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Default Mode Contributions to Automated Information Processing

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Abstract: Concurrent with mental processes that require rigorous computation and control, a series of automated decisions and actions govern our daily lives, providing efficient and adaptive responses to environmental demands. Using a cognitive flexibility task, we show that a set of brain regions collectively known as the default mode network play a crucial role in such “autopilot” behavior, i.e. when rapidly selecting appropriate responses under predictable behavioral contexts. While applying learned rules, the default mode network shows both greater activity and connectivity. Furthermore, functional interactions between this network and hippocampal, parahippocampal areas as well as primary visual cortex correlate with the speed of accurate responses. These findings indicate a memory-based “autopilot role” for the default mode network, which may have important implications for our current understanding of healthy and adaptive brain processing.

Significance Statement: In addition to dealing with variable demands of the environment in everyday life, we are continuously faced with routine, predictable challenges that require fast and effective responses. In an fMRI-based cognitive flexibility task, we show greater activity/connectivity centered on the default mode network during such automated decision-making under predictable environmental demands. Furthermore, we report on a significant correlation between this network and hippocampal connectivity, and individual differences in the participants’ ability to make automated, fast and accurate responses. Together, these results suggest a novel “autopilot” role for this network that may have important theoretical implications for our understanding of healthy brain processing in meeting worldly demands.

Essential to our survival, the human brain has evolved a remarkable ability to deal with multiple, ever-changing demands in the environment (1). Often termed cognitive flexibility, this capacity to adjust our behavior under variable contexts helps us generate appropriate responses to attain goals or to avoid danger (2). For instance, rerouting a car due to heavy traffic, updating our beliefs in the face of new information, or shifting from one conversation to another all constitute daily examples of such flexible thinking. Converging evidence from healthy control studies as well as patients with psychopathology suggests that this type of a mental process is mediated by the interactions between cortico-striatal brain regions (3).

However, the successful pursuit of goals for adaptive purposes also requires a level of cognitive stability or maintenance (4). In fact, a considerable portion of our daily lives comprises learned, automatic, reflexive or habitual behaviors under specific contexts in stable environments, as opposed to the controlled and effortful processes commonly scrutinized in experimental settings (5). Taking a leisurely stroll in the park, driving to work, or knowing how to behave at a dinner table all involve adaptive decisions and actions based on learned constructs of the world around us. Complementary to cognitive flexibility, this type of memory-based behavior allows us to provide context-specific, fast and efficient responses to environmental demands.

A set of brain regions, collectively known as the default mode network (DMN), may play a crucial role in such “autopilot” behavior (6, 7). Extensive evidence suggests that regions belonging to this large-scale, associative brain network display their highest engagement under stable environmental conditions (8), including task-free resting state scanning (9). Though early investigations have mainly highlighted the DMN’s contribution to spontaneous internal thoughts that arise during such unconstrained states of rest (10), greater DMN activity/connectivity has also been observed when participants were required to access their memory stores during task-based functional magnetic resonance imaging (fMRI) studies. Retrieval of autobiographical memory (11), ignition of strong semantic associations (12) and higher demands for working memory (13) have all been related to the recruitment of specific DMN regions.

In this regard, with its strategic positioning along functional gradients of cortical organization (14), the DMN reportedly exemplifies the neural center for a mental map of associative memory, which is learned from regularities in the environment (15, 16). As such, the automated use of this internalized information to deal with routine “worldly” demands may

constitute an important aspect of this network's contribution to human cognition. However, whether the DMN embodies the neural correlate of memory-based, automated information processing that aids fast, efficient and context-specific responses require further investigation.

In this experiment, we tailored a variant of a commonly used cognitive flexibility task, the Wisconsin Card Sorting Task (WCST), to create experimental contexts with varying levels of demand for access to learned information to be used in automated decision-making. A total of 28 healthy participants were presented with four permanent reference cards as well as one alternating target card, drawn from a pool of 60 cards. The goal of this task was to sort the target card to one of the reference cards using a set of rules (i.e. sorting dimensions) and feedback indicating choice accuracy (Fig. 1A). While the sorting dimensions for the task included color, shape and number, the rule for the control condition was identity i.e. the target card was identical to one of the reference cards.

Each rule was repeated four times with the total task consisting of 16 (4 blocks x 4 rules) blocks of 10 trials. Importantly, although the participants were notified when the rule had changed (i.e. after every 10 trials), they were not told the new sorting dimension. Thus, during the first few trials following the rule change, participants had to rely on feedback to deduce the context, and make appropriate selections. This trial-and-error stage was defined as the "acquisition" (learning) phase of each block. Once the rule was firmly established, participants could then rely on the learned responses from memory for choosing the appropriate card, here referred to as the "application" phase. We operationally stratified the task into these two phases after completion of half the trials, to produce separate subsets: trials 1-5 and trials 6-10, maximized for "acquisition" and "application" content, respectively.

Based on the autopilot account of DMN function, we hypothesized that (i) the DMN regions would be more active in the application phase relative to the rule acquisition phase of the paradigm, i.e. when the task demanded greater access to learned, memory-based information for fast, automated and efficient responses; (ii) the connectivity of the DMN regions would be altered to reflect this network's differential contribution during the rule-application phase of the cognitive flexibility task, and (iii) greater functional interaction of the DMN regions would be predictive of faster and more accurate decision making, specifically in the application phase. In addition, this performance relationship would be dissociated from that of the dorsal attention network (DAN), traditionally linked to the controlled and effortful processing of attention-demanding, external information (17, 18).

Results

Differential Brain Activity during Cognitive Flexibility Task

In line with our expectations for the behavioral stratification of the task, participants were less accurate in the acquisition phase, with an average of 91.92 % correct responses, than in the application phase with an average of 98.94 % correct responses ($t_{(27)} = 17.64$, $p < 0.0001$) (Fig. 1B, SI Appendix, Table S2). Similarly, the correct response latency was longer for the acquisition phase (1252.31 ms) in comparison with the application (1119.30 ms) phase of the task condition ($t_{(27)} = 8.28$, $p < 0.0001$). This phase-specific result of a slower response was also significant in the control conditions ($t_{(27)} = 6.82$, $p < 0.0001$); however, after multiple comparison correction, no significant difference was observed in accuracy ($t_{(27)} = -2.12$, $p = 0.17$). These results indicate that the participants were less accurate and slower in finding the correct response under novel environmental demands, whereas once the rule was acquired, the responses were faster and more accurate, demonstrating context-specific, learned decision-making.

Having demonstrated the expected differentiation in behavioral performance, the next step was to examine the relative differences in brain activity between the acquisition and application phases of the cognitive flexibility task. Similar to the brain areas observed in effortful task performance (Fig. 1C, SI Appendix, Table S3), in a given environmental context (i.e. task rule) we postulated that a greater number of regions commonly associated with controlled, effortful processing would be more active in the acquisition phase as compared to the application phase (1, 18). This would allow more perceptual information to be extracted from the environment to aid the decision-making process. In contrast, greater DMN activity would be observed during the application phase in comparison with the acquisition phase, allowing the use of memory-based information for responding to environmental demands.

Comparable to this hypothesis, the results revealed a highly symmetrical bilateral set of fronto-parietal, insular, subcortical and cerebellar brain regions more active in the acquisition as compared to the application phase of the task (Fig. 2A, SI Appendix, Table S4). These areas, often referred to as the multiple-demand network (19), have been previously shown to engage during the WCST (20) as well as other tests of cognitive flexibility (2).

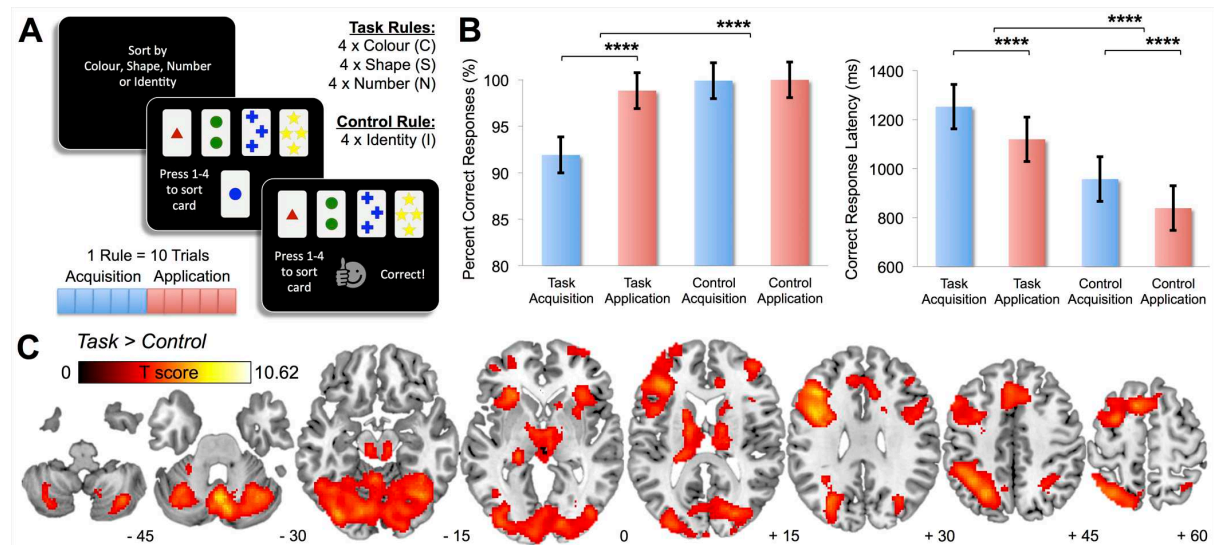


Figure 1. Experimental design, behavioral and brain activation results for the cognitive flexibility task. (A) During a single trial, in addition to four permanent reference cards, participants were presented with a target card chosen from a pool of 60 cards. Following the “Sort” prompt, a block of 10 trials commenced for a given sorting dimension (color, shape, number or identity) that was undisclosed to the participants. In each trial, they were presented with feedback indicating choice accuracy. (B) In comparison with the control condition, percent correct responses were lower and correct response latency was longer in the task condition. Further dividing these results, the participants performed worse in the acquisition in comparison with the application phases of both the task and control conditions (SI Appendix, Table S2) (**** denotes $p < 0.0001$ and the error bars represent standard error). (C) The conventional contrast of *task* > *control* blocks revealed activity centered on an extensive system of brain areas encompassing regions commonly associated with the fronto-parietal, dorsal attention, cingulo-opercular, salience and visual networks (SI Appendix, Table S3). There were no significant results in the *task* < *control* contrast. The reported clusters are uncorrected at the voxel-level ($p = 0.001$) and FWE corrected for multiple comparisons at the cluster-level ($p = 0.05$).

From a large-scale brain network organization perspective, these co-activating brain regions have been largely associated with the fronto-parietal, dorsal attention, cingulo-opercular, salience and visual networks (21), which have been denoted as “externally directed” networks. More specifically, the dorsal attention network (DAN) activity has been previously shown to anti-correlate with that of the DMN during resting state conditions (17).

On the other hand, as compared to the acquisition phase, the application phase displayed greater activity centered on the default mode as well as somatomotor network regions including the ventromedial (orbitofrontal) prefrontal cortex, parts of the ventral anterior cingulate cortex, posterior cingulate cortex and precuneus, medial temporal lobe structures including the hippocampal formation and parahippocampal gyrus as well as the right amygdala, superior and middle temporal gyri, posterior insula, Heschl’s gyri and rolandic operculum, middle cingulate and paracentral lobule, postcentral and precentral gyri, parts of the left angular gyrus and the left middle occipital gyrus (Fig. 2B, SI Appendix, Table S5).

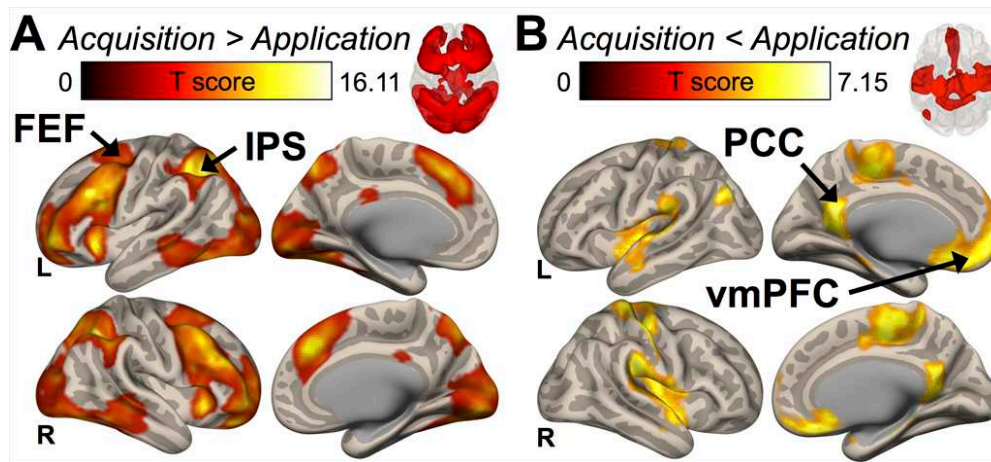


Figure 2. Differential task-evoked activity profiles of distinct brain regions in the acquisition and application phases of the cognitive flexibility task. While the (A) *acquisition > application* contrast revealed regions commonly associated with the fronto-parietal, dorsal attention (e.g. frontal eye fields – FEF, inferior parietal sulcus – IPS), cingulo-opercular, salience and visual networks from a large-scale brain network organization perspective, (B) the *acquisition < application* contrast showed greater activity in regions commonly associated with the default mode (e.g. posterior cingulate cortex, PCC, ventromedial prefrontal cortex, vmPFC), and somatomotor networks (SI Appendix, Tables S4-5). The reported clusters are uncorrected at the voxel-level ($p = 0.001$) and FWE corrected for multiple comparisons at the cluster-level ($p = 0.05$).

Although the DMN has not been extensively studied in tasks of cognitive flexibility, emerging evidence suggests its contribution to tasks associated with this function (22, 23), i.e. our ability to apply learned rules. For instance, Provost and colleagues have investigated the brain's responses to changing or continuous application of WCST rules in an experiment in which the participants were explicitly informed about the relevant rules to be applied (24). In line with findings from our experiment, in which the participants had to implicitly deduce the rule via trial-and-error, the continuous application of the same rule was linked to greater activity in regions commonly associated with the DMN, suggesting the potential contribution of this set of brain regions to memory-based, automated phases of goal-oriented tasks.

Altered Brain Network Connectivity during Cognitive Flexibility Task

Following this observed differential activity of brain regions commonly associated with controlled, effortful processing (e.g. DAN) and those belonging to the DMN in the acquisition and application phases of the WCST task, respectively, our next objective was to determine the extent of the dorsal attention and default mode networks' interactions with the rest of the brain during task performance. Specifically, we aimed to assess any changes in the functional connectivity of these two networks, which are commonly anti-correlated at rest (17) and are purported to mediate externally and internally directed cognition, respectively (25).

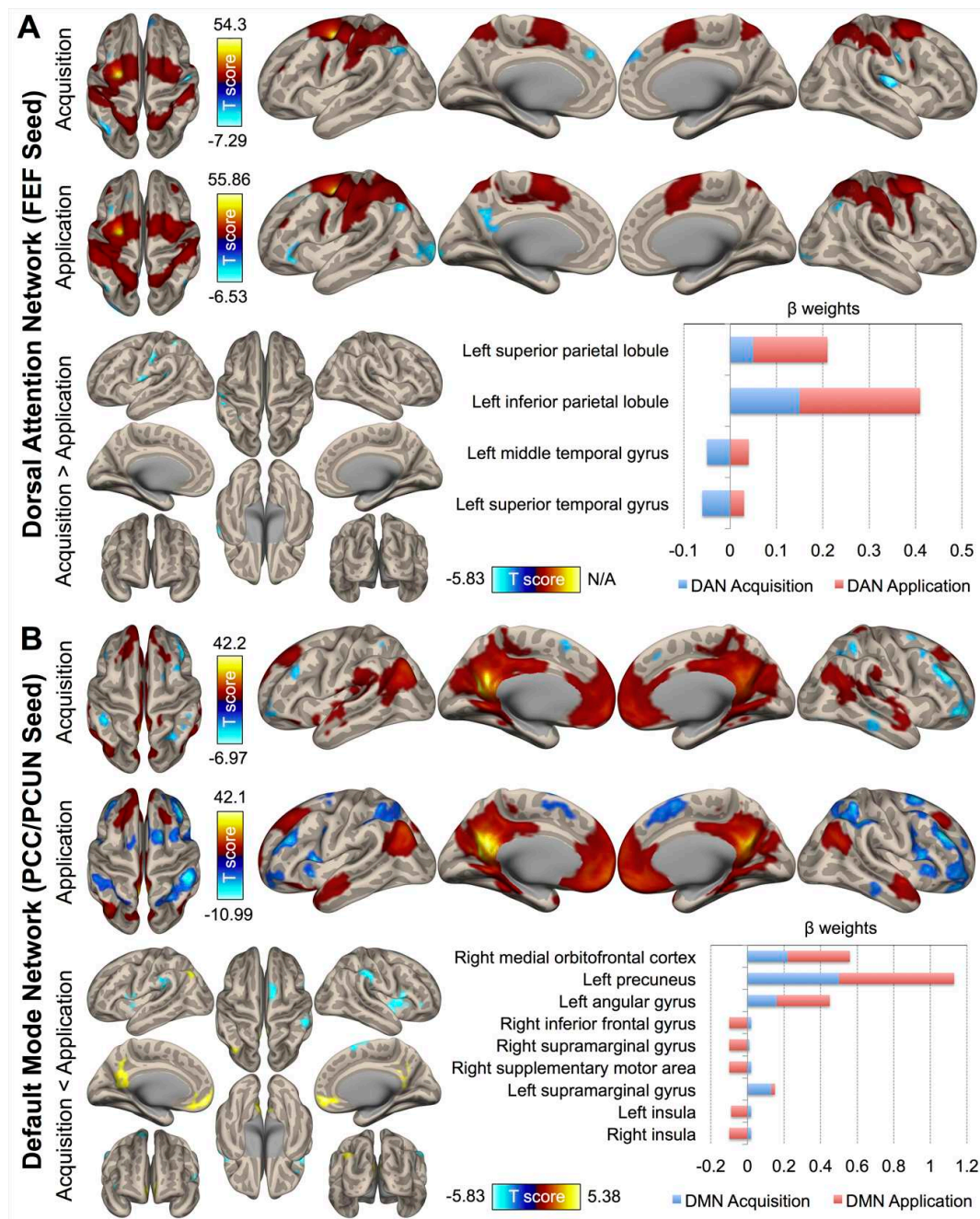


Figure 3. Altered functional connectivity patterns of dorsal attention and default mode networks in the acquisition and application phases of the cognitive flexibility task. Both networks revealed expected connectivity maps in both phases of the task. While **(A)** DAN included the frontal eye fields and the inferior parietal sulcus, **(B)** DMN encompassed the posterior cingulate, medial prefrontal cortex, bilateral angular gyri, superior frontal gyrus, medial temporal lobe structures and the temporal poles. **(A)** As compared to the application phase, in the acquisition phase, DAN illustrated reduced connectivity with the left middle/superior temporal, and inferior/superior parietal gyri (SI Appendix, Tables S6-8). **(B)** In comparison with the acquisition phase, in the application phase the DMN showed greater connectivity with the posterior cingulate cortex/precuneus, ventromedial prefrontal cortices, left angular gyrus and reduced connectivity with bilateral insular gyri, and right pre-supplementary motor area (SI Appendix, Tables S9-11). The reported clusters are uncorrected at the voxel-level ($p = 0.001$) and FWE corrected for multiple comparisons at the cluster-level ($p = 0.05$). The bar charts display the connectivity values (beta weights) of the clusters that showed a significant change between the acquisition and application phases of the task.

First, we examined DAN connectivity during acquisition and application phases of the WCST, using a seed on the left frontal eye field (FEF) (26). In both phases of the task condition, the results revealed an extensive DAN that encompassed the FEF and inferior parietal lobule as has been previously discussed in the literature (17). However, the DAN illustrated altered connectivity with the middle/superior temporal, and inferior/superior parietal gyri in the acquisition phase compared to the application phase (Fig. 3A, SI Appendix, Tables S6-8), i.e. regions which have all been previously implicated in attentional control relevant to the task at hand (27, 28).

Next, we investigated DMN connectivity in the two phases of the task using a seed that was placed on the left posterior cingulate cortex/precuneus (PCC/PCUN) region, a main hub of the DMN. In both the acquisition and the application phases, the results revealed an extensive DMN as defined in the literature (29). However, the DMN showed greater connectivity to a range of areas in the application phase as compared to the acquisition phase, including the PCC/PCUN, ventromedial prefrontal cortices, and left angular gyrus. In addition, reduced connectivity was observed with the bilateral insular gyri, and right pre-supplementary motor area as well as increased anti-correlation with regions commonly linked to the DAN (Fig. 3B, SI Appendix, Table S9-11). These findings indicate the robust temporal correlations of these two networks throughout the two phases of the WCST, with alterations in their functional connectivity in response to the variable demands for access to external or memory-based information to be used in the decision-making. Most importantly, the results indicate continuous DMN engagement in a goal-oriented task with alterations in its spatial topography in response to changing demands for access to learned information.

Double Dissociation of Brain and Behavior Relationships

Following these results on the altered, yet continuous engagement of DAN and DMN regions during the two phases of the WCST, the final question we asked was whether the connectivity of these two networks in their respective phases would differentially relate to behavioral performance. Beyond the DMN's usual association with task-unrelated internal mentation (30), our aim was to illustrate this network's contribution to WCST performance via memory-based, automated decision-making that is differentiated from the contribution of the DAN (traditionally associated with controlled, effortful information processing).

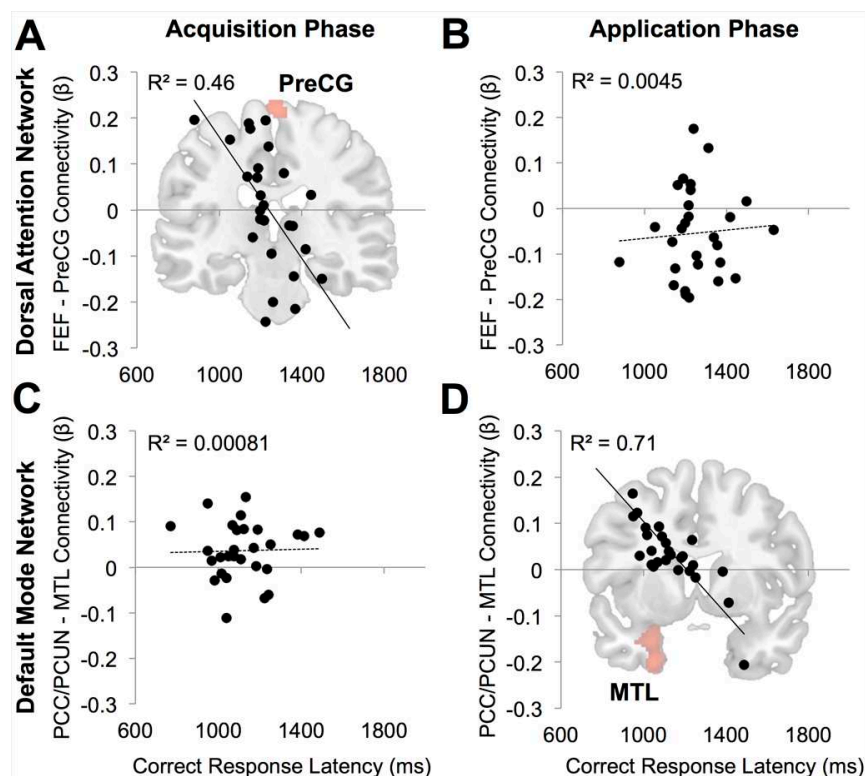


Figure 4. Double dissociation of the brain and behavior correlations in the acquisition and application phases of the cognitive flexibility task. (A) While the DAN (FEF seed) connectivity with a left-lateralized cluster (shown in red) on the pre/post central gyrus, paracentral lobule (PreCG) correlated with better performance (i.e. faster reaction time) in the acquisition phase ($p < 0.0001$), (B) no such correlation with any brain regions was found in the application phase. (The correlation between FEF and PreCG in the application phase is shown for illustration purposes). (D) In contrast, connectivity of the DMN (PCC/PCUN seed) with both the left lateralized medial temporal lobe (MTL) structures (hippocampal/parahippocampal gyri and amygdala) (shown in red) as well as the bilateral primary visual cortices correlated with better performance in the application phase ($p < 0.0001$). (C) However, no such correlation was found in the acquisition phase with any brain region. (The correlation between PCC/PCUN and MTL in the acquisition phase is shown for illustration purposes) (SI Appendix, Tables S12-13). The reported clusters were uncorrected at the voxel-level ($p = 0.001$) and multiple comparison corrected at the cluster level using the Family Wise Error (FWE) detection technique ($p = 0.05$).

For that purpose, we first investigated the relationship between DAN connectivity and reaction time to correct responses in the acquisition and application phases of the WCST. The results indicated that greater connectivity between FEF and somatomotor regions (pre and post central gyrus, and the paracentral lobule) in the acquisition phase, correlated with faster reaction times, thus better performance (Fig. 4A, SI Appendix, Table S12). However, no such correlation between the FEF and any brain regions was found in the application phase (Fig. 4B). This connectivity between the FEF and the precentral gyrus is believed to control saccades when processing visual information (28, 31), which is an important component of

this task, i.e. facilitating an extensive visual search and extraction of information during rule acquisition.

For the DMN, greater connectivity of the PCC/PCUN with the parahippocampal gyrus, hippocampal formation, amygdala and primary visual cortices correlated with faster reaction time to correct responses, and thus better performance, in the application phase of the WCST (Fig. 4D and Table S13). Nevertheless, no such correlation of the PCC/PCUN with any other brain region was found in the acquisition phase (Fig. 4C). Given the vast amount of literature that indicates the role of medial temporal lobe structures in context-specific, memory-based information processing (32, 33) and the visual nature of the task at hand, it is plausible that the observed correlation indicates the participants' ability to access and utilize learned responses in dealing with stable environmental contexts during the application phase of the WCST.

In summary, these brain and behavioral results reveal a double dissociation in which the relative DAN and DMN connectivity in the acquisition and application phases of the WCST, respectively, correlate with enhanced behavioral performance. Specifically, these results strongly suggest the DMN's task-relevance in the application phase of the WCST, indicating its on-going contribution to learned, automated and fast responses for decision-making under a given behavioral context (or rule).

Discussion

Despite the mounting evidence on its extensive structural and functional connections (34) and implication in a variety of neuropsychiatric as well as neurodegenerative disorders (35), the exact functional role of the DMN in human cognition remains elusive. To this end, the major aim of this study was to provide evidence for this network's positive contribution to the performance of an externally directed, attention-demanding, goal-oriented, non-self-referential task of cognitive flexibility, and to outline a general framework within which it may operate to contribute to adaptive cognition. Overall, the findings allude to the involvement of the DMN in automated information processing, i.e. when rapidly selecting appropriate responses under specific, predictable environmental demands.

Recent models of brain function suggest that our brains are wired in a way that maximizes the anticipation of external events (36). The internalization of statistical regularities through worldly experiences forms the foundations of our expectations (priors or best guesses), which

can then be used to interpret, predict and act upon environmental demands (36-38). Indeed, the intrinsic activity of the brain, specifically that of the DMN which uses a considerable portion of our brain energy supplies (9), is suggested to reflect such internal models of the world that could aid in the interpretation of our surroundings (16, 39-41). Though such predictive processing may constitute the common mechanism by which the brain processes information as a whole; what may distinguish the DMN is its ability to provide a common workspace for convergence of information with its extensive functional and structural connections to the rest of the brain, and specifically its access to memory-based information (34). This integrative capacity of the DMN (13) is thought to be a hallmark of consciousness (42), the levels of which has been previously associated with DMN integrity (43).

From this perspective, the relatively increased activity/connectivity of the DMN in the application phase of the WCST observed in this study may indicate this network's ability to integrate memory-based information (13), generating top-down associative predictions under stable environmental contexts (16) for automated, fast and efficient decision-making. In contrast, unpredictable, novel or salient events, beyond the scope of the DMN's memory-based processing, such as the one required in the acquisition phase of this task, may demand further external attention and perceptual information for making decisions. This would increase the involvement of networks commonly associated with controlled, effortful processing such as the fronto-parietal, cingulo-opercular, salience and dorsal attention networks (18). Thus, the anti-correlation previously reported between the DMN and DAN (17) might represent these networks' differential but complementary roles in facilitating the theorized predictive processing of the brain. Therefore, the spectrum of differential involvement of these two networks may not be based on the dichotomy of internally versus externally directed cognition, but may rather be dependent on the predictability of the environmental demands, requiring either learned (memory-based) or novel (perception-based) responses. Indeed, recent evidence suggests a dynamic interplay between the DMN and DAN in the redirection of attention, potentially controlled by the salience and/or fronto-parietal network's influence on determining the saliency and predictability of incoming information (44-46).

Such duality in decision-making under varying levels of predictability in the environment has been extensively discussed in the scientific literature. Norman and Shallice have argued for stored schemas that automatically take over processing in familiar environmental contexts, while the supervisory attentional system was postulated to play an intentional inhibitory role

when the environmental rules changed (47). Along a similar line of thought, Kahneman and Tversky have also devised an influential two-system view of brain processing (48); one (System 1) required to carry out automated decision-making in order to provide fast best-guesses, and another (System 2) used to make calculated, and effortful decisions.

Based on our results, we propose that the DMN may contribute to an “autopilot mode” which makes memory-based predictions to aid decision-making under established behavioral contexts, whereas control networks are involved in a “manual mode” that overrides the automatic system when the brain fails to reliably predict the environment. This proactive framework of brain function may provide an all important scaffold to explain not only the DMN’s ongoing activity in stable “rest” conditions, but also its contribution to social interactions (e.g. theory of mind, intuition and stereotyping), a conscious sense-of-self, creativity and a variety of other cognitive domains (49) that all require the stable use of learned information for the top-down prediction of the world around us. Hence, future studies will be required to assess the potential role that the DMN may play in the formation of habitual behavior for the neuroeconomics of decision-making, and its potential breakdown in disorders such as addiction, obsessive-compulsive disorder or clinical depression.

Materials and Methods

Participants. Ethical approval was obtained from the Cambridge Psychology Research Ethics committee in accordance with the Declaration of Helsinki. All volunteers gave informed consent prior to their participation. Following the exclusion criteria, this right-handed, healthy control group consisted of 28 participants (22 – 34 years old, mean = 26.8, SD = 2.8, 13/15 female to male ratio) with an average National Adult Reading Test (NART) score of 121.22 (SD = 3.17).

Experimental Paradigm Specifications. The experimental paradigm was a variant of the WCST (50) that was modified for the scanner environment utilizing a mixed design. Stimuli were delivered and responses recorded using an open source software package called PsychoPy (Version 1.83). In addition to the task and control blocks conventionally used in this paradigm, we operationally stratified the task into “acquisition” and “application” phases. Full details about the experimental paradigm, and procedures followed for the preprocessing and analysis of both the behavioral and imaging data are provided in the SI Appendix, Materials and Methods.

MRI Data Acquisition. The participants were scanned in a Siemens MAGNETOM Tim Trio 3T scanner (32-channel head coil) at the Wolfson Brain Imaging Centre, Cambridge. The scanning session started with a high resolution T1-weighted, magnetization-prepared rapid gradient-echo (MPRAGE) structural scan (TR = 2300 ms, TE = 2.98 ms, slice thickness = 1.00 mm). The echo planar imaging (EPI) sequence parameters for the WCST functional data acquisition were as follows: 37 slices in each volume, 3.0 mm slice thickness, 3.0 x 3.0 x 3.0 voxel size, TR = 2000 ms, TE = 30 ms, flip angle = 78 degrees. The number of 3D volumes varied according to the speed of the participants' responses to the task (mean = 347 volumes, SD = 12).

MRI Data Preprocessing. MRI data preprocessing and statistical analyses were carried out using the SPM software package (Version 12.0), based on the MATLAB platform (Version 15a). For preprocessing, functional volumes were slice-time and motion corrected, coregistered to the high resolution structural image, spatially normalized to the MNI space using the unified-segmentation algorithm (51), smoothed with an 8 mm FWHM Gaussian kernel, and carried forward onto statistical analyses.

MRI Data Analysis. *Task-evoked Activation Analysis.* Subject-level analyses with the appropriate contrasts were set up using the general linear model (GLM). For the *task > control* and *task < control* contrasts the design matrix included the onsets and durations of the task and control conditions. When comparing the acquisition and application phases of the task, the events were modeled as impulses, including the onsets of the correct/incorrect responses for the two phases of the task with zero duration. The resulting subject-specific contrast maps were carried forward onto group-level analysis using one-sample *t*-tests.

Functional Connectivity Analysis. For the seed-based functional connectivity analysis, the MNI coordinates of two seed regions representing DAN and DMN (17, 26) were selected from the literature. The closest local peaks to these coordinates (in terms of Euclidean distance) were identified in the *acquisition > application* (for DAN) and *acquisition < application* (for DMN) contrasts of the group-level task-evoked activation analysis. Subsequently, spheres with 6 mm radius were constructed around the MNI coordinates of the left FEF [-25 -8 50] for the DAN and left PCC/PCUN [-12 -54 18] for the DMN. A strict temporal preprocessing pipeline of nuisance regression included motion and CompCor components attributable to the signal from white matter and cerebrospinal fluid (52) as well as a linear detrending term. The subject-specific six realignment parameters, the main effect

of task-conditions and their first order derivatives were also included in the analysis as potential confounds. Given the mixed design of this WCST variant, a low-pass temporal filter was not employed. The *Conn* functional connectivity toolbox (Version 15.h) (53) was used in order to assess phase-specific changes in functional connectivity (i.e. acquisition versus application) using the weighted GLM method. Following this procedure, seed-based functional connectivity analyses were performed for each subject using the average signal from the spheres placed on the MNI coordinates for the 2 ROIs described above. Group-level analyses were carried out using *t*-statistics in which a one-sample *t*-test assessed the group-level spatial extent of DMN and DAN connectivity in the acquisition and application phases, whereas a paired *t*-test between these phases examined any changes in these networks' functional connectivity.

Brain and Behavior Correlation Analysis. The voxel-based correlation analysis involved using the connectivity maps obtained from the seed-based functional connectivity analyses for the two phases in separate linear regressions with the reaction times to correct responses used as the variable of interest. All reported findings for the MRI data analyses were uncorrected at the voxel-level ($p = 0.001$) and multiple comparison corrected at the cluster level using the Family Wise Error (FWE) detection technique ($p = 0.05$).

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References

1. Duncan J (2010) The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn. Sci.* 14(4):172-179.
2. Kehagia AA, Murray GK, & Robbins TW (2010) Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Curr. Opin. Neurobiol.* 20(2):199-204.
3. Cools R, Clark L, & Robbins TW (2004) Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. *J. Neurosci.* 24(5):1129-1135.
4. Armbruster-Genc DJ, Ueltzhoffer K, & Fiebach CJ (2016) Brain Signal Variability Differentially Affects Cognitive Flexibility and Cognitive Stability. *J. Neurosci.* 36(14):3978-3987.
5. Helie S, Waldschmidt JG, & Ashby FG (2010) Automaticity in rule-based and information-integration categorization. *Atten Percept Psychophys* 72(4):1013-1031.
6. Elton A & Gao W (2015) Task-positive Functional Connectivity of the Default Mode Network Transcends Task Domain. *J. Cogn. Neurosci.* 27(12):2369-2381.
7. Raichle ME (2015) The brain's default mode network. *Annu. Rev. Neurosci.* 38:433-447.
8. Kucyi A, Esterman M, Riley CS, & Valera EM (2016) Spontaneous default network activity reflects behavioral variability independent of mind-wandering. *Proc. Natl. Acad. Sci. U. S. A.* 113(48):13899-13904.
9. Raichle ME, *et al.* (2001) A default mode of brain function. *Proc. Natl. Acad. Sci. U. S. A.* 98(2):676-682.
10. Binder JR, *et al.* (1999) Conceptual processing during the conscious resting state. A functional MRI study. *J. Cogn. Neurosci.* 11(1):80-95.
11. Spreng RN, *et al.* (2014) Goal-congruent default network activity facilitates cognitive control. *J. Neurosci.* 34(42):14108-14114.
12. Krieger-Redwood K, *et al.* (2016) Down but not out in posterior cingulate cortex: Deactivation yet functional coupling with prefrontal cortex during demanding semantic cognition. *Neuroimage* 141:366-377.
13. Vatansever D, Menon DK, Manktelow AE, Sahakian BJ, & Stamatakis EA (2015) Default mode dynamics for global functional integration. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 35(46):15254-15262.

14. Margulies DS, *et al.* (2016) Situating the default-mode network along a principal gradient of macroscale cortical organization. *Proc. Natl. Acad. Sci. U. S. A.* 113(44):12574-12579.
15. Constantinescu AO, O'Reilly JX, & Behrens TE (2016) Organizing conceptual knowledge in humans with a gridlike code. *Science* 352(6292):1464-1468.
16. Bar M (2009) The proactive brain: memory for predictions. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 364(1521):1235-1243.
17. Fox MD, *et al.* (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc. Natl. Acad. Sci. U. S. A.* 102(27):9673-9678.
18. Hugdahl K, Raichle ME, Mitra A, & Specht K (2015) On the existence of a generalized non-specific task-dependent network. *Front. Hum. Neurosci.* 9:430.
19. Fedorenko E, Duncan J, & Kanwisher N (2013) Broad domain generality in focal regions of frontal and parietal cortex. *Proc. Natl. Acad. Sci. U. S. A.* 110(41):16616-16621.
20. Buchsbaum BR, Greer S, Chang WL, & Berman KF (2005) Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. *Hum. Brain Mapp.* 25(1):35-45.
21. Smith SM, *et al.* (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc. Natl. Acad. Sci. U. S. A.* 106(31):13040-13045.
22. Vatansever D, Manktelow AE, Sahakian BJ, Menon DK, & Stamatakis EA (2015) Cognitive Flexibility: A Default Network and Basal Ganglia Connectivity Perspective. *Brain Connect.*
23. Dang LC, Donde A, Madison C, O'Neil JP, & Jagust WJ (2012) Striatal dopamine influences the default mode network to affect shifting between object features. *J. Cogn. Neurosci.* 24(9):1960-1970.
24. Provost JS & Monchi O (2015) Exploration of the dynamics between brain regions associated with the default-mode network and frontostriatal pathway with regards to task familiarity. *Eur. J. Neurosci.* 41(6):835-844.
25. Boly M, *et al.* (2008) Intrinsic brain activity in altered states of consciousness: how conscious is the default mode of brain function? *Ann. N. Y. Acad. Sci.* 1129:119-129.
26. Vincent JL, Kahn I, Snyder AZ, Raichle ME, & Buckner RL (2008) Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J. Neurophysiol.* 100(6):3328-3342.

27. Ciaramelli E, Grady CL, & Moscovitch M (2008) Top-down and bottom-up attention to memory: a hypothesis (AtoM) on the role of the posterior parietal cortex in memory retrieval. *Neuropsychologia* 46(7):1828-1851.
28. Ptak R & Schnider A (2010) The dorsal attention network mediates orienting toward behaviorally relevant stimuli in spatial neglect. *J. Neurosci.* 30(38):12557-12565.
29. Andrews-Hanna JR, Smallwood J, & Spreng RN (2014) The default network and self-generated thought: component processes, dynamic control, and clinical relevance. *Ann. N. Y. Acad. Sci.* 1316:29-52.
30. McKiernan KA, D'Angelo BR, Kaufman JN, & Binder JR (2006) Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage* 29(4):1185-1191.
31. Vernet M, Quentin R, Chanes L, Mitsumasu A, & Valero-Cabre A (2014) Frontal eye field, where art thou? Anatomy, function, and non-invasive manipulation of frontal regions involved in eye movements and associated cognitive operations. *Front. Integr. Neurosci.* 8:66.
32. Eichenbaum H (2004) Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron* 44(1):109-120.
33. Smith DM & Mizumori SJ (2006) Hippocampal place cells, context, and episodic memory. *Hippocampus* 16(9):716-729.
34. Horn A, Ostwald D, Reisert M, & Blankenburg F (2014) The structural-functional connectome and the default mode network of the human brain. *Neuroimage* 102 Pt 1:142-151.
35. Whitfield-Gabrieli S & Ford JM (2012) Default mode network activity and connectivity in psychopathology. *Annu. Rev. Clin. Psychol.* 8:49-76.
36. Friston K (2010) The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11(2):127-138.
37. Clark A (2012) Whatever Next ? Predictive Brains , Situated Agents , and the Future of Cognitive Science .1-86.
38. Hohwy J (2013) *The predictive mind* (Oxford University Press, Oxford, United Kingdom ; New York, NY, United States of America) First edition. Ed pp ix, 282 pages.
39. Raichle ME (2006) The brain's dark energy. *Science (New York, N.Y.)* 314:1249-1250.
40. Carhart-Harris RL & Friston KJ (2010) The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain* 133(Pt 4):1265-1283.

41. Northoff G, Duncan NW, & Hayes DJ (2010) The brain and its resting state activity--experimental and methodological implications. *Prog. Neurobiol.* 92(4):593-600.
42. Tononi G (2008) Consciousness as integrated information: a provisional manifesto. *Biol. Bull.* 215(3):216-242.
43. Guldenmund P, Vanhaudenhuyse A, Boly M, Laureys S, & Soddu A (2012) A default mode of brain function in altered states of consciousness. *Arch. Ital. Biol.* 150(2-3):107-121.
44. Menon V & Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function* 214(5-6):655-667.
45. Gao W & Lin W (2012) Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Hum. Brain Mapp.* 33(1):192-202.
46. Uddin LQ (2015) Salience processing and insular cortical function and dysfunction. *Nat. Rev. Neurosci.* 16(1):55-61.
47. Norman D & Shallice T (1986) Attention to Action. *Consciousness and Self-Regulation*, eds Davidson R, Schwartz G, & Shapiro D (Springer US), pp 1-18.
48. Tversky A & Kahneman D (1974) Judgment under Uncertainty: Heuristics and Biases. *Science* 185(4157):1124-1131.
49. Buckner RL, Andrews-Hanna JR, & Schacter DL (2008) The brain's default network: anatomy, function, and relevance to disease. *Ann. N. Y. Acad. Sci.* 1124:1-38.
50. Berg EA (1948) A simple objective technique for measuring flexibility in thinking. *J. Gen. Psychol.* 39:15-22.
51. Ashburner J & Friston KJ (2005) Unified segmentation. *Neuroimage* 26(3):839-851.
52. Behzadi Y, Restom K, Liao J, & Liu TT (2007) A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *Neuroimage* 37(1):90-101.
53. Whitfield-Gabrieli S & Nieto-Castanon A (2012) Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity* 2(3):125-141.