasing difficulty) and includes both

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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, requiring the participant to select the correct response. 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=2530ms, 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 2000ms; and TE of 30ms. Prospective acquisition correction[27] 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. 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

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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 boxcar function (corresponding to a block) convolved with the canonical hemodynamic response function (HRF).

MD fROIs definition and response estimation

To define the MD fROIs, following Fedorenko et al.[6] and Blank et al.[19], we used eighteen anatomical regions[28] across the two hemispheres. These regions (parcels) covered the portions of the frontal and parietal cortices where MD activity has been previously reported, including bilateral opercular IFG (L/R IFGop), MFG (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. 2)**. (See **Supp. Part 2b** for info on how language fROIs definition was constrained.) Within each MD parcel, we selected the top 10% of most responsive voxels in each individual participant based on the *t*-values for the Hard>Easy spatial WM contrast. This approach ensures that a 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[18] to ensure that the data used to identify the ROIs are independent from the data used to estimate their response magnitudes[29]. 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. The responses were then 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

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averaged across the 18 fROIs within the MD network to derive one value per condition for each participant. (An alternative approach would have been to examine fROI *volumes* – number of MD-responsive voxels at a fixed significance threshold – instead of effect sizes. However, first, effect sizes and region volumes are generally quite strongly correlated; and second, effect sizes tend to be more stable within participants than volumes[30].)

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Author contributions

M.A. and E.F. designed research. M.A., I.B., Z.M., and E.F. performed research. M.A., I.B., Z.M., A.A., and E.F. analyzed data. M.A. and E.F. wrote the paper.

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Figures

Figure 1

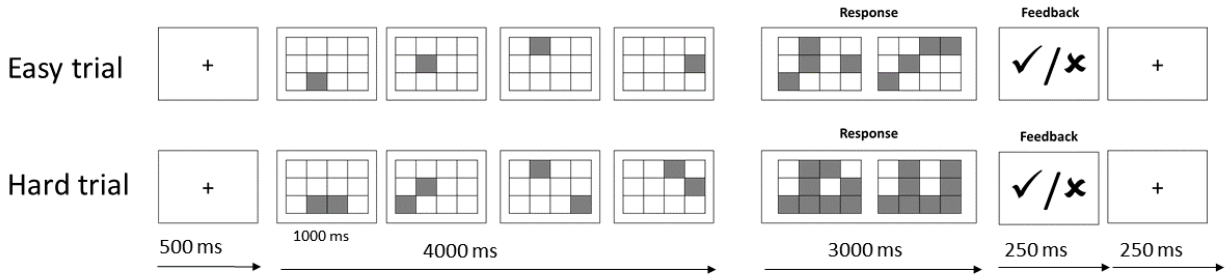


Figure 2

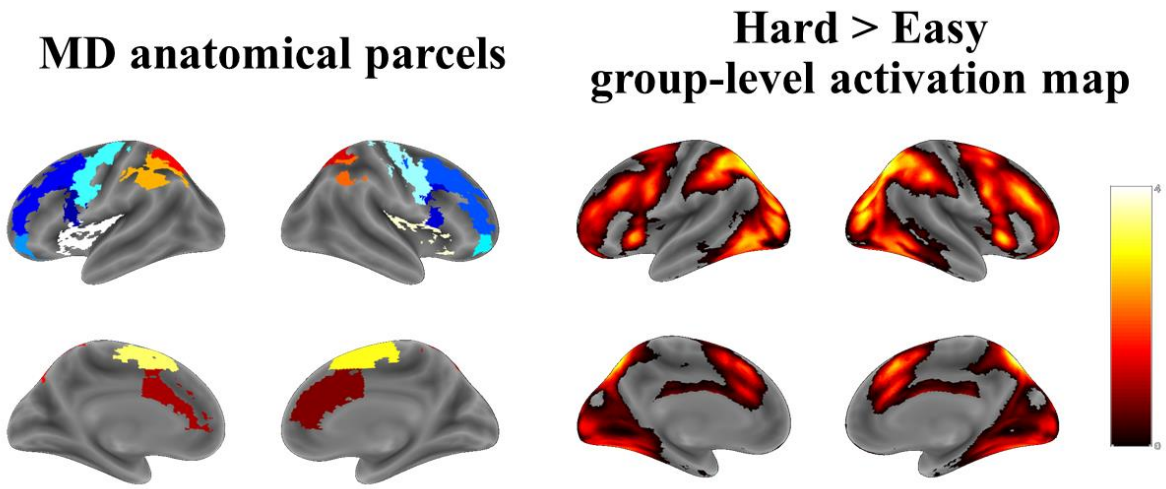
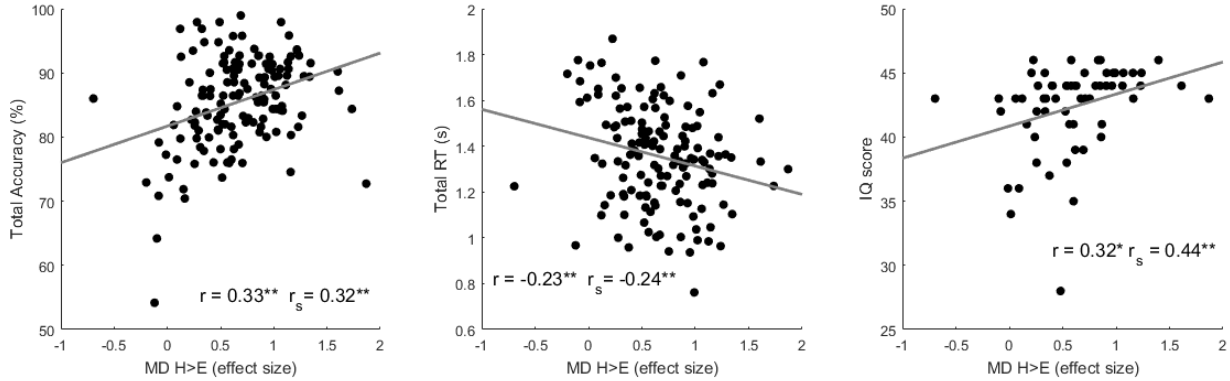


Figure 3



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Figures legends

Figure 1. Spatial working memory task. Sample easy and hard trials.

Figure 2. The Multiple Demand system. Left: MD anatomical parcels used to constrain individual fROI definition. Right: Group-level representations of neural activity for the Hard>Easy contrast. Individual unthresholded *t*-maps were averaged across 140 participants.

Figure 3. Brain-behavior relationships. MD Hard>Easy effect size predicts overall accuracy (*left*) and reaction time (*middle*) in the spatial WM task, as well as IQ (*right*) as measured by an independent test (KBIT). r (Pearson correlation), r_s (Spearman correlation), ** $p<0.001$, * $p<0.05$