

Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex

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A considerable body of previous research on the prefrontal cortex (PFC) has helped characterize the regional specificity of various cognitive functions, such as cognitive control and decision making. Here we provide definitive findings on this topic, using a neuropsychological approach that takes advantage of a unique dataset accrued over several decades. We applied voxel-based lesion-symptom mapping in 344 individuals with focal lesions (165 involving the PFC) who had been tested on a comprehensive battery of neuropsychological tasks. Two distinct functional-anatomical networks were revealed within the PFC: one associated with cognitive control (response inhibition, conflict monitoring, and switching), which included the dorsolateral prefrontal cortex and anterior cingulate cortex and a second associated with value-based decision-making, which included the orbitofrontal, ventromedial, and frontopolar cortex. Furthermore, cognitive control tasks shared a common performance factor related to set shifting that was linked to the rostral anterior cingulate cortex. By contrast, regions in the ventral PFC were required for decision-making. These findings provide detailed causal evidence for a remarkable functional-anatomical specificity in the human PFC.

executive function | Wisconsin Card Sorting Test | Trail-Making Test | Stroop Test | Iowa Gambling Task

The prefrontal cortex (PFC) is widely regarded as the pinnacle of brain evolution in humans (1). Its functional organization has long been under scientific scrutiny and has often been subsumed under the rubric “executive functions” (1, 2). Although some early theories attributed a unitary “central executive” to the PFC (3), scientific findings of the past decades have suggested that executive processes fractionate into distinct cognitive functions concerned with motivating behavior (valuation) and controlling behavior (cognitive control), which have been proposed to draw on two partially distinct PFC networks (1, 4–6). Comparative neuroanatomy suggests a functional and anatomical distinction between ventral PFC with strong connections to the limbic system and dorsolateral PFC (dlPFC) with connections to posterior cortical areas in the parietal lobe (7). Cognitive control, which is thought to draw on multiple processes, including task switching, response inhibition, error detection and response conflict, and working memory (2, 4, 8), has been associated with the dlPFC and the anterior cingulate cortex (ACC), as well as other sectors of the PFC that together may constitute a rostro-caudally organized hierarchy for behavioral control and planning (9–11). In contrast, valuation, reward learning, and decision-making functions have been mainly associated with ventral and medial sectors of the PFC (vmPFC) (10, 12–18). Overall, then, the broad functions of “cognitive control” and “valuation” appear to draw on partly distinct, but interacting, networks within the PFC to generate adaptive behavior (6, 19, 20), although this distinction is sometimes framed between various levels of control and motivation (20) or between executive functions (monitoring and task setting) and behavioral/emotional self-regulation (6, 21). Valuation provides a way to compare among rewards, setting the motivated goals that cognitive

control functions can subsequently translate into planning of actions, flexible switching between them, and response monitoring.

Much of the evidence regarding functional-anatomical networks in the PFC has come from work using functional imaging. Some lesion studies have supported a causal role for different sectors of the PFC in cognitive control and decision-making (13, 16, 22–24), but these studies used isolated neuropsychological tasks, involved small subject samples, or focused on particular a priori hypothesized sectors of the PFC, limiting the scope of their neuroanatomical conclusions. Furthermore, some results from fMRI have not been borne out by lesion findings (23, 25, 26). For instance, the involvement of the dorsal ACC in Stroop performance suggested by fMRI (27) has been called into question by the finding that patients with ACC lesions are not impaired on the Stroop task (25). Thus, the issues of whether distinct networks in PFC support distinct cognitive-behavioral operations, together with their precise neuroanatomical location, remain unresolved, especially in regard to whether particular subsectors of the PFC are necessary for particular functions, an inferential strength not available from fMRI studies alone.

Here we address these open questions by providing a comprehensive mapping of multiple tasks that measure cognitive control and decision-making in a large sample of well-characterized patients with focal brain lesions that were plotted onto a reference brain. We used nonparametric voxel-based lesion-symptom mapping (VLSM) (28) in 344 participants who were assessed by using a large battery of standardized neuropsychological tasks. Of these participants, 165 had damage in the frontal lobes that included sectors of the PFC, supplementary motor area (SMA), or premotor cortex (PM).

Results

We selected five neuropsychological target scores: four that emphasize cognitive control and one that measures value-based decision-making.

The four cognitive control tasks were as follows: the Part B – Part A difference score from the Trail-Making Test (TMT), a measure of executive response switching; the Perseverative Errors score from the Wisconsin Card Sorting Test (WCST), which measures impairments in set switching; the Color-Word Interference score from the Stroop Test (STROOP), a measure of response inhibition; and the Number of Words score from the Controlled Oral Word Association Test (COWA), which measures verbal fluency, divergent thinking, and response creativity. As an index of value-based decision-making and reward learning,

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we used the Net Score (advantageous minus disadvantageous choices) from the Iowa Gambling Task (IGT) (see *SI Materials and Methods* for a description of the neuropsychological tests). All these tasks have been extensively used and well standardized, and they have been shown to detect impairments reliably in clinical populations such as ours. As expected, the cognitive control-related tasks were all weakly, but positively intercorrelated ($r = 0.16-0.43$), whereas their correlation with the IGT was generally lower ($r = 0.09-0.20$) (Table S1), a pattern that remained even after the covariates were statistically removed from the data (see below).

To isolate cognitive control and value-based decision-making, we removed the covariance of four basic cognitive skills that our tasks also draw on (2) (verbal abilities, spatial abilities, verbal memory, and spatial memory) by using multiple linear regression (*Materials and Methods* and *SI Materials and Methods*). All subsequent analyses were based on these covariate-corrected task residuals, which were then submitted to lesion overlap analyses by using nonparametric VLSM (28). This analysis compares the scores at every voxel in the brain (corrected for multiple comparisons) between that subset of patients whose lesion includes a given voxel versus that subset whose lesion does not. Lesion density maps (Fig. S1) and power analyses (Fig. S2) confirmed that we had sufficient lesion coverage in the PFC, and most other regions of the brain, to detect significant lesion-deficit relationships on our target tasks (see Fig. S3 for further quantification of lesions in the PFC).

Performance on tasks engaging cognitive control was associated with dorsal sectors of the medial PFC and both ventral and dorsal sectors of the lateral PFC (Fig. 1A). Significantly lower

performances on the TMT and WCST were associated with damage to the ACC. Lower performance on the TMT was associated with damage to a focal region of left rostral ACC, whereas lower performance on the WCST was associated with damage to a slightly more anterior region of the ACC and left medial superior frontal gyrus, together with multiple right hemisphere regions including temporal (superior temporal gyrus, posterior middle temporal gyrus), parietal (angular gyrus), and frontal (precentral gyrus) cortices, and subcortical regions (head of the caudate). The commonalities across these two tasks suggest that the rostral ACC is critically involved in response/set switching (29), whereas related executive functions such as error (30) and conflict detection (27, 31) have been associated with the (more posterior) dorsal ACC. Lower performance on the STROOP was associated with damage to left dlPFC (middle frontal gyrus), which is consistent with the previously described role of this region in response inhibition (23, 30, 32). Lower performance on COWA was associated with damage to extensive sectors of the left frontoparietal cortices, anterior PFC, and insula, an intriguing finding considering that we had already removed verbal ability and memory from task scores (33). The pattern of relative lateralization across cognitive control tasks is consistent with right hemisphere involvement in error monitoring, particularly with conceptual responses (e.g., WCST), and left hemisphere involvement in setting and maintaining task context (e.g., the different instructional conditions of the Stroop) (6, 34).

In contrast with the above findings, the Iowa Gambling Task (IGT) was the only task associated with ventral sectors of the medial PFC, lateralized to the left. The IGT was also associated with dorsal sectors of the anterior PFC on the right, and with the

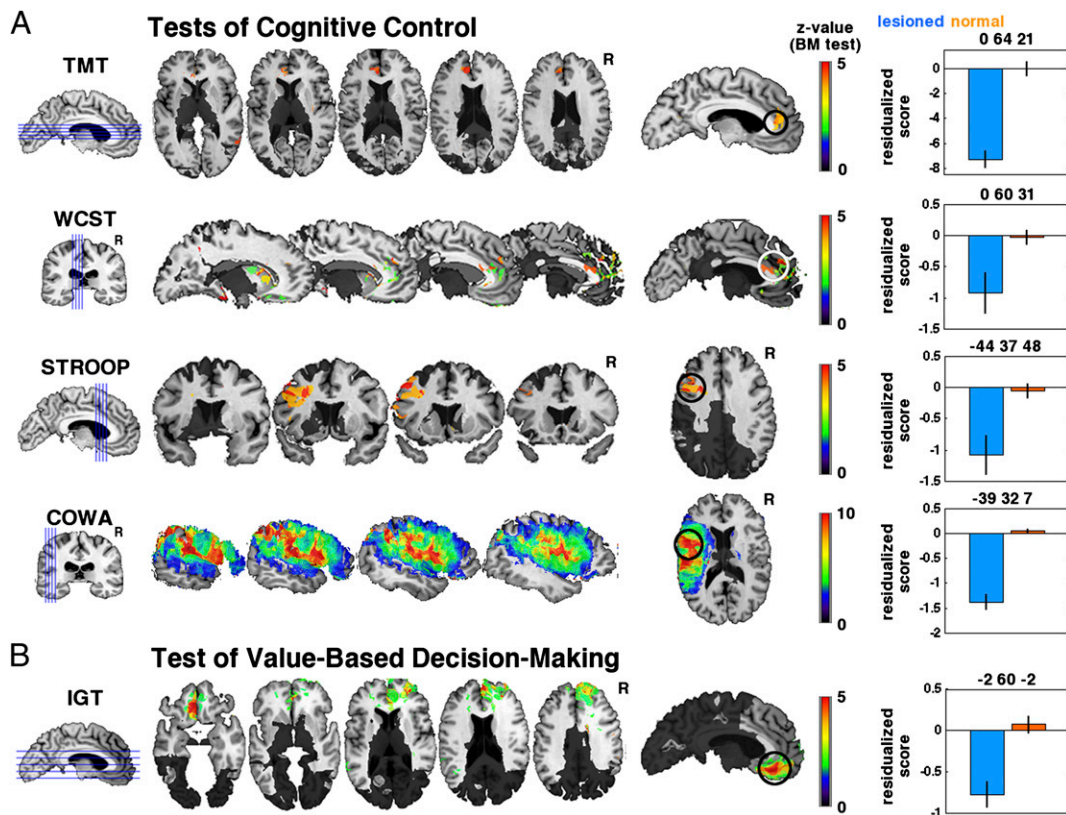


Fig. 1. Results from the lesion overlap analysis of different tests of cognitive control and value-based decision making. VLSM results are thresholded at $P < 0.05$ (FDR) and projected on a template brain in neurological convention (R = right; all midsagittal hemispheric views are left hemisphere). (A) Results for the TMT, STROOP, WCST, and COWA. (B) Results for the IGT. The graphs at *Right* show the mean test score (error bars = SEM) for the participants with lesions in the local maximum of each particular test compared with participants with lesions elsewhere. The respective local maximum is highlighted by the white and black circles on the overlay in the middle column. Grayed out areas show regions without sufficient statistical power to detect a lesion deficit effect (see Fig. S2 for complete power maps).

ACC, frontal pole, and the superior and middle frontal gyri both medially and laterally (Fig. 1B). Our vmPFC finding is consistent with previous lesion work in small samples (e.g., refs. 16 and 35), including studies using other gambling tasks that separate risk-taking from motor impulsivity (36, 37), and with functional imaging studies on reward learning (18, 38–40). However, the recruitment of additional PFC regions varies to some extent depending on the particular gambling task administered (37, 41). We have noted (10, 22) that selective impairments on the IGT can result from damage to the vmPFC, and we (34) and others (42) have also pointed out that damage to other sectors of the PFC involved in working memory can result in impaired IGT performance.

To visualize the overlap and uniqueness of lesion-deficit effects across all tasks, we projected our primary statistical VLSM results from the large sample [$P < 0.05$, false discovery rate (FDR)] onto a single template brain (Fig. 2A) and computed the extent of their pairwise anatomical overlap (Fig. 2B). Most tasks showed remarkable anatomical specificity, with near-zero overlap ratios, with two notable exceptions: TMT and WCST shared a common locus in the rostral ACC, and the significant effect for STROOP in the dlPFC was completely included in the large lesion effect for COWA. Interestingly, IGT showed essentially zero overlap with any of the cognitive control tasks (Fig. 2B), consistent with the conclusion that brain systems implicated in cognitive control versus value-based decision-making in the PFC are at least partially dissociable anatomically. The findings demonstrate that largely nonoverlapping sectors of the PFC subserve cognitive control and valuation, respectively.

The sample sizes for these findings varied to some extent across different tasks (Table S1, bold type) because of inclusion of all participants to maximize statistical power and brain coverage. We next analyzed results from a subset of 62 patients who had

complete data on all five target tasks. This analysis is important because it removes the possibility that differing sample sizes might contribute to the dissociations we reported. We carried out the same VLSM analyses in this smaller sample within the same regions found earlier (Fig. S4). Relative to the task-related regions identified in the larger sample, this analysis corroborated the primary findings for the TMT, IGT and, to a lesser degree for WCST, STROOP, and COWA, because of the more exclusive focus of lesion densities in the anterior PFC.

The above findings show that specific sectors of the PFC are required for the performance of different executive functions. Because we used multiple tasks to assess cognitive control (TMT, WCST, STROOP, COWA), we further investigated whether there might also be brain regions shared among all tasks measuring cognitive control. Using data from 104 patients who had complete datasets on all four cognitive control tasks, we conducted a factor analysis on the same residualized scores that were entered into the previous analysis and analyzed the resultant single “cognitive control factor” (factor loadings: TMT = 0.60, STROOP = 0.52, COWA = 0.49, WCST = 0.43) with VLSM (Fig. 3A). Significantly lower performance on this factor was associated with damage to the left rostral ACC, at a location partially overlapping with the location found to be associated with lower scores on the TMT and WCST (Fig. 3B). Other significant effects associated with this cognitive control factor were observed in the left precentral gyrus (ventral to the location of effects for STROOP), middle OFC and putamen, and the right globus pallidus. Thus, despite clear differences in the association of lower performance in the individual tasks with location of damage, the results of this analysis suggest that these tasks also all draw upon a cognitive control component that critically depends on the rostral ACC.

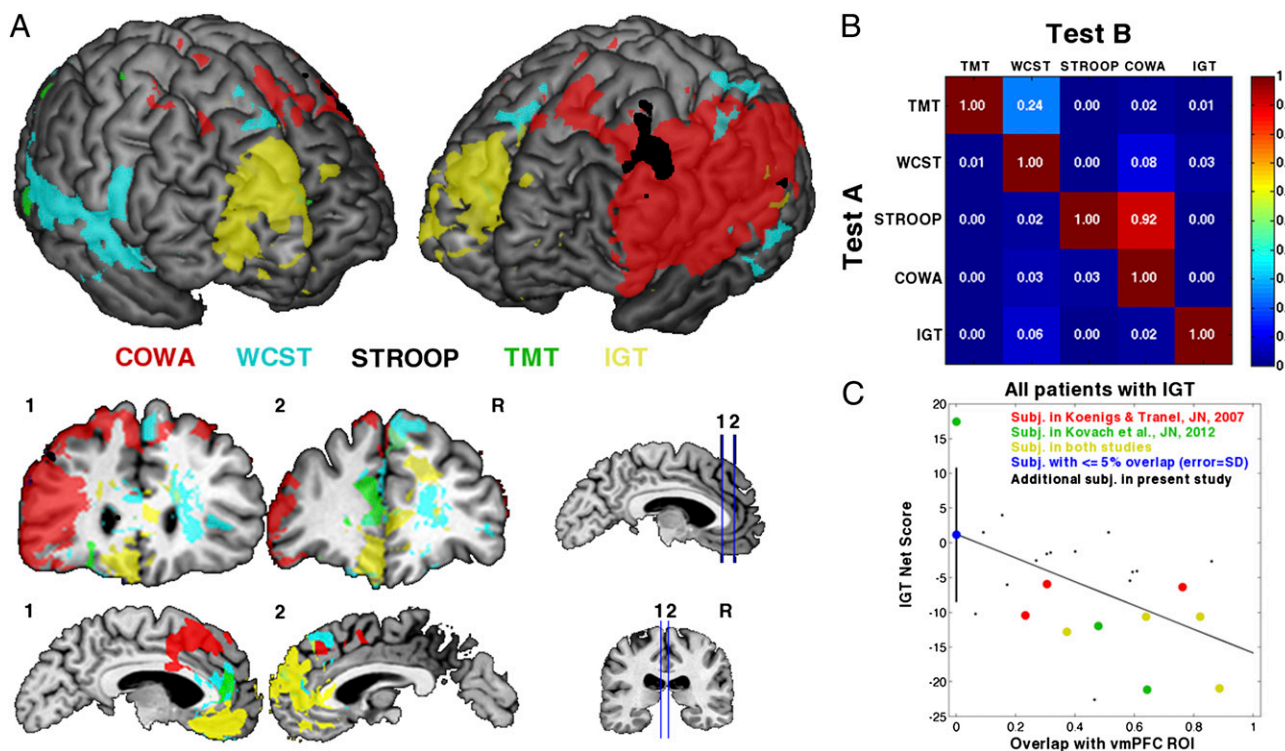


Fig. 2. Results for all VLSM analyses projected onto a template brain in neurological convention (R = right). (A) All results are thresholded at $P < 0.05$ (FDR) and coded in different colors. (B) Overlap ratio [(Number of significant voxels in Test A and Test B) / (Number of significant voxels in either A or B)]. This ratio quantifies the volumetric overlap in those regions significant for one task relative to another task (minimum = 0, maximum = 1). Because of the different number of significant voxels in each test (base rate), the overlap matrix is asymmetrical. (C) Scatter plot ($r = -0.37$, $P = 0.0001$) of IGT performance and the extent to which individual lesions overlap with the vmPFC. Highlighted are patients who participated in other decision making tasks along with the IGT.

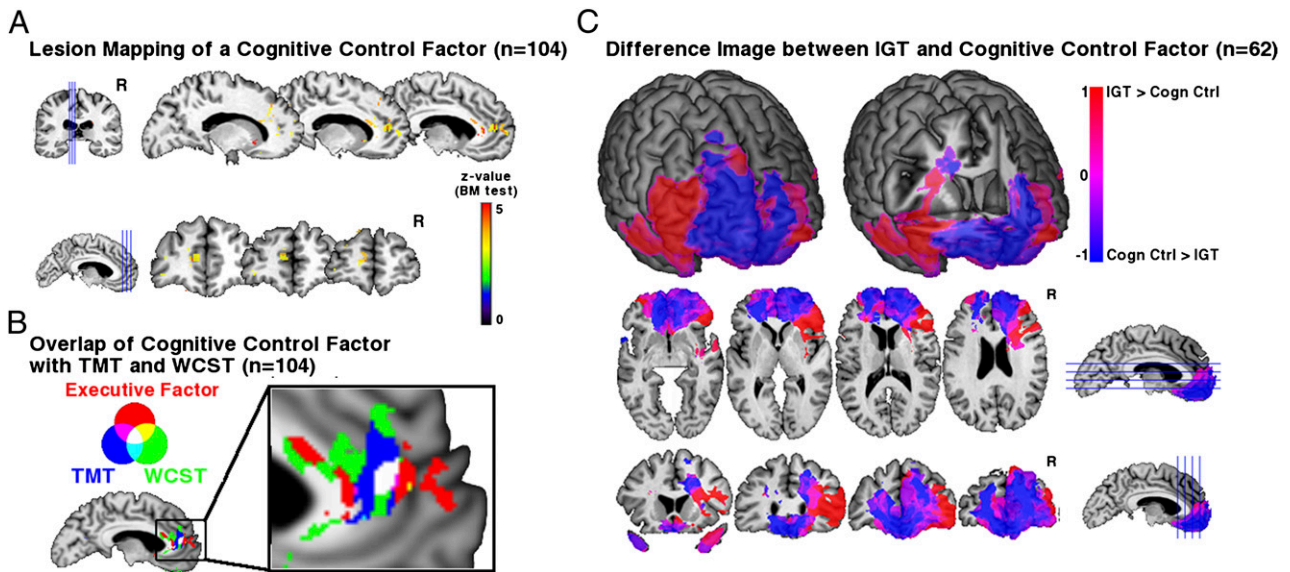


Fig. 3. (A) Results of a VLSM analysis of the factor scores of a cognitive control factor. The loadings were computed by extracting a single factor using common factor analysis. (B) The cognitive control factor correlates with a region in the ACC that was significant for TMT and WCST (magnification of the sagittal slice). (C) Difference image between IGT and the cognitive control factor scores. The images map out the mean differences between both z-scored variables highlighting a valuation network (i.e., patients with lower IGT scores) in blue and a cognitive control network (i.e., patients with lower executive factor scores) in red. (Top) Whole-brain reconstructions (with part of dorsal PFC cut away on the right to visualize internal details). (Middle and Bottom) Slices as indicated.

To obtain a summary view of the distinct prefrontal networks for cognitive control and valuation, we returned to our subsample of 62 patients who had scores on all tasks and projected their mean within-subject difference scores on the IGT and the common cognitive control factor onto a template brain (Fig. 3C). This analysis delineated a medial network consisting of vmPFC, frontal pole, and medial frontal cortex associated with valuation (i.e., patients with lower IGT scores) (14, 17) and a right-lateralized lateral network including ventro- and dorsolateral PFC associated with cognitive control (i.e., patients with lower cognitive control factor scores) (4, 11, 32, 43–45). Interestingly, the rostral ACC exhibited difference values around zero, which suggests that this region is not clearly dominated by either cognitive control or valuation.

Discussion

This comprehensive assessment of lesion-related deficits in cognitive control and value-based decision-making demonstrates a robust anatomical specificity of cognitive functions within the PFC made possible through our assessment of performance across multiple tasks. Our findings support the conclusion that the rostral ACC plays an essential role in flexibly shifting between cognitive tasks and response sets, whereas lateral structures in the dlPFC play an essential role when competing responses need to be inhibited (27, 44). These regions contribute to a control network (Fig. 3C, red areas) that maintains goals by flexibly adjusting attentional and working memory resources to changing environments and task demands (4). In contrast, the left vmPFC is a critical component of a valuation and reward learning network (Fig. 3C, blue areas) that is concerned with evaluating incoming stimuli and computing their expected future reward to guide choices (17). These findings provide comprehensive lesion-based evidence for a high degree of functional-anatomical specificity in the human PFC.

Our findings also provide important insights into the component processes of cognitive control. Within the left ACC, only TMT and WCST shared directly overlapping neural sectors, consistent with the correlated demands made by these two tasks in flexibly switching between response or instruction sets (45). In fMRI studies, activity in this shared region of the rostral ACC has been related to uninstructed set-shifting as it occurs in the

WCST (46) and to error detection (30), although WCST-related activations also often occur more dorsally and in conjunction with a frontoparietal network involving executive attention and working memory (44). In the macaque, lesions to the anterior sectors of the cingulate sulcus impair rule switching (47). Interestingly, a recent human neuroimaging study showed that activity in the rostral ACC is modulated by estimates of the volatility of outcome contingencies (48), a process akin to tracking (and shifting) between tasks or stimulus sets, as tested in the WCST and TMT. Computationally, the ACC is thought to accomplish these functions with the aid of striatal dopaminergic input that facilitates the representation of action values and prediction errors in the ACC (49), both of which are important for detecting shifts in environmental contingencies and adapting ongoing behavior accordingly. The division of labor between these two networks has its neurobiological correlate in the ventromedial and dorsolateral sectors of the PFC, highlighted in the difference image shown in Fig. 3C. The interaction between these two networks converges in the ACC, which exhibits difference values around zero, suggesting that it is dominated neither by the control nor the valuation network. Our overlap analysis of the cognitive control factor (Fig. 3A and B) suggests that the key function of the rostral ACC may be set shifting, whereas more posterior subregions within the dorsal ACC, as well as areas of right dlPFC, may be recruited for functions such as error detection (30) and conflict monitoring (27, 31) that are important for cognitive flexibility (6).

Lower performance in the STROOP was only associated with lesions in the left dlPFC, a finding consistent with previous lesion studies (23, 25), but only partly consistent with early neuroimaging studies (e.g., ref. 27), which emphasized response conflict detection in the dorsal ACC as the critical component for Stroop performance and assigned a role of inhibitory control to the (left) dlPFC. The consistent implication by neuroimaging studies of these two regions in Stroop performance has been supported by a meta-analysis (32). A possible explanation that reconciles these findings is that the behavioral reaction time differences, which constitute the principal Stroop summary score, capture the increased effort of inhibiting prepotent responses, whereas fMRI activation at the time of stimulus presentation reflects the response conflict induced by interference items.

Another possibility is that the ACC is only recruited for Stroop performance under the unblocked stimulus presentation that is typical of fMRI studies, contrary to most lesion studies that use the standardized blocked presentation of the Stroop items (26).

There was a strong effect of left vmPFC damage on performance in the Iowa Gambling Task. IGT scores are calculated as the difference between the number of choices from two advantageous (net positive reward outcome) minus two disadvantageous (net negative reward outcome) decks, a measure of how well participants learn the expected value of the decks to guide their choice. Furthermore, impaired performance on the IGT and the extent to which lesions overlapped with the vmPFC were significantly correlated ($r = -0.37$, $P = 0.0001$) (Fig. 2C). Our findings are consistent both with previous lesion studies in smaller samples (e.g., ref. 35), and with several fMRI studies (14) that suggest that the vmPFC represents the expected reward value of a choice (38, 39). Similar conclusions are supported by electrophysiology (17) and lesion studies (50) in the monkey. Our findings are also consistent with lesion findings reporting that damage to the vmPFC can spare performance on the WCST (51) and TMT (24).

The IGT is a widely used valuation task (21), but to broaden the sampling of behavior in the domain of value-based decision-making, we identified a subset of our patients who have been tested on other value-based decision-making tasks, albeit in different studies (52, 53). These patients, whose lesions encompassed our left vmPFC “hotspot” for the IGT (Fig. 1B), exhibited specific decision-making deficits in the Ultimatum Game (52) and the Explore-Exploit task (53) and were also impaired on the IGT (Fig. 2C), supporting a general role of this area in value-based decision-making that generalizes beyond the specific demands of the IGT.

The connectivity of the vmPFC (as distinct from that of the dlPFC; ref. 7) positions it well to integrate and represent the value that is expected from a choice (54). Interestingly, the IGT also showed an effect in the right fronto-polar cortex extending into the right ACC and the middle and superior frontal gyri. The former is commonly associated with highly abstract planning and subgoal processing and is part of a rostro-caudal hierarchy of abstraction (11). There is also evidence for a distinction in frontopolar cortex between more medial sectors that subserve stimulus-oriented attention (SOA) versus more lateral sectors that subserve stimulus-independent attention (SIA) (50). The lesion effect for the IGT in our study encompasses both of these sectors, perhaps indicating that the task requires both attention to the card decks (SOA) and the updating of each deck's values (SIA).

The ACC has an established role in error detection and conflict monitoring (27, 30, 31). These regions may reflect interactions between the valuation network and the cognitive control network in performance of the IGT. The predominantly left-lateralized vmPFC effect we found may result from interactions with sex: Whereas both men and women showed strong lesion effects for the IGT in the left vmPFC, only men also showed an effect in the right vmPFC (Fig. S5), consistent with prior studies (42, 55). Alternatively, the left-lateralized IGT effect may be due to effector-specific, contralateral value representations in the vmPFC in our mostly right-handed participants (317 of 344) (56).

Our study involved a large sample of patients, but even so, it is important to qualify the findings by considering the heterogeneity of the distribution of lesions. Although we had sufficient statistical power to detect lesion-deficit associations over most of the brain in principle (Fig. S2), power was greatest in those regions with the densest lesion overlaps for a task. In all cases, this region was the prefrontal cortex, making our conclusions particularly robust with respect to the sectors of PFC that we describe. However, our findings do not rule out (and in some cases support) a role for structures outside the frontal lobes in the cognitive tasks we studied. Thus, although we demonstrate an anatomical dependency on and dissociation of functions for particular sectors of the PFC, there is little question that these

regions implement cognitive control and decision-making as part of larger neuroanatomical networks.

We would hasten to add that the structure-function mappings we report here by no means exhaust the functions of the PFC, which is known to participate in other high-level cognitive processes such as theory of mind (1) and self-referential processing (57, 58). Also, it is important to acknowledge that our results are relative to the particular tasks for which data were available, and different neuropsychological measures might produce somewhat different anatomical results. However, we used clinically relevant tests with well-established construct validity (21), and provided that underlying constructs were kept constant, we would not expect findings from other tests to differ in major ways from those that we obtained. Moreover, the definitiveness of the brain-behavior relationships we report here is enhanced by our uniquely large sample size.

Finally, important open questions remain regarding how connectivity between ventromedial and dorsolateral regions of the PFC implements their network functions, how the roles of these regions and networks may differ across individuals and contexts, and how deficits arising from lesions within them may be partly compensated by plasticity and reorganization. The present set of findings provides a comprehensive description of the core sectors of the PFC, on the foundation of which such questions could be investigated in future studies.

Materials and Methods

For brevity, we provide an overview of the materials and methods. A detailed description can be found in *SI Materials and Methods*.

Participants. The 344 participants were drawn from the Patient Registry of the Department of Neurology at the University of Iowa Hospitals and Clinics. This registry served as the source of neuropsychological and neuroanatomical data (disease frequencies in *SI Materials and Methods*). All patients underwent comprehensive neuropsychological evaluation by following methods of the Benton Neuropsychology Laboratory and approved by the University of Iowa Institutional Review Board, which included tests that were selected as target indices for this study (cognitive-dependent measures). Sample sizes for each test are listed in bold type in [Table S1](#).

Preprocessing of Neuropsychological Data. Cognitive control scores were converted to standard scores by using published norms. Scale direction for TMT and WCST was reversed to facilitate an easier interpretation of the findings, whereby a higher score always means better performance.

Performance of cognitive control tasks typically requires multiple cognitive processes (e.g., memory, language, and perception) (21). Performance scores indexing verbal skills, visual-spatial reasoning, and both verbal and visual memory were derived from additional neuropsychological tests and used as covariates to partial out their effects from the five target scores. The residuals of this regression were then submitted to the VLSM analysis reported in this article.

Preprocessing of Neuroanatomical Data. The visible lesion of each patient's MRI or CT scan was traced manually slice by slice on corresponding regions of a reference brain by a neuroanatomical expert (H.D.). Tracing was only carried out when the matching between corresponding slices in the lesioned brain and the reference brain was achieved with confidence. Because of the manual tracing technique, no automated spatial normalization was necessary.

Statistical Lesion Analysis. We used nonparametric VLSM (28) to map out significant lesion-deficit relationships. This analysis is implemented in nonparametric mapping, which is part of the MRICron software. This mass-univariate analysis compares the scores on each task between patients with and without a lesion at each and every voxel in the brain. We used a threshold of 5% FDR to control for multiple comparisons. Maps of statistical power (59) (Fig. S2) use the nonparametric Wilcoxon-Mann-Whitney probability to estimate a power threshold (see *SI Materials and Methods* for details).

Difference Images. Difference images highlight neuroanatomical differences between two tasks. In these images, the mean difference between individual z-scores of two different tasks are color coded and projected onto a template brain in a voxel-wise manner. We computed the pair-wise difference scores between the IGT and the cognitive control factor (Fig. 3C). A positive mean

difference value between IGT and the cognitive control factor (red areas in Fig. 3C) maps out reduced cognitive control, whereas a negative value (blue areas in Fig. 3C) delineates a reduction in decision-making performance on the IGT.

Lesion Overlap Between Cognitive Tasks. Lesion overlap was calculated as the number of overlapping voxels with a significant lesion effect in all pairs of target scores (e.g., STROOP \cap COWA) divided by the number of significant voxels in either score (e.g., STROOP or COWA) and plotted in the overlap matrix (Fig. 2B). This matrix reveals in a condensed display the mutual exclusivity of the neural correlates of each test (overlap measure near zero) and potential "inclusion" phenomena between two tests (e.g., STROOP and

COWA) by using test-specific base rates in the calculation of the percent overlap measures, which can result in asymmetrical entries in the overlap matrix (see *SI Materials and Methods* for details).

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