Brief Communications

Keeping Memory Clear and Stable—The Contribution of Human Basal Ganglia and Prefrontal Cortex to Working Memory

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Successful remembering involves both hindering irrelevant information from entering working memory (WM) and actively maintaining relevant information online. Using a voxelwise lesion–behavior brain mapping approach in stroke patients, we observed that lesions of the left basal ganglia render WM susceptible to irrelevant information. Lesions of the right prefrontal cortex on the other hand make it difficult to keep more than a few items in WM. These findings support basal ganglia–prefrontal cortex models of WM whereby the basal ganglia play a gatekeeper role and allow only relevant information to enter prefrontal cortex where this information then is actively maintained in WM.

Introduction

Why do some people have a memory like an elephant while that of others resembles a sieve? One crucial determinant for the individual working memory (WM) capacity is the ability to inhibit irrelevant information from entering memory (Vogel et al., 2005). A recent fMRI study located the competence to filter relevant from irrelevant information for memory storage in the prefrontal cortex (PFC) and left basal ganglia (BG) (McNab and Klingberg, 2008). In this and in an earlier study (Todd and Marois, 2004), the right parietal cortex was found to be sensitive to memory load, i.e., the number of items that have to be remembered. Other studies have stressed the role of the PFC in maintaining and manipulating information in WM (D'Esposito et al., 1998; Miller and Cohen, 2001; Müller and Knight, 2006).

It was the aim of the present investigation to clarify which brain regions are necessary to sustain filtering and maintenance of information in WM. While brain activation techniques such as fMRI show which regions are involved in a task, brain disruption techniques such as the lesion method enable one to infer that the region is required (Rorden and Karnath, 2004; Chatterjee, 2005; Müller and Knight, 2006). We thus studied stroke patients with varying brain lesions due to stroke in a visual spatial working memory task applying a voxelwise lesion–behavior brain mapping (VLBM) analysis. This procedure tests whether the magnitude of a behavioral variable (i.e., the ability to filter irrelevant information and the ability to store information) is significantly associated with a certain location in the brain (Rorden et al., 2007).

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Materials and Methods

The WM task involved three different conditions: patients had to remember the position of three red dots without distracting items on display, they had to remember the positions of three red dots while ignoring two simultaneously presented yellow dots, or they had to remember the position of five red dots with no other objects on display. We then computed the corrected (hits minus false alarms) hit rate differences between three target trials with versus without distractors to assess filtering ability and the differences between no distractor trials with five versus three targets to assess load-sensitive maintenance. Timing of the paradigm can be depicted from Figure 1.

Sixty-one randomly selected patients with cortical damage due to stroke as demonstrated by magnetic resonance imaging (MRI) were investigated. Thirty-one patients had right-sided (51%) and 30 patients left-sided brain damage (49%). Lesions were mainly in the territory of the A. cerebri media, but parts of the territories of the A. cerebri anterior and A. cerebri posterior were also affected (Fig. 2*A*,*B*). Exclusion criteria were visual field defects, diffuse brain damage, intake of psychoactive drugs within 24 h before examination, or insufficient communication abilities. The latter introduced a bias for lesions to be smaller in the language-dominant left hemisphere; the difference, however, was not statistically different (Mann–Whitney test $p = 0.143$). Medications that were regularly taken were anti-platelet-aggregating drugs, anticoagulants, cholesterol synthesis enzyme inhibitors, or anti-hypertensive drugs; none of these were expected to interfere with cognitive function. Clinical parameters were assessed as described previously (Karnath et al., 2005a). For patients with neglect symptoms (all right-sided lesions), the stimulation monitor was located on the ipsilesional side to reduce their direction-specific inattention. With this procedure, our neglect patients did not show significantly more misses for targets presented on the left versus right side (paired *t* test; $p = 0.155$). Furthermore, as we analyzed differences of accuracy rates rather than absolute values, a deficit in de-

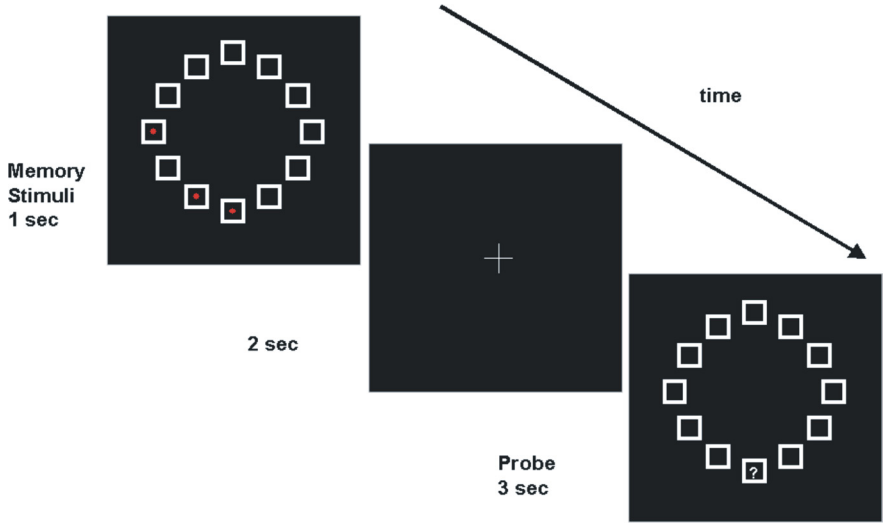

Figure 1. Experimental design: Trials started with the presentation of the 12 position grid and either three red dots, five red dots, or three red dots with two yellow dots. Subjects had to remember the positions of the red dots only.

tecting left-sided stimuli per se would not have a systematic effect. Finally, no lesions usually related to neglect (right temporoparietal cortical junction) were found to be associated with the processes of interest. Clinical variables are shown in Table 1.

MRI scans were performed on all patients. We used diffusion-weighted imaging (DWI) within the first 48 h after stroke and fluid-attenuated inversion recovery (FLAIR) sequences when imaging was conducted later than 48 h after the stroke. The DWI sequence comprised 38 axial slices with an interslice gap of 3.3 mm. FLAIR images were acquired with a slice thickness of 1 mm. The mean time between lesion and MRI was 6 d (SD 2.2 d); in other words, the patients were tested in the acute phase before substantial reorganization of brain function would make interpretation of the results more difficult. Moreover, the fact that relative instead of absolute behavioral measures were assessed makes it unlikely that unspecific disease effects contributed to the results reported here. The boundary of the lesion was delineated directly on the individual MRI image for every single transversal slice using MRIcron software (Rorden et al., 2007) (http://www.sph.sc.edu/comd/rorden/mricron/). Both the scan and the lesion shape were then mapped into stereotaxic space using the normalization algorithm provided by SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). Lesions were presented on a T1-weighted template MRI scan from the Montreal Neurological Institute (MNI). The extension and location of the lesion shapes were controlled by a second experimenter (C.H.) who was blind to the performance of the patients in the working memory paradigm. MNI coordinates were assigned to cerebral structures in general, including subcortical areas such as the basal ganglia and white matter using an MNI-space utility software tool (www.ihb.spb.ru/~pet_lab/MSU/MSUMain.html). Only voxels damaged in at least 3% of patients were included into the analysis.

Filtering ability was assessed with a statistical VLBM analysis that treated the difference in accuracy rates between the no-distraction condition with three targets and the distraction condition (i.e., with additional irrelevant items) with the same amount of targets of each patient as the dependent, continuously measured variable. Accuracy rates were defined as corrected hit rates, i.e., hits minus false alarms to account for differences in response strategies between subjects. Right- and left-sided lesions were analyzed separately. Working memory capacity was assessed in a second VLBM analysis whereby the dependent, continuously measured variable was the difference in corrected hit rates between the no-distraction condition with three targets and the no-distraction condition with five targets.

We used the nonparametric Brunner Munzel test with the significance level set to $p < 0.05$ (Rorden et al., 2007). To prevent a rise in the probability of familywise error, we computed a false discovery rate (FDR) correction in all analyses.

Results

The patients reached the highest accuracy in the three-target-no-distractor condition (hits: 78%, false alarms: 14%), and lower accuracy in the five-target-no-distractor condition (hits: 67%, false alarms: 20%) and in the three-target-plus-distractor condition (hits: 65%, false alarms: 19%). Accordingly, the repeated-measurement ANOVA revealed a main effect for the factor task (three levels) ($F_{(1,60)} = 56.263$; $p = 0.001$). Pairwise comparisons revealed significant differences between the three-target-no distractor and both the three-target-plus-distractor and the five-target-no-distractor conditions (paired t test $p < 0.001$).

The VLBM analysis related to filtering ability revealed an association of this function with lesions of the left putamen ($x = -28$, $y = -8$, $z = 13$) and adjacent white matter ($x = -28$, $y = -8$, $z = 18$) (FDR-corrected α level of $p < 0.05$) (Fig. 2*C*). No significant voxels in the right hemisphere were identified with this analysis. Figure 2*D* shows the VLBM analysis for the factor WM capacity, indicating that white matter lesions of the right frontal lobe ($x = 23$, $y = -2$, $z = 34$) as well as the inferior frontal gyrus ($x = 42$, $y = 19$, $z = 13$), the head of the caudate nucleus ($x = 11$, $y = 14$, $z = 9$), and the insular cortex ($x = 44$, $y = 11$, $z = 12$; $x = 34$, $y = -8$, $z = 18$) were significantly associated with low WM capacity (FDR-corrected α level of $p < 0.05$). No voxels in the left hemisphere were identified. In an additional analysis, we conducted a VLBM analysis for factor WM capacity excluding patients with neglect and extinction. Anatomical results remained unaffected (Fig. 2*E*).

We supplemented the VLBM analysis by using a traditional approach where we compared the behavior of patients whose lesions involved the left basal ganglia and right frontal cortex, respectively, with patients that spared these regions. The following subgroups were built for this analysis: 10 left-sided patients with lesions of predominantly the left putamen, nine right-sided patients with predominantly prefrontal lesions, 20 left-sided patients without predominantly basal ganglia damage, and 22 right-sided patients without prefrontal damage. However, it has to be noted that such a traditional approach of building *post hoc* subgroups for lesion analysis is very problematic (cf. Rorden and Karnath, 2004). In the present case, the *post hoc* subgroups show an obvious confound with lesion size. Patients with right hemisphere lesions with frontal involvement had larger lesions (lesion volume 57.8 cc) than patients without frontal involvement (lesion volume 8.35 cc; independent samples t test $t = 5.12$; $p < 0.001$). Similarly, patients with left hemisphere lesions with putamen involvement (lesion volume 10.3 cc) showed larger lesions than patients without affection of the putamen (lesion volume 1.97 cc; independent samples t test $t = 2.52$; $p = 0.018$). From a conceptual standpoint, given that patients with large right-hemisphere lesions are roughly more likely to have frontal involvement, then the threshold criterion will select more subjects with frontal involvement, and thus bias the results to show frontal effects. Again, along these same lines, patients with large left-hemisphere lesions are more likely to have putamen involvement, which would again bias the statistics. This caveat

needs to be kept in mind when we assess how the four subgroups' behavior was affected by adding distracters to the to-be-memorized items (filtering deficit) and by increasing memory load (memory deficit), respectively (Fig. 3*A*,*B*). The mixed ANOVA analysis revealed an interaction between group (four levels) and cognitive deficit (filtering vs memory) with $F = 19.729$; $p < 0.001$. As could be expected from Figure 3, a *post hoc* analysis (Bonferroni corrected) indicated that the 10 patients with lesions affecting the left-sided putamen showed worse filtering ability than the left-sided lesion patients without involvement of the putamen ($p < 0.001$). Furthermore, the nine patients with lesions involving the right-sided prefrontal structures were stronger affected by increased memory load than the other right-sided patients ($p < 0.001$).

Discussion

We observed that lesions of the left putamen and surrounding white matter specifically impaired performance when the to-be-remembered targets were presented together with task-irrelevant items. Lesions of the right frontal lobe on the other hand impaired performance especially when memory load was increased from three to five items. Thus, we conclude that the left putamen is involved in hindering irrelevant information from entering working memory, whereas the right prefrontal cortex is crucial for active maintaining relevant information online in WM. These findings substantiate computational models of WM (Frank et al., 2001; Gruber et al., 2006; Hazy et al., 2006; O'Reilly and Frank, 2006). These models proposed that the striatum should play a dopamine-dependent gate-keeping function and should control the information flow into working memory whereas memory representations are maintained in PFC. In detail, one model suggested that parallel loops interconnect the frontal cortex with the basal ganglia.

Due to direct signals originating from "Go" neurons in the dorsal striatum, a disinhibition of the frontal cortex results via an inhibition of the substantia nigra pars reticulata leading to a gating-like modulation and updating of WM representations in PFC. An indirect pathway involving "No Go" neurons in the dorsal striatum that inhibit the inhibitory globus pallidus supported by neurons in the subthalamic nucleus that excite the substantia nigra pars reticulata acts as a counterplayer. By these mechanisms, the gate to WM in PFC is locked for irrelevant infor-

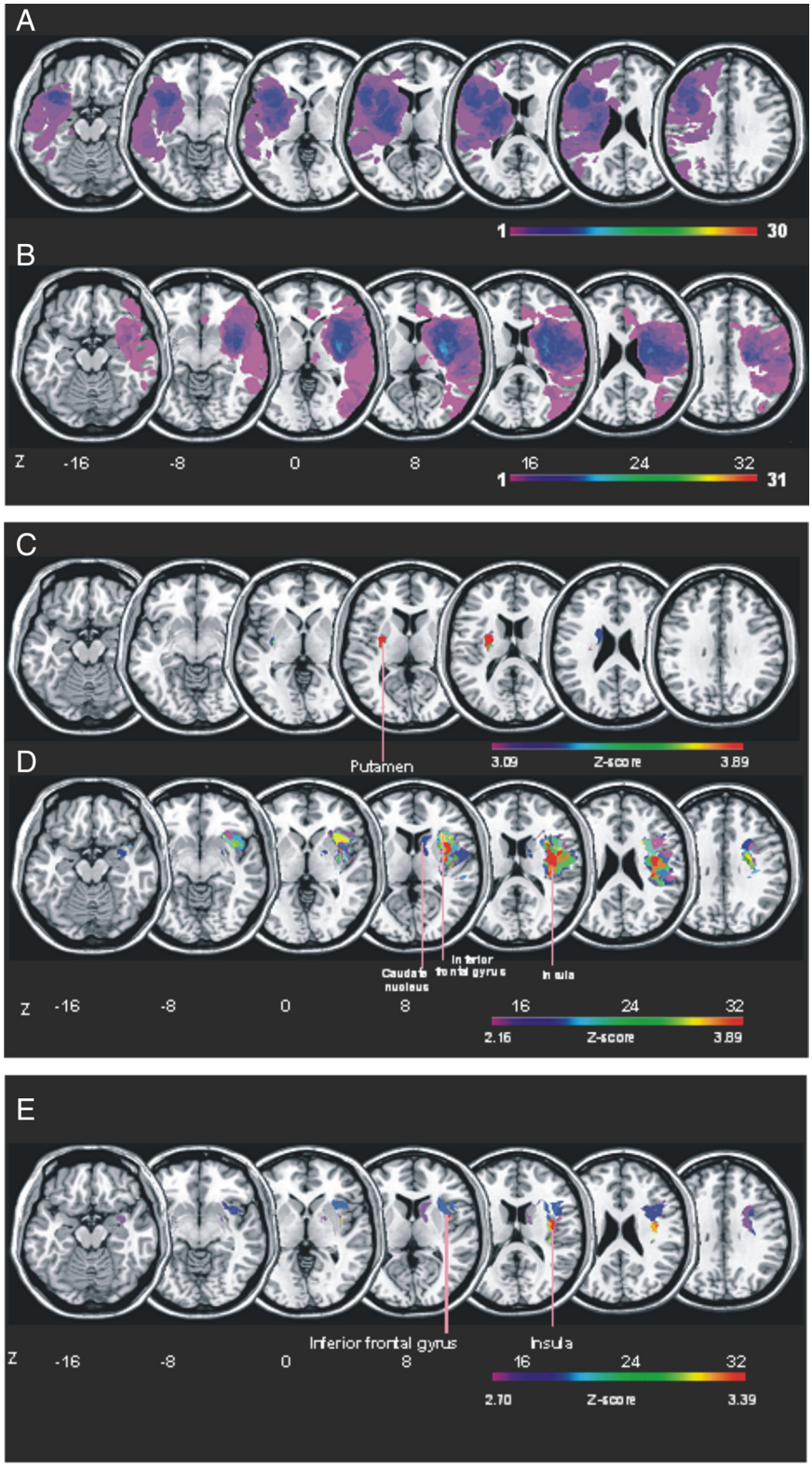

Figure 2. ***A***, Overlay lesion plot of all 30 left-sided lesion patients. The number of overlapping lesions is illustrated by different colors coding increasing frequencies from violet ($n = 1$) to red ($n = 30$). ***B***, Overlay lesion plot of all 31 right-sided lesion patients. The number of overlapping lesions is illustrated by different colors coding increasing frequencies from violet ($n = 1$) to red ($n = 31$). ***C***, VLBM analysis of filtering ability, left-sided brain lesions. The behavioral variable was determined by calculating the corrected hit rate differences between the conditions with versus without distraction and three targets. Lesions of the putamen were associated with deficits in filtering ability (FDR-corrected α level of $p < 0.05$). ***D***, VLBM analysis of WM capacity, right-sided brain lesions. The behavioral variable was determined as the corrected hit rate difference between the no-distraction conditions with five versus three targets. Right-sided lesions of the inferior frontal gyrus and insular cortex were associated with poor WM capacity (FDR-corrected α level of $p < 0.05$). Talairach *z*-coordinates (Talairach and Tournoux, 1988) of each transverse section are given. ***E***, VLBM analysis of WM capacity, right-sided brain lesion patients without neglect.

Table 1. Demographic and clinical data of all left- and right-brain-damaged patients

	Right-sided lesions	Left-sided lesions
Number	31	30
Sex	17 f; 14 m	10 f; 20 m
Etiology	31 infarcts	29 infarcts, 1 bleeding
Age (years) [median (range)]	68 (20–84)	68 (32–85)
Time interval lesion-clinical examination (d) [median (range)]	7 (2–15)	6 (2–24)
Lesion volume (in cc) [median (range)]	10.7 (0.1–85.4)	2.9 (0.25–139.6)
Contralesional paresis (MRC scale) [median (range)]	4 (0–5)	5 (1–5)
Visual extinction (% present)	10	0
Neglect (% present)	13	0
MMSE [median (range)]	25 (18–30)	27 (18–30)

f, Female; m, male; MMSE, Mini-Mental State Examination.

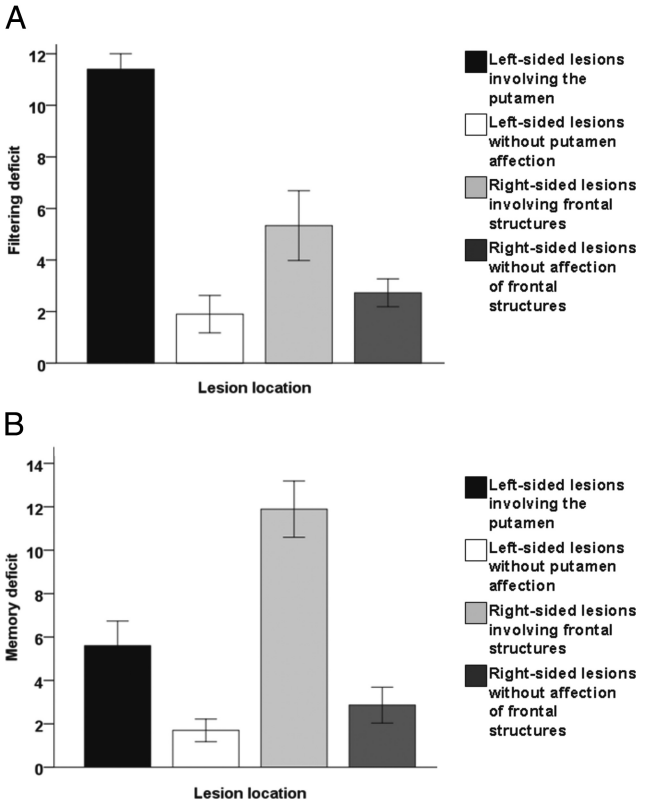

Figure 3. Subgroup analysis comparing patients with left-sided lesions involving the putamen ($n = 10$) (black bar), left-sided lesion patients without affection of the putamen ($n = 20$) (white bar), right-sided patients with lesions encompassing frontal structures such as the inferior frontal gyrus ($n = 9$) (bright gray bar), and right-sided lesion patients without affection of the frontal lobes ($n = 22$) (dark gray bar). ***A***, Filtering deficit. The *y*-axis represents the difference in accuracy rates (corrected hit rate) between the condition with three memory items and no distracters and the condition with three memory items and two distractors. A large value indicates that subjects was strongly impaired by the presence of distractors, i.e., has low filtering ability. Error bars indicate the SEM. ***B***, Memory deficit. The *y*-axis represents the difference in accuracy between the condition with three memory items and the condition with five items (both without distractors). A large value therefore indicates that subjects had difficulties when memory load was increased. Error bars indicate the SEM.

mation (Frank et al., 2001; Hazy et al., 2006). Transferring this model to our data, lesion of the left putamen would cause disruption of the "Go" and "No Go" neurons of the striatum leading to an imbalance of the gating mechanism. Alternatively or additionally, the striatal lesions may have caused a dysfunction of distant cortical areas via diaschisis (Karnath et al., 2005b). Structural MRI scans might not necessarily show the full functional extent of a lesion. (Cortical) areas that appear structurally intact in anatomical scans may not necessarily be functioning normally due to an abnormal perfusion. Therefore, normalized perfusion-weighted imaging (Karnath et al., 2005b), which measures the amount and latency of blood flow in certain regions, provides a promising tool to address these issues in future studies.

Likewise, as the prefrontal lesions mainly affected the subgyral white matter, malfunctioning in distant areas might have contributed to the memory disturbance in these patients as well. The finding that the relevant lesions were observed in inferior and insular regions rather than in more dorsal regions may partly be explained by the fact that these lesions were more common in our sample. However, other data indeed indicate that more inferior frontal regions support memory maintenance, whereas dorsal frontal areas are found to be involved in manipulation of information within WM, a process that was not required in our study (D'Esposito et al., 2000). Finally, with regard to the insular cortex and the caudate nucleus, it was shown in animal studies that this area is part of an orbital prefrontal network that might also play a role in working memory processes (Levy et al., 1997; Saleem et al., 2008; White, 2009).

Unpredicted by the models, we observed a hemispheric specialization, which at least for the BG is in line with a recent fMRI study (McNab and Klingberg, 2008). In this study a significant correlation between individual WM capacity and filtering set activity (operationalized by the signal difference between distraction vs no-distraction trials) was observed in left BG.

Discrepant to our study, two fMRI studies identified the parietal, not the frontal cortex, to be memory load sensitive (Todd and Marois, 2004; McNab and Klingberg, 2008). One explanation might be that the parietal cortex is sensitive to overall cognitive load, but that this is not specific to memory load per se. Increasing the number of items in a display, for example, also increases attentional load. Indeed, an fMRI study by Tomasi et al. (2007) found that parietal cortex was driven both by cognitive load in an attention and memory task, whereas PFC was load-driven only in the WM task. This may indicate that PFC is more specifically related to WM—an assumption also supported by the existing computational models of WM (Gruber et al., 2006; Hazy et al., 2006; O'Reilly and Frank, 2006). This notion does not rule out the involvement of PFC in attention per se. For example, the PFC might have been involved in attentional processes that were relevant in both the distracter absent and present trials. In that case the PFC's role would have been concealed in our analysis that was based on differences between these conditions.

A possible limitation might be that performance in acute stroke patients is vulnerable to other factors such as, e.g., concentration. However, the patients in the present study were (1) thoroughly selected to include only vigilant patients in the study and (2) assessed based on differences in accuracy rates so that general deficits would have cancelled each other out. Furthermore, testing patients in the chronic phase of their disease would have introduced another, possibly more severe, confound: reorganization of brain function and structure. Thus, testing patients in the acute phase of disease may allow more valid conclusions regarding the cortical function in the normal brain.

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