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Broad domain generality in focal regions of frontal and parietal cortex

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Unlike brain regions that respond selectively to specific kinds of information content, a number of frontal and parietal regions are thought to be domain- and process-general: that is, active during a wide variety of demanding cognitive tasks. However, most previous evidence for this functional generality in humans comes from methods that overestimate activation overlap across tasks. Here we present functional MRI evidence from single-subject analyses for broad functional generality of a specific set of brain regions: the same sets of voxels are engaged across tasks ranging from arithmetic to storing information in working memory, to inhibiting irrelevant information. These regions have a specific topography, often lying directly adjacent to domain-specific regions. Thus, in addition to domain-specific brain regions tailored to solve particular problems of longstanding importance to our species, the human brain also contains a set of functionally general regions that plausibly endow us with the cognitive flexibility necessary to solve novel problems.

Multiple-demand system | cognitive control

A striking feature of the human brain is that it contains cortical regions specialized for particular mental tasks, from perceiving visual motion, to recognizing faces, understanding language, and thinking about others’ thoughts (e.g., refs. 1 and 2). However, an equally striking feature of human cognition is our ability to solve novel problems on the fly for which we cannot have ready-made, specialized brain machinery. We innovate on recipes when a key ingredient is missing, we think through the possible causes—and possible solutions—when our car breaks down on the highway, and we invent white lies on the spot in awkward social situations. How are we so cognitively versatile and innovative, and what brain regions endow us with the ability to solve new problems that neither our evolutionary history nor our individual experience has specifically prepared us for?

Based on previous neuroimaging data, a plausible neural substrate for cognitive flexibility is provided by a specific set of frontal and parietal brain regions the activity of which does not appear to be closely tied to specific cognitive demands. Instead, activity in these regions increases for a wide range of complex behaviors (e.g., refs. 3 and 4). Comprising this network are regions on the dorsolateral surface of the frontal lobes (along the inferior frontal sulcus/middle frontal gyrus), parts of the insular cortex, regions along the precentral gyrus, presupplementary and supplementary motor area (preSMA, SMA), parts of the anterior/mid cingulate, and regions in and around the intraparietal sulcus. We will refer to these regions as the multiple-demand or MD system, following Duncan (4). Across both human and nonhuman primate studies, these regions are commonly linked to cognitive or executive control processes likely involved in many different kinds of behavior (e.g., refs. 5 and 6), including focused attention, goal maintenance, strategy selection, performance monitoring, and other activities. In line with the apparent functional generality observed with functional MRI (fMRI), single-cell recording studies have shown that many neurons in the frontal and parietal lobes exhibit substantial flexibility, adapting their response properties to code the specific information required in current behavior (e.g., refs. 7–12).

However, although the neurophysiological evidence from non-human primates is tantalizing, it is not obvious that similar functional generality would be present in humans. Indeed, previous work has established that larger brains are associated with greater functional differentiation of brain regions (e.g., refs. 13–15; see ref. 16 for a recent discussion). At present, most evidence in humans comes from studies that rely on traditional group analyses (e.g., refs. 17–19) or metaanalyses of activation peaks pooled across studies (e.g., refs. 20–25). These methods have been shown to overestimate activation overlap across tasks because of inter-subject variability in neuroanatomy (e.g., refs. 26–28). In particular, a group analysis can reveal overlapping activations for two tasks even when these tasks activate distinct, nonoverlapping brain regions in each subject. The functional generality that emerges in the group analysis would be spurious in this case, obscuring the true underlying architecture. Thus, most of the available evidence that has been offered for the functional generality of the MD system in the human brain is in principle consistent with the opposite hypothesis, that this network is actually composed of a set of distinct but nearby regions, each engaged during different tasks. The concern is not just an esoteric theoretical possibility. We recently showed that the widely claimed overlap between language and executive processes in the frontal lobes (e.g., ref. 29) is not found in analyses of individual subjects (30). Might prior findings of overlap in activation across multiple demands, also primarily based on group analyses and comparisons across studies, also disappear in analyses of individual subjects? Very few prior studies have tested this question. One study found such overlap for three attentional tasks in parietal regions (31), and another found overlap across four tasks in frontal regions (32). Here we build

Significance

One of the oldest debates in cognitive neuroscience concerns the degree of functional specialization present in the human brain. Prior work has discovered several highly specialized components dedicated to particular mental functions, like face recognition or motion perception. However, our cognitive versatility suggests the additional existence of more general-purpose machinery. Building on prior neuroimaging evidence, along with neurophysiological evidence from non-human primates, we searched for such domain-general brain regions in humans. Seven diverse demanding cognitive tasks produced overlapping activation at the individual-subject level in a number of frontal and parietal brain regions. Thus, human cognition arises from hardware that includes not only specialized components, but also very general-purpose ones that plausibly enable us to solve novel problems.

Author contributions: E.F., J.D., and N.K. designed research; E.F. performed research; E.F. analyzed data; and E.F., J.D., and N.K. wrote the paper.

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on these initial results to test the existence of functionally
general brain regions more stringently and comprehensively.

To this end, we test the engagement of the MD regions in
seven diverse tasks (Fig. 1). Each task has a difficult condition
and an easier control condition. To test for activation overlap
among these tasks, we first used one contrast as a "localizer" to
identify regions in each subject individually that are sensitive
to cognitive demand, and then we measured the responses of these
functional regions of interest (fROIs) to the other tasks.

The tasks were chosen to vary along several dimensions. First,
the tasks differed in the kinds of representations they involved:
four tasks [the localizer task, verbal working memory (WM),
verbal multisource interference task (vMSIT), and Stroop] used verbal
representations, two tasks (math and MST) used Arabic
numerals, and the spatial WM task used spatial locations.
Second, the tasks differed in the kinds of cognitive processes they
 taxed most strongly: the localizer task required participants to
read sequences of nonwords or sentences and to respond to
a memory probe at the end of each; WM tasks required keeping
sets/sequences of elements in memory for a brief period; the
math task required manipulating representations and storing/
updating intermediate results; and the two MSIT tasks and
Stroop required inhibiting a prepotent response and selecting a
task-relevant response. Finally, six tasks required a manual
response (a button press), and one task (Stroop) required a vocal
response.

Note that these tasks were not designed to be directly
comparable to one another, even though they have all been shown to
produce behavioral difficulty effects with the hard condition,
leading to lower accuracies and longer reaction times (2, 27). As
a result, differences among tasks in the magnitude of the overall
response or in the size of the hard > easy effect may be hard to
interpret. In the present study, we focus on whether a given brain
region does or does not show a significantly greater response
during the hard compared with the easy condition of each task.
Furthermore, these tasks were not designed to test any particular
hypotheses about specific functions of any of the MD brain regions
(although in the Discussion we briefly relate these data to some
existing proposals). What is important about this set of tasks is their
diversity in terms of the representations they involve and the
mental processes they engage, which provides the critical test of
whether the MD regions get engaged by a variety of cognitive tasks.

Results
Consistent with previous findings, traditional group analyses
revealed several regions in the frontal and parietal cortices that
are robustly activated by the hard > easy contrast across tasks (SI
Text, Figs. S1 and S2, and Table S1). In Fig. 2 we show the ag-
gregate representation of these activation maps, highlighting the
most robustly activated areas (and the masks used to create them)
in the prefrontal (primarily left) and parietal regions, presumably
because of the attentional enhancement of visual representations
in the more difficult conditions. Finally, we observe activity in the
cerebellum, consistent with work implicating some regions of the
cerebellum in high-level cognitive functions (e.g., refs. 33–35).

These results are broadly consistent with prior work, but like
the prior work leave open the important possibility that activa-
tions for different tasks do not in fact overlap at the critical level
of individual subjects. In the present paper we test this hypothe-
sis, focusing on the frontal and parietal regions. To do so, we
first defined fROIs in each subject by intersecting subject’s
localizer activation (thresholded at P < 0.001, uncorrected) with
the volume of anatomical ROIs previously implicated (e.g., ref. 20)
in domain-general functions (see SI Text and Fig. S3 for a dem-
stration that similar results obtain when different tasks are
used as localizers). The fROI definition procedure adopted here
is similar to the group-constrained subject-specific approach re-
cently introduced by Fedorenko et al. (27; see also ref. 36), ex-
cept that anatomical parcels are used instead of group-level
functional parcels to constrain the selection of subject-specific
voxels. [A complementary analysis using the group-constrained
subject-specific method on the whole brain (27, 36) found the
same pattern of results, with no new frontal/parietal functionally
general regions.] For all regions, fROIs could be defined in at
least 70% of the subjects (and for 11 of 18 regions fROIs could
be defined in >80% of the subjects; see Table S2 for details).

Fig. 3 shows the response profiles of the individually defined
fROIs across hard and easy conditions for each of the seven tasks
(see Table S3 for the statistics). The responses to the localizer
task conditions are estimated using independent data (a left-out
run not used for fROI definition). Most of the regions show
reliable hard > easy effects for all (or six of seven) tasks. [Fur-
thermore, at least half of the voxels in these fROIs on average
show individually significant hard > easy effects within individual
subjects for the other six tasks (Fig. S4)]. These regions include
parts of the precentral gyrus bilaterally, the opercular part of the
inferior frontal gyrus (IFG) bilaterally, the right middle frontal
gyrus, the SMA bilaterally, the inferior and superior parietal cor-
tex bilaterally, and the insula bilaterally. Three of the regions—the
orbital parts of the middle frontal gyrus in the left hemisphere
and, to some extent, in the right hemisphere, and the left ACC—
show weaker results, with significant hard > easy effects for
fewer tasks. Is this pattern of increased response to greater difficulty across
tasks restricted to these regions, or does the brain as a whole
show the same pattern? As discussed next, functionally general
responses demonstrated above appear to be spatially restricted to
the MD system. First, (2; see also 37–38) showed that brain
regions sensitive to linguistic stimuli—responding more strongly

![Fig. 1.](image-url) A schematic illustration of the seven tasks. (Note: The timing for the spatial WM and verbal WM tasks is identical to the timing of the Math task.) (Adapted from ref. 2.)
to meaningful and structured stimuli, like sentences, than to various degraded versions of those stimuli (e.g., lists of unconnected words or nonwords)—respond weakly or not at all during the same demanding cognitive tasks examined here. These regions instead appear to require a particular type of stimulus (language) to drive them, much as many high-level visual regions require specific visual information (e.g., ref. 1). Language-responsive regions thus show a very different profile of response from the MD regions identified here, despite often lying immediately adjacent to the MD cortex (30; see Fig. S5 for sample activation maps showing both contrasts).

Second, to test the idea that any large anatomical region—like the ones used in the current analysis—contains a substantial number of voxels that respond more to difficult conditions than to easier conditions across tasks, we performed an analysis using four control regions: bilateral superior and middle temporal pole regions, which have been implicated in a wide range of mental processes (e.g., ref. 39) but are not considered to be part of the MD system. The analysis procedures were identical to those used above, and the results are shown in Fig. S6. Although in each region a little less than half of the subjects have a few localizer-responsive voxels (seven voxels per region) on average, (i) the nonwords > sentences effect does not replicate in a left-out run (ts < 1.5), and (ii) these voxels do not show the hard > easy effect for any of the other six tasks (ts < 1.5). These results indicate that it is not the case that any large anatomical region contains voxels with the properties of the MD system. (Note that these results are not simply a result of signal dropout in the temporal poles. For example, the language-responsive portions of the same regions—that is, regions defined by the sentences > nonwords contrast—show highly robust and replicable responses in the left-out run: ts > 3.8, Ps < 0.0005.)

Finally, in addition to the language-responsive regions and regions in the temporal poles discussed above, a set of brain regions that have become known as the “default mode network” (e.g., ref. 40) show a response profile that is essentially the opposite of that exhibited by the regions of the MD system. These regions—which include parts of the medial temporal lobe, parts of the medial prefrontal cortex, the posterior cingulate cortex, and the precuneus—deactivate in response to demanding cognitive tasks.

In summary, the activations reported here and in previous studies—greater responses to more cognitively demanding conditions—albeit extensive, are spatially restricted to a specific set of brain regions: the MD system.

Discussion

Using the most stringent method currently available for human fMRI (activation overlap within individual subjects), we found that brain regions throughout the MD system respond across a wide range of demanding cognitive tasks. These results extend previous conclusions about the MD system in three key respects. First, almost all prior claims of functional generality were based on group analyses (e.g., refs. 17–19) or metaanalyses of activation peaks pooled across studies (e.g., refs. 20–25), where apparent activation overlap could have resulted spuriously from data in which each subject individually shows functional segregation (e.g., ref. 28). Extending previous reports focusing on selected parts of the MD system (30–32), the present data show that activation overlap is not an artifact of group averaging, but is present within individual subjects. Second, by testing a large number of tasks varying in both the content and operations invoked, we demonstrate broader functional generality of the MD response than previously shown. Finally, the present study characterizes the spatial topography of the MD system (Fig. 2) and its regional specificity (Figs. S5 and S6), in which abutting regions often show strikingly different profiles.

Taken together, these results provide both the strongest evidence to date for the existence of the MD system in humans, and a richer anatomical and functional characterization of that system. More generally, the present data show that the strikingly domain-specific brain regions that have been characterized over the last 15 y (e.g., ref. 1) are complemented by an extensive system of brain regions exhibiting the diametrically opposite property of broad functional generality.

In the present paper we have focused on the similarity in the functional profiles among the regions of the MD system. However, we assume that some functional differentiation exists among these regions, and it remains an important goal for future research to identify such dissociations. We briefly mention a number of recent proposals here. Some proposals have attempted to
link particular MD regions to specific cognitive functions. For example, Aron et al. (41) have argued for the specific role of the right IFG in inhibitory control (see ref. 42 for a similar proposal with respect to the left IFG). Others (43–45) have argued for a division between the ACC: critical in detecting conflict, and the lateral prefrontal cortex, responding to the ACC signal with strengthened cognitive control (cf. 46–47). Still others (48; see 49 and 50 for a related proposal) have hypothesized that an anterior–posterior gradient exists on the lateral surface of the frontal lobes, with the more anterior regions supporting more hierarchically complex operations. A few studies have reported differences between frontal and parietal regions (e.g., refs. 51–55), including differences in the timing of neural activity (e.g., refs. 56 and 57), or between the left and right hemisphere MD regions (e.g., refs. 58–61). Finally, knowing that MD regions are involved in a variety of methodologies may help to understand the existence of subnetworks within the broader MD system, with the number and functional interpretation of these subnetworks varying across proposals (e.g., refs. 6, 62–70). For example, Dosenbach et al. (62) have proposed that the MD system includes two subsystems: one subserving transient control and the other subserving more sustained control processes. Based on resting-state correlation analyses, Power et al. (66) identified three subnetworks in the cortices previously linked to cognitive control: the dorsal attention network, the fronto-parietal task control network, and the cingulo-parietal control network (see refs. 71 and 72 for a functional dissociation between the first two networks). In evaluating these proposals further in future studies and in developing new ones, it is important to remember that all parts of the extended MD system can be driven by increased task difficulty of many forms, including simple tasks with little obvious element of hierarchical control (e.g., refs. 73–75). In our data, the main exception was the rather weak MD pattern observed for the most anterior part of the lateral prefrontal cortex, and for the left ACC. Regardless of what the true functional organization of the MD system turns out to be—and in line with single unit evidence for a functional dissociation (76, 77)—we suspect that control representations and processes generally involve close interaction and information exchange among multiple MD regions. At the level of resolution of fMRI, the result is broadly similar activity across multiple task domains.

Parts of the MD system resemble regions that have been linked to oculomotor control (e.g., refs. 76 and 77). Indeed, in some of our tasks (e.g., spatial WM), the hard condition plausibly required more eye movements than the easy condition during at least some stages of the task. Furthermore, the materials used (as referred to in the Methods and Materials sections) are observed across different localizer contrasts (SI Text and Fig. S3). The optimal long-term solution might be to use a combination of two or more MD tasks for localization purposes, to identify the most robust and stable MD voxels.

Of course, even at the single-subject level, the resolution of fMRI does not come close to that of single-cell recordings in nonhuman primates. Nevertheless, complementing our results, several studies have used multivoxel pattern analyses (86) to show that MD regions code many specific properties of attended stimuli, responses and tasks in the fine-grained patterns of spatial activity (e.g., refs. 32, 87–93). Such results dovetail with analogous findings of widespread, adaptive coding of task-relevant information in single neurons of frontal and parietal cortex (8, 12).

Ever since Gall, Flourens, and Broca, neuroscientists have debated whether the human brain is made up of highly specialized components, each responsible for a task, a set of tasks, or a more general function, or whether instead each brain region is broadly engaged in a wide range of cognitive tasks. Careful individual-subject–based analyses of fMRI data over the last 15 years have revealed a high degree of functional specificity for at least a few regions of the human brain (1). Here we use similar individual-subject–based analyses of fMRI data to provide strong evidence for the functional generality of a set of regions in the frontal and parietal lobes that are broadly engaged in a wide range of tasks, from mental arithmetic, to holding information in working memory, to filtering and suppressing task-irrelevant information. The evidence presented here for the broad functional generality of these regions comes together with prior evidence for the extreme domain-specificity of other brain regions to paint a rich and fascinating picture of the functional architecture of the human brain: Human cognition is accomplished by the joint efforts of both highly specialized and very general-purpose cognitive and neural mechanisms.

Materials and Methods

Participants. Forty right-handed participants (28 females) from the Massachusetts Institute of Technology (MIT) and the surrounding community were paid for their participation. All subjects were native speakers of English with the ages of 18 and 50, had normal or corrected-to-normal vision, and were naive as to the purposes of the study. All participants gave informed consent in accordance with the requirements of Internal Review Board at MIT.

Design. The tasks included reading sequences of nonwords and sentences and performing a memory-probe task after each (the localizer task), and one or more of the following: an arithmetic task, a spatial and a verbal WM task, two versions of the MSIT (84), and the classic Stoop task (Fig. 1). Each task used a blocked design and included a harder and an easier condition. We used the nonwords > sentences contrast as the localizer contrast because it was present in each of the 40 participants (but see SI Text and Fig. S3 for a demonstration that the results are similar when other contrasts are used as localizers).

Consent for Reuse. This study was conducted in accordance with the ethical guidelines of the American Psychological Association and the American Psychological Society.
Procedure. Each participant was run on the localizer manipulation, and between 13 and 16 participants performed each of the other tasks. In the localizer task, participants were run to determine their best spatial mapping (A–P) distance (200 mm and matrix size 96 mm × 96 mm, TR = 2000 ms, and TE = 30 ms). The first 5 s of each run were excluded to allow for steady-state magnetization.

Statistical Analyses. MRI data were analyzed using SPM5 (www.fil.ion.ucl.ac.uk/spm) and custom Matlab scripts (available from http://web.mit.edu/evelina9/www/fundoc.html and www.nitrc.org/projects/spm_sm). Each subject’s data were motion-corrected and then normalized in a common brain space (the Montreal Neurological Institute template) and resampled into 2-mm isotropic voxels. Data were then smoothed using a 4-mm Gaussian filter and high-pass filtered (at 200 s). For the individual-subject fROI analyses, we used the wfu_pickatlas tool (95) to create anatomical ROI masks for brain regions within which MD activity has been previously reported (Fig. 3). (For the ACC region, we edited the mask manually to restrict the region to the dorsal part of the anterior cingulate.) Then we intersected each anatomical ROI with each subject’s activation map for the localizer contrast (thresholded at P < 0.001, uncorrected), to define each subject’s fROIs. (No spatial continuity constraints were imposed on these fROIs: any voxel that passed the specified threshold and fell within the boundaries of the anatomical parcel was included in the ROI definition. However, visual examination of the resulting fROIs revealed that for most subjects and regions a fROI took the form of a set of contiguous voxels with occasional small noncontiguous sets nearby.) These regions were defined in each hemisphere separately, for a total of 18 fROIs. To estimate the responses of these fROIs to various conditions, we averaged the responses across the voxels in each individual fROI and then averaged these values across subjects for each region. To estimate the responses to the localize conditions, we used all but the first run to define the fROIs and the first run to estimate the responses, so that the data used to estimate the effects were always independent of the data used for ROI definition (e.g., refs. 96 and 97).

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