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An Information-Theoretical Approach to Contextual Processing in the Human Brain: Evidence from Prefrontal Lesions

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Context shapes perception, thought, and action, but little is known about the neural mechanisms supporting these modulations. Here, we addressed the role of lateral prefrontal cortex (PFC) in context updating and maintenance from an information-theoretic perspective. Ten patients with PFC lesions and 10 age-matched controls responded to bilaterally displayed visual targets intermixed with repetitive and novel distracters in 2 different task contexts. In a predictable context, targets were always preceded by a novel event, whereas this temporal contingency was removed in an unpredictable context condition. We applied information theory to the analysis and interpretation of behavioral and electrophysiological data. The results revealed deficits in both the selection and the suppression of familiar versus novel information mainly observed at the visual hemifield contralateral to PFC damage due to disrupted frontocortical and frontosubcortical connectivity. The findings support a deficit in the representation of the temporal contingency between contextually related novel and familiar stimulation subsequent to lateral PFC damage.

Keywords: associative learning, cognitive control, information theory, novelty, working memory

Introduction

The neural mechanisms for processing contextually related information have attracted considerable interest in recent years. Animal and human research points to a key role of prefrontal and posterior multimodal association cortices for the integration of contextual information (Donchin and Coles 1988; Cohen et al. 1996; Miller and Cohen 2001). Postrolandic parietal and temporal unimodal and multimodal association cortices are important for setting up the spatial context (Rafal and Posner 1987; Rafal et al. 1990; Rushworth and Taylor 2006), whereas the lateral prefrontal cortex (PFC) seems critical for establishing the temporal contingencies between contextually related events (Fuster et al. 2000; Fuster 2002; Koechlin et al. 2003). For instance, visual orienting toward contextually novel events depends primarily on innate reflexive neural programs (Sokolov 1963; Pierrot-Deseilligny et al. 2004). However, visual reflexes can be modulated within a temporal context of past experiences and future goals with obvious advantages for adaptive and flexible intentional behavior (Miller and Cohen 2001). These contextual modulations have been proposed to depend on an intrinsic interplay between exogenous and endogenous sources of information in distributed neural networks including PFC (Crick 1984; Tononi and Edelman 1997; Edelman and Tononi 2000; Miller and Cohen 2001; Friston 2005).

There are contrasting views as to whether temporal context influences cognitive control at a preperceptual (Näätänen 1990; Rafal et al. 1990), perceptual (Sokolov 1963; Donchin and Coles 1988), decisional (Nieuwenhuis et al. 2005; Daw et al. 2006), or sensorimotor (Hommel et al. 2001; Koechlin et al. 2003) stages of neural processing. This issue can be framed in anatomical terms regarding where contextual representations are held and updated in the brain (e.g., at subcortical, unimodal sensory, or posterior vs. prefrontal multimodal association cortices). Two recent models make opposite predictions about how context modulates brain physiology and behavior: the "context-updating" (Donchin 1981; Donchin and Coles 1988) and the "guided-activation" models (Cohen et al. 1996; Braver et al. 2002).

The context-updating model posits that the modulations of an endogenous "P300" component of the human event-related potential (ERP) index updating of working memory representations triggered by a mismatch between a task event and its perceptual context (Donchin and Coles 1988). The neural mechanisms indexed by these P300 brain potentials have been linked to stimulus change detection (Donchin 1981), perceptual distinctiveness (Polich 2003), and stimulus categorization (Donchin and Coles 1988). The novelty or familiarity of the eliciting event within its immediate temporal context determines the type of P300 activation observed. Contextually novel events elicit transient "novelty P3" activations with maximal amplitudes over frontocentral scalp regions (Polich 2003) that depend on the integrity of a distributed neural network including lateral PFC (Knight 1984), mesial temporal cortices (Knight 1996; Ranganath and Rainier 2003), temporoparietal cortices (Knight and Scabini 1998), as well as subcortical structures (Ranganath and Rainier 2003; Nieuwenhuis et al. 2005). Familiar target events elicit transient "target P3b" activations with maximal intensity over midparietal scalp regions. However, the context-updating model does not fully account for novelty P3 activity to task-irrelevant distracters (Donchin and Coles 1988; Dien et al. 2004). To date, there is no integrative view of the human P300 response that explains both the selection of targets and the suppression of contextually related distracters and how each of these operations tax our capacity for processing information in working memory (Miller 1956). Such an integrative theory of the human P300 response should account for those aspects shared by novelty P3 and target P3b activations (i.e., do they both index context-updating operations in working memory?), as well as for those aspects that are unique (i.e., do they each index the updating of different neural representations?).

We utilized an integrative model of PFC function to examine these 2 questions (Miller and Cohen 2001). The guided-activation model considers a functional hierarchy of representations from unimodal association to posterior and prefrontal multimodal association cortices (Fig. 1; cf., also Fuster 2002; Koechlin et al. 2003), thus providing a benchmark for testing

predictions about context-updating operations at 3 different levels of cortical representation (Braver et al. 2002). This model assumes that activation of any perceptual element leads to updating of its associated units in the neural network, including higher ordered memory units and appropriate responses (Miller and Cohen 2001). The frequency of updating of each perceptual element then determines the relative strength of the intervening sensorimotor pathways but also the relative recruitment of PFC, with more frequently updated representations requiring lesser PFC resources (Miller and Cohen 2001). The mean probability of occurrence of a task event offers an approximate measure of the information-processing resources associated with a stimulus and has been routinely adopted in most past ERP research (Donchin 1981; Polich 2003). Indeed, rare targets and novel distracters elicit larger P300 activations and tax working memory more than repetitive standard stimulation. However, such coarse estimations fail to consider the mutual information conveyed through the co-occurrence of contextually related distracter and target events, nor do they consider information transmission for perceptual representations (i.e., visual objects) as different from that conveyed at higher ordered levels of neural representation (i.e., memory chunks or semantic categories; Tononi and Edelman 1997; Koechlin and Summerfield 2007).

The model depicted in Figure 1 illustrates the perceptual and motor elements of a simple perceptual judgment task, consisting of 3 contextually related visual stimuli (s1, s2, and sx) and 2 behavioral outcomes (r0 and r1) represented at visual association and premotor cortices, respectively (adapted from Miller and Cohen 2001). By means of explicit instructions and learning, visual targets (s2) become associated with an overt motor response (r1), whereas standard (s1) and novel (sx) distracters require withholding any overt responses (r0). In the model of Miller and Cohen, these sensorimotor (S–R or stimulus–response) pathways are assumed to be held outside the PFC, for example, at posterior multimodal association cortices (e.g., s1–r0 and s2–r1 pathways in Fig. 1*a*; Rushworth and Taylor 2006). Finally, superordinate PFC units are assumed to connect stimuli with responses in a context-sensitive way through subsets or "chunks" of subordinate sensorimotor pathways, very much like a "switch operator in a system of railroad tracks" (Miller and Cohen 2001, p. 184). Lateral PFC lesions severely disrupt novelty P3 activity but leave target P3b activity relatively intact (Knight 1984, 1997). Accordingly, we examined the hypothesis that familiar and novel information each have distinct superordinate PFC representations, although they may partly share subordinate sensorimotor representations, as shown in Figure 1*a*,*b*, respectively.

We also followed original recommendations by George Miller (1956) for estimating the amount of information transmitted between contextually related stimuli and responses (or "input–output correlations"; Miller 1956) along the 3 layers in the hierarchy of representations in Figure 1 (see also Koechlin et al. 2003). Information theory offers a dimensionless yardstick for exploring the universal properties of human working memory independent of specific sensory or motor demands in target and distracter trials and helps formalize concepts such as "context," "novelty," or "stimulus saliency" (Miller 1956; Koechlin and Summerfield 2007). Information-theoretic analyses based on the joint and conditional probabilities between task stimuli and responses were used to estimate the mutual information conveyed through the temporal co-occurrence of targets and distracters and to clarify whether this contextual information was conveyed through subordinate S–R pathways at postrolandic scalp regions or through superordinate PFC representations (cf., Table 1 and see Appendix in the Supplementary Material).

Using this novel approach, we examined predictions from the "guided-activation" and "context-updating" models about the role of PFC in updating and maintenance of contextual information by comparing the behavior and brain responses of 10 patients with unilateral PFC lesions (Fig. 2), with a group of age-matched healthy controls. We addressed 2 important issues: 1) whether distracter-locked novelty P3 activations also reflect context-updating operations and 2) whether the neural representations involved are different from those of target-locked P3b activations (cf., Donchin and Coles 1988; Dien et al. 2004). In so doing, we manipulated contextual predictability through

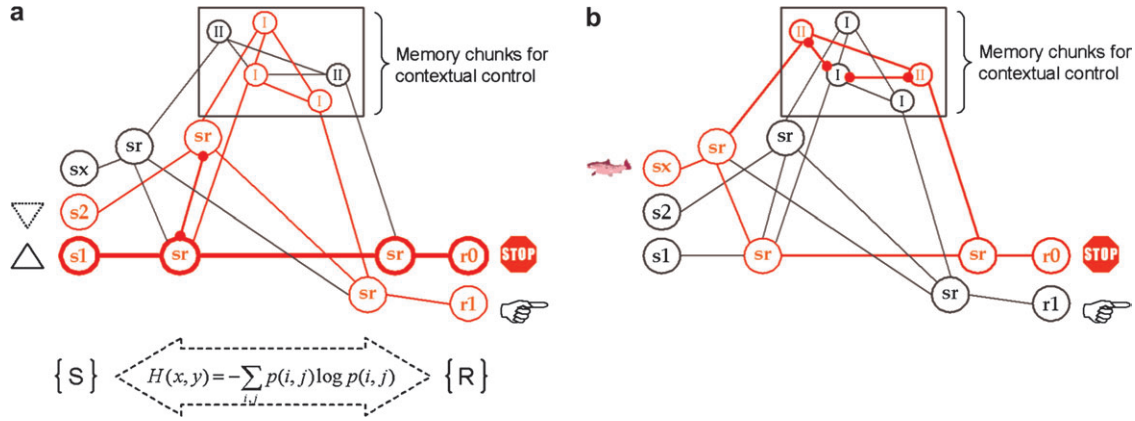

Figure 1. Integrative model of PFC function (adapted from Miller and Cohen 2001). (*a*) Neural representation of familiar information. Well-rehearsed visual discriminations require online maintenance of one superordinate neural representation (memory chunk I), which holds other subordinate sensorimotor units (sr) in an active state at posterior multimodal association cortices, thus providing intervening pathways linking perceptual and motor representations (i.e., s1–r0 and s2–r1). The onset of a familiar task event causes updating of the corresponding units at posterior and prefrontal multimodal association cortices, with the more frequently updated units holding the stronger representations. (*b*) Neural representation of novel information. The onset of a novel event (sx) leads to the updating of superordinate memory representations (memory chunk II). The onset of a predictive novel event causes a momentary conflict between new/old superordinate memory chunks that rapidly turns into anticipatory activation of sensorimotor target pathways (S–R_{Target} in Table 1; see main text for an explanation). Thick lines indicate well-established pathways mediating a prepotent behavior. Red indicates active units or pathways. Solid circles represent conflict between antagonistic sensorimotor units. Novel events are coded as a variable (sx) because their memory representation remained undetermined until the stimulus was visually displayed.

Table 1
Mean probability of task events and probability for updating their corresponding neural representations in the hierarchy of Figure 1

Levels in the hierarchy of Figure 1	Elements in the hierarchy (and codes used in Fig. 1)	Updating probability
Superordinate multimodal sensorimotor representations (memory chunks)	Chunk I (s1–r0 and s2–r1)	0.9
	Chunk II (sx–r0)	0.1
Subordinate multimodal sensorimotor representations (S–R pathways)	$S–R_{Target}$ (s2–r1)	0.2
	$S–R_{Standard}$ (s1–r0)	0.7
	$S–R_{Novel}$ (sx–r0)	0.1
Visual representations (visual objects)	Target (s2)	0.2
	Standard (s1)	0.7
	Novel (sx)	0.1

Note: Shannon's mutual information, $H(x,y)=-\sum_{i,j} p(i,j)\log p(i,j)$, was used to estimate information transmission between elements in the hierarchy of Figure 1 (see the Appendix in the Supplementary Material).

the temporal contingency between novel distracters and familiar targets in a simple visual attention task and then examined how this influenced neural activity and the ability to perform easy visual discriminations. PFC-lesioned patients and controls responded to inverted triangles (targets) embedded in rapid trains of repetitive upright triangles (standard distracters) and unique "oddball" color pictures (novel distracters) randomly displayed to both visual hemifields (cf., Barcelo et al. 2000). In one condition, infrequent novel events conveyed no contextual information about the next visual target response (unpredictable context). In another condition, novels were always followed by a visual target either at the same or at the opposite visual hemifield (predictable context; Fig. 3). The same instructions were used in both task contexts, and the novel–target contingency was manipulated implicitly by varying the statistical regularities between task events (see Table A2 in the Appendix of Supplementary Material). Our bifield stimulus display limited the patients' ability to use their intact PFC to compensate for deficits and allowed us to compare the patients' behavior and brain activations at the visual hemifields both ipsilateral and contralateral to PFC damage (i.e., this bifield display effectively added 1 bit of information across all other task conditions, see Materials and Methods in the Supplementary Material; cf., Barcelo et al. 2000). The combined manipulation of temporal and spatial context also allowed us to dissociate the modulation of information at multimodal PFC from the transmission of information at retinotopically organized visual association cortices (Miller and Cohen 2001; Friston 2005).

The context-updating model does not make any explicit predictions about distracter-locked novelty P3 activations or about the role of PFC versus posterior association cortices in updating contextual representations, although task-relevant P300 activations have been linked to temporal–parietal cortical regions (Donchin 1981; Knight and Scabini 1998). The context-updating model predicts larger parietal P3 activity to unexpected target events in unpredictable—compared with predictable—stimulus contexts. Alternatively, we hypothesized that the more informative predictive novels would elicit the larger novelty P3 activations (Barcelo et al. 2006). In turn, target P3b amplitudes should not be affected by contextual predictability because this did not alter the mutual information conveyed by target stimuli for response selection in the present task (see Table A1 in the Appendix of Supplementary Material). These predictions are contrary to the context-updating model but are consistent with our estimations of mutual information (see the Appendix in the Supplementary Material, Koechlin and Summerfield 2007) and with a series of task-switching studies showing that novelty P3 and target P3b activations index context-updating operations at 2 hierarchically distinct levels of neural representation: target P3b indexed updating of familiar sensorimotor representations at posterior association cortices (Fig. 1*a*), whereas cue-locked novelty P3 activations indexed updating of novel superordinate sensorimotor representations (Fig. 1b, cf., Barcelo et al. 2002, 2006).

The guided-activation model explicitly implicates PFC in processing contextually related target and distracter information

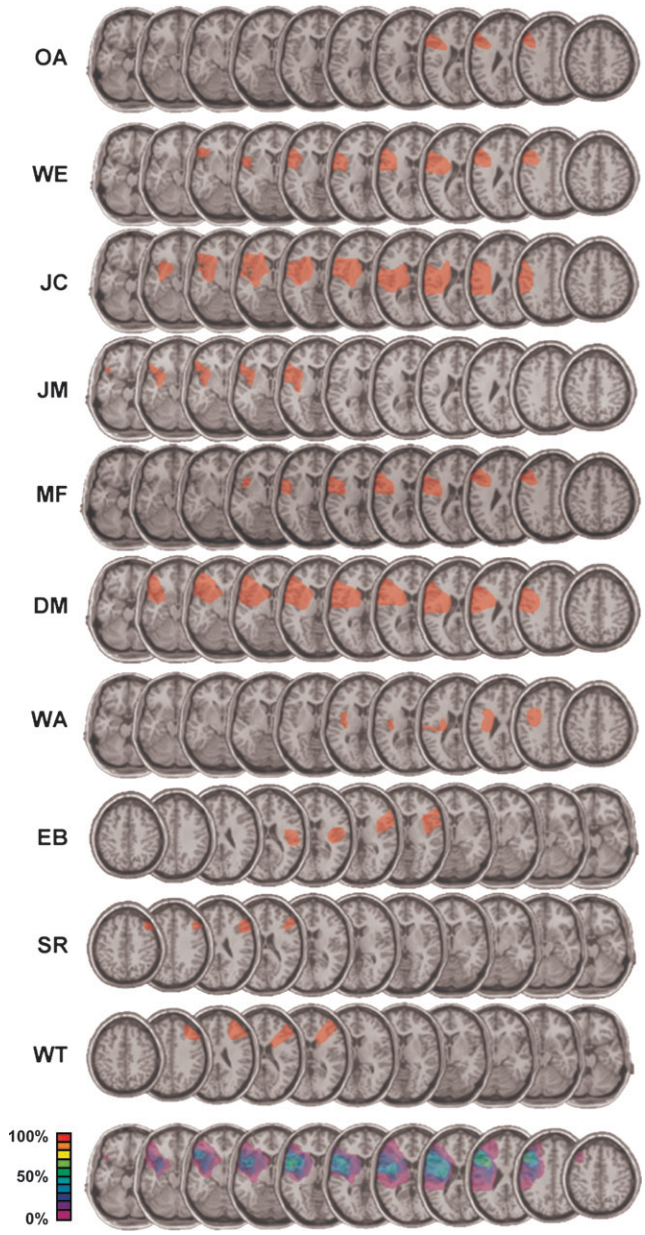

Figure 2. Lesion reconstruction for prefrontal patients. Prefrontal damage was due to stroke (9 cases) and craniotomy (1 case). Lesions are transcribed onto axial templates using 5-mm cuts. Each row shows the extent of damage in an individual patient. Maximal lesion overlap (>67%) was observed in Brodmann areas (BA) 6, 8, 9, and 46, and encompassed portions of the middle and superior frontal gyri. Variable amounts of damage in BA 6, 8, 9, 10, 44, 45, and 47 occurred in individual patients. The average tissue loss was 41.4 cm^3 per patient. Software permitted reconstruction of the lateral perspective of the lesion, determination of lesion volume, and putative cytoarchitectonic area damaged (cf., Barcelo et al. 2000).

(Fig. 1*a*,*b*, Miller and Cohen 2001; Braver et al. 2002). Although, this model has not been previously tested using human lesion P300 ERP data, 4 of its general predictions about cognitive control are relevant to the present study. First, the model predicts a role of PFC in setting up and holding online the task context, rather than any isolated stimulus or perceptual features. Second, lateral PFC enables cognitive control in response to conflict signals from subcortical or frontomedial structures (Miller and Cohen 2001; O'Reilly et al. 2002). Third, a paradoxical amelioration of context-induced errors should follow context-processing deficits in PFC patients (Braver et al. 2002, p. 440). Finally, this model predicts that a unitary PFC-dependent representation of context can explain the selection of target information, the inhibition of distracter information, and working memory operations (Miller and Cohen 2001; Braver et al. 2002).

We explored specific predictions about the role of PFC versus posterior association cortices in the elicitation of the human P300 response. However, one should not dismiss the role of subcortical structures in the cognitive control of visual orienting to novel events (Zink et al. 2003; Pierrot-Deseilligny et al. 2004; O'Reilly 2006), in line with age-old ideas about the hierarchical architecture of control in the nervous system (Jackson 1884). At least 2 sources of extra-PFC influences are worth considering: First, the extracortical control of vision involving well-defined corticotectal connectivity (Goldman and Nauta 1976; Rafal et al. 1990; Gaymard et al. 2003; Pierrot-Deseilligny et al. 2004; Johnston and Everling 2006). Second, subcortical and/or posterior cortical structures have been proposed to support successful delayed target discriminations in the absence of distracters in monkeys and humans with extensive PFC lesions (Malmo 1942; Knight 1984), in accord with the distinct neural substrates for the exploitative processing of familiar information as opposed to the exploration of novel information (Daw et al. 2006; O'Reilly 2006).

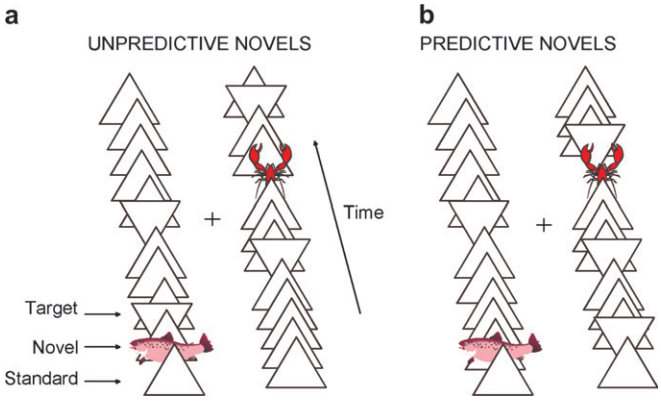

Figure 3. Experimental task design. Inverted triangles (targets) were rapidly and randomly flashed to both visual hemifields within trains of repetitive upright triangles (standard distracters) and unique color images (novel distracters). The temporal contingency between novels and targets was manipulated in each of 2 sessions: (*a*) Unpredictable context, only 20% of novel stimuli were followed by a target. (*b*) Predictable context, all novel events were followed by a target at either the same or the opposite visual hemifield. In both sessions, the mean stimulus probability was 0.7, 0.2, and 0.1 for standards, targets, and novels, respectively (see Table 1). Stimulus duration was 107 ms. Stimuli were displayed 5 degrees to the left or right of a central crosshair and subtended 5 degrees of visual angle. Subjects were instructed to fixate the central crosshair and press a button upon target detection (see Supplementary Material; cf., Barcelo et al. 2000).

Results

Behavior

Missing Errors and False Alarms

Controls correctly responded to 93.6% of targets compared with an overall 81.0% hit rate in patients ($F_{1,18}$ = 7.3, P < 0.02). Patients missed more targets at their contralesion—rather than ipsilesion—visual hemifield ($F_{1,18}$ = 8.5, P < 0.01; 11.6% contralaterally vs. 7.4% ipsilaterally missed targets; cf., Barcelo et al. 2000). Error rates were lower at the ipsilesion visual field for predictable targets (2.6% ipsi- vs. 4.2% contralesion, P < 0.01), with relatively larger miss rates for ipsilesionally displayed unpredictable targets (6.9% ipsi- vs. 4.8% contralesion, P < 0.05). Contextual predictability did not influence miss rates of targets displayed contralaterally to lesion.

Patients committed more false alarms than controls ($F_{1,18}$ = 7.7, P < 0.02; mean false alarm rates of 1.0% vs. 2.5% for controls and patients, respectively). False alarm rates were lower in the predictable context ($F_{1,18}$ = 7.8, P < 0.02).

Reaction Times

The pattern of results for response accuracy was mirrored by reaction times (RTs) (Fig. 4). RTs were slower in patients than controls ($F_{1,18}$ = 6.3, P < 0.03; mean ± standard error of the mean [SEM] for patients: 583 ± 10 ms; controls: 516 ± 11 ms). PFC patients had a contralesion target detection deficit (interaction group by visual field of target display: $F_{1,18}$ = 9.1, P < 0.008), with RTs 590 versus 577 ms for contralesion versus ipsilesion targets, respectively. Across patients and controls, responses to predictable novel–target pairings were faster (mean ± SEM: 531 ± 15 ms) than those following unpredictive novels (555 ± 14 ms) or standards (556 ± 14 ms) (interaction of predictability by distracter type: $F_{1,18}$ = 10.3, P < 0.005). A main effect of distracter type ($F_{1,18}$ = 4.8, P < 0.04), and its interaction with group ($F_{1,18}$ = 4.7, P < 0.05), revealed that controls benefited more than patients from contextual predictability for speeding up their target responses. Across both visual hemifields, controls made faster target responses following a predictive novel (mean ± SEM: 504 ± 11 ms) than following a standard (529 ± 10 ms),

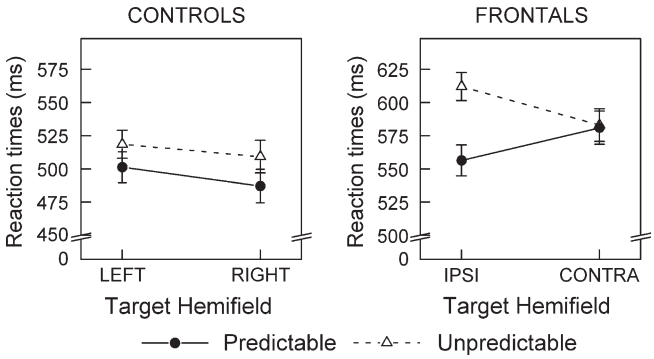

Figure 4. Behavioral results. Mean RTs (and SEM) for visual discriminations of predictable and unpredictable targets displayed at the ipsilesion and contralesion hemifields of patients (left and right hemifields for the age-matched controls). Only data from novel–target pairings are illustrated here as data from standard–target pairings have been reported elsewhere (Barcelo et al. 2000). Contextual predictability only influenced visual discriminations of targets flashed at the ipsilesion (good) visual hemifield of patients. For targets flashed at their contralesion hemifield, patients were neither impaired nor benefited from the information conveyed by the preceding novel stimulus. Normal age-matched controls showed a significant benefit for predictable novel–target pairings evenly distributed across both hemifields of vision.

whereas the patients' responses did not differ between these 2 conditions (583 ± 20 ms vs. 583 ± 11 ms for targets following standard and novel events, respectively).

PFC patients benefited from target predictability only at their ipsilesion visual hemifield (interaction of group by predictability by target field: $F_{1,18} = 6.8$, $P < 0.02$), and this effect was specific for novel–target pairings ($F_{1,18} = 8.5$, $P < 0.01$; Fig. 4). In controls, the response benefit for predictable targets was equivalent across both hemifields. In the patient group, the costs and benefits, respectively, conveyed by unpredictive and predictive novels were observed only when the following target appeared at the ipsilesion visual hemifield ($F_{1,9} = 11.8$, $P < 0.003$). For contralesion targets, RTs were not influenced by the contextual information conveyed by the preceding novel stimulus (Fig. 4, frontals). The visual hemifield of novel display did not influence this visual target effect (interaction of group by predictability by target field by novel field: $F_{1,18} < 1$). In line with missing error rates, contextual predictability improved the speed of visual discriminations only when targets were displayed at the ipsilesion visual field of patients.

Standard–target pairings were not influenced by contextual predictability. Therefore, predictability effects could be specifically attributed to the mutual information conveyed by the novel events about the next target trial and were not related to unspecific factors such as reduced effort or overall difficulty in trial blocks with fully predictable visual target discriminations.

Electrophysiology

Standard, target, and novel events elicited well-known sensory ERPs recorded as positive (P1) and negative (N1) voltage deflections with maximal intensity over temporooccipital regions contralateral to the hemifield of visual display. As reported previously, loss of top-down PFC-dependent input reduced these visual P1 and N1 responses over the temporooccipital cortex ipsilateral to the lesion (Barcelo et al. 2000; Yago et al. 2004). These sensory brain potentials were not influenced by manipulations of contextual predictability and will not be discussed further (see Table 2).

Brain Responses to Novel Events

Contextually novel events elicited a series of stereotypical brain potentials in controls (labeled P2, N2, novelty P3, and N4 in Fig. 5; see Table 2 for a summary of ERP results), all with a frontal or frontocentral maximal voltage distribution. All these brain potentials were altered in the patients, but some were also modulated by contextual predictability (Fig. 5). Lateral PFC lesions reduced P2 amplitudes (peak latency 250 ms at Fpz; Fig. 5, Controls) over frontopolar and frontal regions ($F_{1,18} > 4.5$, Ps < 0.05 at Fpz and Fz; Fig. 5, Frontals). This P2 reduction was larger at recording sites contralateral to the visual field of stimulation (interaction of visual field by electrode: $F_{1,18} = 9.0$, $P < 0.01$; not shown). In both patients and controls, novel events also elicited a transient negative field potential with a frontocentral scalp distribution (N2; peak latency 340 ms at Fz; Fig. 5, Controls). Patients exhibited increased N2 amplitudes ($F_{1,18} = 8.8$, $P < 0.01$ at Fpz; Fig. 5), as well as a rostral displacement of their scalp topography. For both controls and patients, larger N2 amplitudes were recorded over frontopolar regions contralateral to the visual field of novel display (interaction of visual field by electrode: $F_{1,18} = 40.9$, $P < 0.0001$) and such an effect was larger in the patients ($F_{1,18} = 9.1$, $P < 0.007$; not shown). Mean N2 amplitudes in response to novels were not influenced by contextual predictability in controls or patients (Fig. 5).

In controls, mean novelty P3 amplitudes were larger in response to predictive compared with unpredictive novels over frontopolar (Fpz; $F_{1,18} = 5.8$, $P < 0.03$) but not at more posterior regions (Fig. 5, Controls). Mean novelty P3 amplitudes were reduced in patients in all conditions ($F_{1,18} = 5.2$, $P < 0.04$ at Fz), and this reduction was larger for predictive than unpredictive novels displayed ipsilaterally to lesion (interaction of group by predictability by visual field: $F_{1,18} = 5.4$, $P < 0.03$). In turn, context did not influence novelty P3 amplitudes to novels displayed in the hemifield contralateral to PFC damage (Fig. 5*a*,*b*, Frontals). These deficits could not be attributed to group differences in the peak latency of novelty P3 ($F_{1,18} = 1.2$, not significant; 443 ms for patients, 458 ms for controls at Fz). Likewise, peak-to-peak N2–P3 amplitudes did not differ between groups (3.4 vs. 4.5 μV at Fz for patients and controls, respectively; $P = 0.3$). Predictive novels elicited the largest novelty P3 responses over frontopolar regions in controls, whereas the largest abnormalities in novelty P3 activity were recorded over midfrontal regions in patients (interaction of group by predictability by electrode: $F_{1,18} = 4.6$, $P < 0.04$). Importantly, predictive novels flashed ipsilaterally to lesion also elicited abnormal sustained negative activity during 50–200 and 400–600 ms poststimulus onset (interaction group by predictability by visual field by electrode: $F_{1,18} = 6.3$, $P < 0.02$). These early and late anomalous sustained negativities showed similar scalp topographies ($F_{19,171} = 1.2$, $P = 0.4$). In turn, the scalp distribution of these abnormal early and late negativities differed from that of novelty P3 activity in the patients ($F_{19,171} = 6.3$, $P < 0.003$, Greenhouse-Geisser = 1.5). These results suggest impaired neural processing of all novel information in PFC patients, consisting of a bilateral disruption in a sequence of stereotypical transient brain responses, together with an anomalous sustained negativity associated with predictive novels displayed to the ipsilesion visual hemifield of patients.

Table 2

Summary of main ERP results in PFC patients as a function of the working memory status (familiar vs. novel), the contextual contingencies (predictable vs. unpredictable), and the hemifield of display of visual information

	Familiar "target" information				Novel "distracter" information			
	Unpredictable		Predictable		Unpredictive		Predictive	
	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra
Prerolandic P300 activations (index activity from superordinate sensorimotor representations)	✓	✓	✓	✓	×	×	C×	×
Postrolandic P300 activations (index activity from subordinate sensorimotor representations)	✓	×	✓	✓	✓	✓	✓	✓
Occipitotemporal P1/N1 activations (index activity from visual representations)[a]	✓	×	✓	×	✓	×	✓	×

Note: ✓, preserved ERP activity; ×, disrupted ERP activity; C, contextual predictability ERP effects observed in patients. Shaded cells indicate those task conditions where contextual ERP effects were found in normal controls.

[a]ERP data not shown as they replicate previous results (cf., Barcelo et al. 2000; Yago et al. 2004).

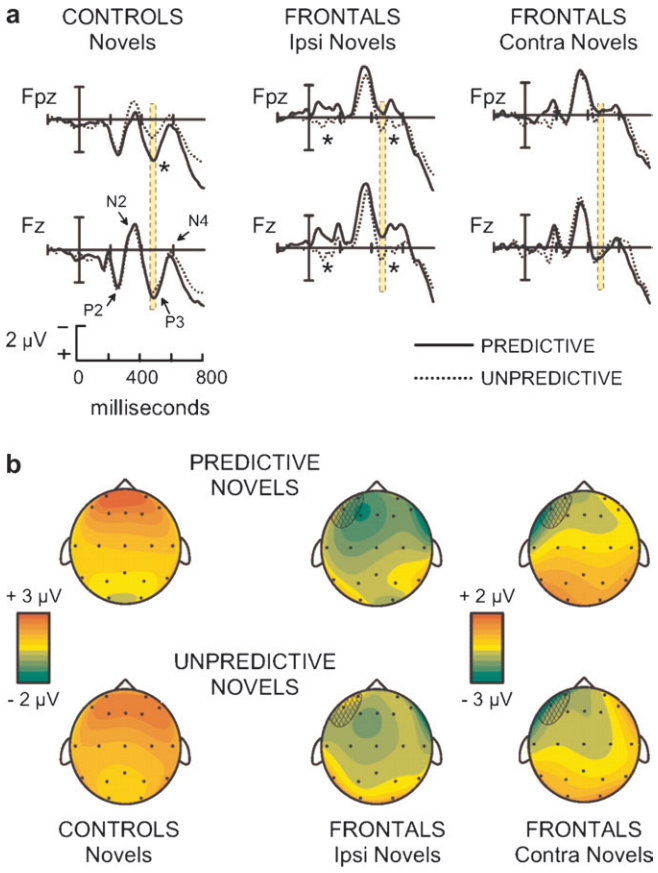

Figure 5. Group-averaged brain responses to visual novels. (*a*) Brain responses to novels displayed at the ipsilesion and contralesion visual hemifields of PFC patients (middle and right columns) are compared with data collapsed across both visual hemifields in controls (left column). Novel events evoked rostrofrontal transient positive P2 and P3 potentials in controls that were severely disrupted in the patients. The frontocentral negative N2 potential was abnormally enlarged and showed a rostral displacement of its scalp topography in patients (see the main text for an explanation). Yellow bars indicate the time window for novelty P3 measurement (460–490 ms). (*b*) Scalp topographies of mean novelty P3 amplitude to predictive and unpredictive novels displayed at the ipsilesion and contralesion visual fields of PFC patients (middle and right columns, respectively) are compared with corresponding novelty P3 activity in controls (left column, data collapsed across both visual hemifields).

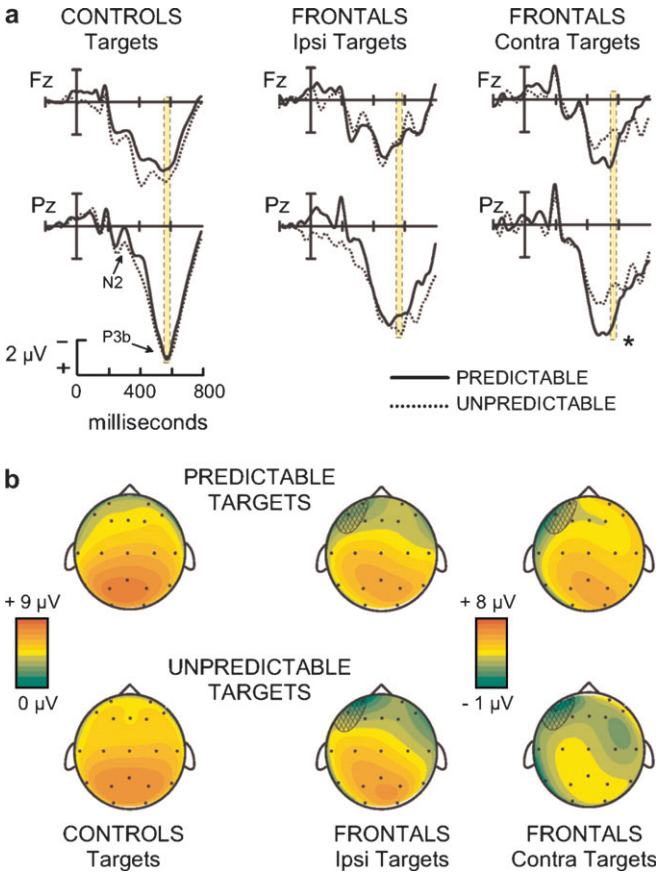

Figure 6. Group-averaged brain responses to visual targets. (*a*) Brain responses to targets displayed at the ipsi- and contralesion visual hemifields of PFC patients (middle and right columns) are compared with data collapsed across both visual hemifields in controls (left column). Target events evoked a regular transient P3b potential with its midparietal maximum in controls that was disrupted only for unpredictable targets displayed at the contralesion visual hemifield of patients. Yellow bars indicate the time window for target P3b measurement (560–600 ms) (*b*) Scalp topographies of mean target P3b amplitude to predictable and unpredictable targets displayed at the ipsi- and contralesion visual hemifields of patients (middle and right columns, respectively) are compared with corresponding target P3b activity in controls (left column, data collapsed across both visual hemifields).

Brain Responses to Target Events

Target events evoked 2 well-known ERP signatures with a temporoparietal and midparietal scalp topography, respectively (labeled N2 and P3b in Fig. 6), none of which were affected by contextual predictability in controls. In the patients, predictable targets elicited normal target P3b activity over midparietal and temporoparietal regions, whereas unpredictable targets displayed contralateral to PFC lesions elicited reduced target P3b activity over midparietal ($F_{1,18}$ = 5.8, P < 0.03 at Pz; Fig. 6*a*, Frontals: contra targets), as well as over ipsi- and contralesional temporoparietal regions (P < 0.004 and P < 0.04, respectively; Fig. 6*b*).

Lesion-Related Asymmetries in Brain Activation

We examined the hemispheric asymmetries in the brain responses to novel distracters and familiar targets between the lesioned and the intact PFC regions in the unpredictable context condition (Fig. 7). Asymmetries were observed in the brain responses to novel distracters, with enhanced P2 activity but reduced novelty P3 activity over the lesioned, as compared with the intact, lateral PFC region ($F_{1,9}$ > 5.6, Ps < 0.04). In contrast, the brain responses to familiar targets showed enhanced target P3b activity and reduced N2 activity over the lesioned, as compared with the intact, lateral PFC region ($F_{1,9}$ > 7.3, Ps < 0.02). The abnormally enhanced N2 amplitudes to all novel distracters did not differ between the lesioned and the intact hemispheres.

Discussion

Lateral PFC-lesioned patients showed behavioral and electrophysiological deficits during the updating and maintenance of contextually related familiar and novel information. At least 3 distinct deficits were identified: 1) a general deficit in processing all novel information, 2) a deficit in acquiring the temporal association between predictive novels and targets, and 3) a deficit in the selection of unpredictable targets. The first 2 deficits corresponded with abnormal brain responses to novel events displayed either ipsilateral or contralateral to PFC damage. Both behavioral responses and target ERPs were abnormal to unpredictable targets flashed contralesionally.

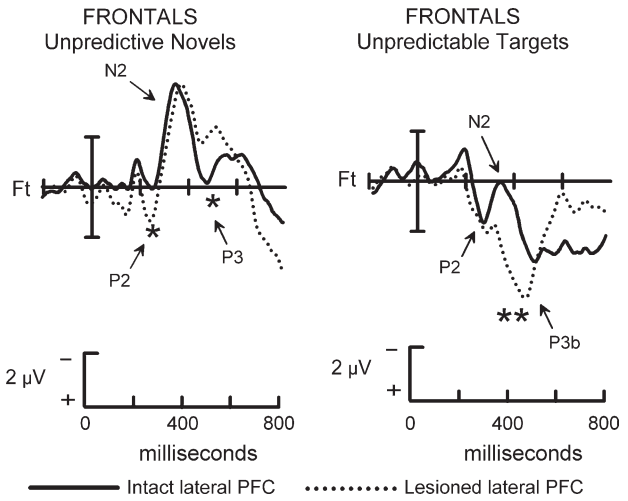

Figure 7. Asymmetrical PFC representation of context. Mean brain responses from lateral frontal (F7/F8) electrodes to novel distracters and familiar targets are shown in the unpredictable context. Paradoxically larger brain responses over the lesioned PFC suggest disinhibition of subcortical (e.g., basal ganglia) structures. Asymmetric transient P2 and P3 activity to unpredictive novels across the lesioned and intact lateral PFC matched the behavioral asymmetry in visual discrimination ability. Comparatively enhanced P2 and reduced P3 activity could reflect differential PFC efficiency in processing familiar versus novel information, respectively (e.g., chunks I and II in Fig. 1*a*,*b*). These results suggest a subcortical contribution to the online maintenance of familiar—and the updating to novel—task information (see the main text for an explanation).

These results support the hypothesis that damage to a unitary PFC representation of context results in several apparently distinct cognitive deficits (Miller and Cohen 2001; Braver et al. 2002). The data also support a crucial role of lateral PFC in updating and online maintenance of both familiar and novel information (Malmo 1942; O'Reilly 2006).

Impaired Processing of All Novel Information in PFC Patients

The behavioral deficits of PFC patients were matched with 2 distinct abnormalities in the brain responses to novel—but not familiar—information: 1) a bilateral disruption in the stereotypical ERPs to all novel events that was influenced neither by the hemifield of novel display nor by contextual predictability and 2) an anomalous and sustained negative potential related to predictive novels displayed ipsilesionally. The frontal topography of these 2 abnormalities supports a disrupted superordinate sensorimotor representation of novel information (i.e., memory chunk II in Fig. 1*b*; Barcelo et al. 2006), rather than a purely perceptual representation of the stimulus context at posterior association cortices.

Bilaterally Disrupted Updating of Novel Information

A well-known sequence of stereotypical brain responses to novel stimulation (e.g., P2, N2, novelty P3, and N4 in Fig. 5) was altered in the patients regardless of the hemifield of novel display or contextual predictability. These ERP abnormalities contrasted markedly with the relatively normal ERP activations recorded to familiar task–relevant targets over the same prerolandic regions and with the normal ERP activations to the same novel stimuli over postrolandic multimodal association regions (Table 2). These results confirm previous findings and lend support to the notion that there are distinct PFC representations for novel and familiar information (Knight 1984). These ERP results also agree with our estimations of information transmission within the hierarchy of representations in Figure 1 (see Tables A1 and A3 in the Appendix of Supplementary Material), suggesting that in spite of not requiring any overt responses, unpredictive novels exceeded the theoretical limit of the human capacity for processing information in working memory (cf., Miller 1956) and did so by conveying information at a superordinate level of representation (Koechlin et al. 2003). Targets also conveyed information for response selection but did so through subordinate sensorimotor representations at posterior association cortices (Tables A1 and A3 in the Appendix of Supplementary Material). Accordingly, the updating of target information demanded mainly temporoparietal—rather than PFC—activations (Figs 1*a* and 6), whereas the updating to a novel memory chunk recruited activity at both PFC and temporoparietal cortices (Figs 1*b* and 5; cf., Miller and Cohen 2001).

The bilaterally disrupted brain responses in patients with unilateral PFC lesions suggest that updating of novel information involves intercallosal cross talk (Knight 1996) that is known to be driven by arousal systems in the brainstem (Sokolov 1963; Crick 1984; Zink et al. 2003; Nieuwenhuis et al. 2005). The prerolandic scalp distribution of disrupted brain responses to all novel information questions their interpretation in terms of forward transmission of information through sensory-specific geniculostriate pathways. In turn, these findings concur with modulatory interactions between exogenous and endogenous sources of information through modality nonspecific bidirectional corticosubcortical pathways (Sokolov 1963; Edelman and Tononi 2000; Friston 2005). One plausible source of exogenous information is arousal systems in the midbrain (Zink et al. 2003; Nieuwenhuis et al. 2005) that communicate with lateral PFC through well-defined prefrontotectal connectivity (Goldman and Nauta 1976; Gaymard et al. 2003; Johnston and Everling 2006).

Ipsilesionally Disrupted Maintenance of Novel Information

This deficit in novelty processing was accompanied by a secondary context-sensitive deficit related to our use of predictive novels as anticipatory cues for target selection. In controls, predictive novels elicited enhanced novelty P3 amplitudes over rostrofrontal regions (Fig. 5). This finding supports the hypothesis that novelty P3 and target P3b activations each index different context-updating operations at different levels in the hierarchy of representations in Figure 1. This finding also raises interpretative problems for the context-updating model that predicts lesser P300 activations in the more predictable stimulus contexts (Donchin and Coles 1988). Alternatively, the more informative novels elicited the larger novelty P3 activations, consistent with our use of predictive novels as contextual cues for anticipatory target selection (cf., Barcelo et al. 2002; Barcelo et al. 2006). Information-theoretic analyses indicated that the extra contextual information of predictive novels was not conveyed through posterior S–R pathways ("sensorimotor control," Koechlin and Summerfield 2007) but rather through superordinate PFC representations ("contextual control," Koechlin et al. 2003; cf., Fig. 1 and Appendix, see Supplementary Material).

In PFC patients, contextual predictability modulated brain physiology and behavior only when novel information accessed the intact PFC of patients through their ipsilesion visual field (Figs 4 and 5). The lack of any contextual modulations for

predictive novels flashed at the visual hemifield contralateral to damage supports a critical role of PFC in establishing the temporal context for the anticipatory control of vision. The lesioned PFC could assist neither in building up the representation of a novel visual object at posterior association cortices (cf., Barcelo et al. 2000) nor in holding it online to establish an association with the following target response. In contrast, when predictive novels were displayed at the good visual hemifield of patients, they implemented the temporal contingency and could readily anticipate the next target response, thus improving their behavioral performance.

Predictive novels elicited further ERP abnormalities in the form of anomalous sustained early 50–200 ms and late 400–600 ms negativities over the lesioned lateral PFC (Fig. 5). These negativities were observed neither in response to unpredictive novels nor when predictive novels were displayed at the contralesional (bad) visual hemifield of patients. There are at least 2 alternative explanations for these abnormal sustained negativities. One, they could reflect volume-conducted compensatory activity from the intact PFC during online maintenance of the novel–target contingency. However, this is unlikely given their maximal intensity over the lesioned cortex. Two, these negativities could index signals from frontomedial (e.g., anterior cingulate) or else subcortical structures (e.g., striatum, midbrain) that could not be regulated by missing PFC representations. This latter hypothesis concurs with evidence that predictive novels were categorized at extremely short latencies, before visual information could reach PFC through classic flow from extrastriate pathways, and with the existence of well-defined prefrontotectal connectivity originally described in primates by Goldman and Nauta (1976). The hypothesis of a subcortical route for the updating of PFC representations of novel information concurs with the critical importance of modality nonspecific pathways for orienting to visual novelty (Sokolov 1963; Crick 1984; Johnston and Everling 2006), with extracortical influences on visual attention (Rafal and Posner 1987; Rafal et al. 1990), and with the disinhibition of subcortical reflexes in patients with cortical lesions (Jackson 1884). The extremely fast timing of these modulations could not be easily inferred from behavioral or metabolic brain imaging studies with a coarser temporal resolution or from ERP studies in humans without cortical lesions (cf., Fig. 5).

The acquisition of contextual predictability presumably required the building up of new sensorimotor associations between target representations and a novel memory chunk assisted by the intact PFC of patients (Fig. 1*a*,*b*), rather than any new linkage between posterior subordinate sensorimotor or perceptual units. The lesioned PFC could not efficiently update to a novel memory chunk, nor could it maintain this novel information online until the onset of the next target. This may explain the absence of contextual effects for novels and targets displayed at the contralesional visual hemifield of patients. In contrast, predictive novels flashed ipsilateral to lesion could be linked to familiar chunk I and led to the anticipation of the next target response, most likely with the support of subcortical structures (Edelman and Tononi 2000; Zink et al. 2003; O'Reilly 2006). In sum, the implicit learning of the temporal contingency between predictive novels and targets required the acquisition and online maintenance of a PFC representation of the novel event and the linkage of this novel memory chunk (Fig. 1*b*) with the neural representation of the forthcoming target stimulus (Fig. 1*a*).

Impaired Inhibition of Novel Distracters in PFC Patients

The patients showed problems inhibiting attentional capture by all novel distracters, most apparent in response to ipsilesion targets following an unpredictive novel event. Behavioral distractibility was independent of the visual hemifield of novel display, consistent with bilaterally disrupted brain responses to all novel stimulation described in the previous section. This finding bears 2 corollaries: 1) the effect was not related to the retinotopy of geniculostriate pathways or to any perceptual representation of the novel–target contingency at visual cortices and 2) this distractibility was sensitive to top-down (predictability) rather than bottom-up (visual field) contextual manipulations suggesting a superordinate locus of this effect (cf., Friston 2005) and consistent with a disrupted updating of superordinate representations of novel information (Fig. 1*b*).

The guided-activation model predicts that damage to a PFC representation of context may either impair or improve behavior depending on whether context helps or hurts performance, respectively (Miller and Cohen 2001; Braver et al. 2002). Accordingly, we found relative impairments versus improvements in contralesional versus ipsilesional visual discriminations under predictable versus unpredictable task contexts, respectively. However, our ERP data argued against a unique PFC locus for these contextual effects. The hemispheric asymmetries in frontally distributed transient P2 and novelty P3 activity to novel distracters and familiar targets suggest an interaction between PFC and other—possibly subcortical—structures as a function of the relative novelty or familiarity of task information (Fig. 7; Zink et al. 2003; McHaffie et al. 2005; O'Reilly 2006). For instance, the absence of any target P2 asymmetry, together with the comparatively larger target P3b responses to familiar targets recorded over the lesioned PFC, supports a subcortical locus for these effects (Fig. 7, Targets). This ERP evidence could reflect an abnormal disinhibition of the ipsilesional striatum during processing of familiar targets in PFC-damaged patients (e.g., unit s2–r1 in Fig. 1*a*; cf., O'Reilly 2006). The purported role of basal ganglia in holding familiar information online could also account for the preserved visual discrimination ability of monkeys with bilateral PFC resections in the absence of distracters (Malmo 1942).

Impaired Selection of Familiar Targets in PFC Patients

A deficit in the selection of familiar information in patients was observed in response to all contralesion targets (cf., Barcelo et al. 2000; Yago et al. 2004). This target selection deficit matched with reduced P3b activity to targets displayed contralesionally—but not ipsilesionally—, and only in the unpredictable—but not the predictable—task contexts (Figs 4 and 6). In line with the guided-activation model, the onset of a predictive novel would quickly activate the sensorimotor units necessary for selecting the next target response (e.g., s2–r1 in Fig. 1*b*). When the next predictable target came up on display, its sensorimotor representation could be readily implemented at posterior association cortices resulting in normal target P3b elicitation. Hence, the selection of the target response in the predictable context could be implemented based primarily on extremely fast top-down control and without any fine-grained perceptual analysis at extrastriate cortices. The acceptable discrimination ability of PFC patients in the predictable context, even at their bad visual hemifield, indicates that the updating of sensorimotor target representations relied mainly on subcortical and/or posterior cortical structures (O'Reilly 2006).

This situation changed radically in an unpredictable context, where the absence of advance information about the identity of the next stimulus forced the brain to carry out a detailed analysis of perceptually similar targets and standard distracters. Contextual uncertainty forced the brain to rely primarily on sensory-driven control for the selection of the next action. However, stimulus identification at the ipsilesion visual cortex was impaired due to loss of intrahemispheric PFC–dependent modulatory input, resulting in faulty perceptual categorization of familiar information (e.g., units s1 and s2 in Fig. 1*a*). A defective perceptual analysis at ipsilesional visual cortices impaired the updating of sensorimotor units at posterior association cortices (Barcelo et al. 2000; Yago et al. 2004). Therefore, contextual uncertainty forced the neural system to implement familiar chunk I based on missing or incomplete perceptual information. The result was elicitation of reduced target P3b activity in a situation with maximal stimulus uncertainty and reduced cognitive control. This visual selective attention deficit could be likened to thalamic selection deficits described by Rafal and Posner (1987), based on the notion of a thalamic link between cortical visual attention and pattern recognition systems during the exploitation of familiar information (Crick 1984; Friston 2005). These results disclose a functional difference between the role of target P3b activations in the selection of familiar target information, in contrast with novelty P3 activations, and contrary to predictions from the context-updating model (cf., Donchin and Coles 1988). The absence of any predictability effects upon target P3b amplitudes in controls agrees with recent P3 results from task-switching studies (Barcelo et al. 2002, 2006), as well as with our information-theoretic analyses showing that targets conveyed the same information for response selection in both our predictable and unpredictable task conditions (see the Appendix in the Supplementary Material).

Summary of Findings and Conclusions

The present results partly support predictions from the guided-activation model that damage to one single PFC representation of context causes 3 different deficits in 1) the online maintenance of novel information, 2) the inhibition of novel distracters, and 3) the selection of familiar target information (Miller and Cohen 2001). The present findings are consistent with a functional hierarchy of neural representations involving anterior and posterior multimodal association cortices (Fuster 1998; Koechlin et al. 2003) that implement cognitive control in cooperation with subcortical structures (Jackson 1884; Malmo 1942; Edelman and Tononi 2000). The results also support the notion that PFC neurons do not merely process information about a stimulus or its perceptual context, but rather about the temporal context of our goal-directed behavior (Tononi and Edelman 1997; Miller and Cohen 2001).

Lateral PFC played a crucial role in updating contextually novel information, whereas subcortical and/or posterior cortical structures seemed to have a larger contribution during the online maintenance and updating of familiar information (McHaffie et al. 2005; O'Reilly 2006). The present findings are consistent with ERP evidence from simple perceptual judgment tasks in PFC patients (Knight 1984, 1997), as well as with ERP evidence from task-cueing paradigms in healthy volunteers (Barcelo et al. 2002, 2006), suggesting activation of functionally distinct neural networks during the exploration of novel versus the exploitation of familiar information (Fig. 1*a*,*b*, Daw et al. 2006).

The early timing and scalp distribution of abnormal frontal negativities supports a subcortical involvement in computing the contextual predictability of novel stimulation (Rafal et al. 1990). Originally described in primates by Goldman-Rakic and Nauta (1976), prefrontotectal pathways could convey sufficient sensory information to lateral PFC for the categorization of a novel, unexpected, or biologically salient visual stimulus (Gaymard et al. 2003; Redgrave and Gurney 2006). Efferent cortical–subcortical connections from brain regions associated with expectation and timing, like PFC and the basal ganglia, offer a potential circuit for the rapid detection of unexpected sensory signals (~50 ms), as enough information can be conveyed through this route to detect a mismatch between visual input and active PFC representations (i.e., a change in luminance and/or spatial location; Johnston and Everling 2006; Redgrave and Gurney 2006). The observed extra-PFC signals in response to predictive novels support a nonrepresentational nature of contextual memories that could be best understood in terms of mutually informed cortical–subcortical dynamics in line with global mapping theories of perceptual categorization (Edelman and Tononi 2000, p. 93–101).

The present ERP findings relied on information-theoretic estimations—rather than on mean stimulus probabilities—of the mutual information between contextually related task events in order to explore the dimensionless properties of human working memory regardless of specific sensory or motor demands in target and distracter trials (Miller 1956; Koechlin and Summerfield 2007). These analyses indicate that the information conveyed by a stimulus for response selection depends on the intrinsic interactions between exogenous (e.g., sensory features) and endogenous (e.g., recent memories and future goals) sources of information along a functional hierarchy of neural representations in the brain. In the present task, the contextual information of a predictive novel stimulus could be best described in terms of large-scale cortical–subcortical dynamics (Tononi and Edelman 1997; Edelman and Tononi 2000; Friston 2005).

Finally, the disrupted brain responses to all novel information in PFC patients lent support to the hypothesis of lateral PFC as a "switch operator" that flexibly connects activation between exploitative and exploratory modes for processing familiar and novel information at the highest level in the hierarchy of cognitive control (Miller and Cohen 2001; Daw et al. 2006). Cognitive deficits in PFC patients can be easily overlooked by neuropsychological assessment methods that use familiar and repetitive material predictably presented at central vision, thus allowing patients with unilateral PFC damage to compensate for their deficits (Knight 1997). Information theory tools could help us gauge stimulus and task uncertainty in order to assess the degree and quality of the information-processing deficits in PFC patients (Miller 1956; Koechlin and Summerfield 2007).

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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An information theoretical approach to contextual processing in the human brain: Evidence from prefrontal lesions

Francisco Barcelo and Robert T. Knight

Supplementary Online Material

Materials and Methods

Participants

Ten patients were selected on the basis of unilateral focal lesions to their lateral PFC as determined by computed tomography (CT) or magnetic resonance imaging (MRI) scanning. Lesions were due to single stroke (9 patients), or craniotomy (1 patient), and were restricted to lateral PF cortex. Maximal lesion overlap (>67% across patients) comprised Brodmann's areas 6, 8, 9 and 46 (Fig. 2). Variable amounts of damage in Brodmann's areas 6, 8, 9, 10, 44, 45 and 47 occurred in individual patients. There were 3 right- and 7 left-lesioned patients. Testing took place at least one year after the injury. Medical complications, psychiatric disturbance, substance abuse, psychoactive drug treatment, or other neurological diseases were criteria for exclusion. All patients had normal or corrected to normal visual acuity. Three patients had upper motor neuron weakness in the limb contralateral to their lesion and responded with their ipsilesion limb. The average age of patients was 65.4 ± 13.5 years (3 female; 7 male). Ten controls were matched for age (66.3 ± 6.5 years), sex, and education to the patients, and were free of neurological or psychiatric disease. The research was approved by the Human Subjects Review Committees of the Martinez Veterans Administration Research Service and the University of California.

Stimuli, Design and Procedures

The task involved the rapid presentation of inverted triangles (targets) interspersed within trains of repetitive upright triangles (standard distracters) and unique color images (novel distracters), drawn from the International Affective Picture System (Lang and others 1988). Highly emotional stimuli such as those showing injured body parts were excluded. Stimuli were randomly displayed 5º to the left or to the right of a central fixation point, and were arranged semirandomly with the constraint that two targets or novel events never appeared sequentially (Fig. 3; see Appendix). The overall probability of each stimulus type within blocks or throughout the session was 0.2, 0.7 and 0.1 for targets, standards and novels, respectively (Table 1). Stimulus duration was 107 ms with an inter-stimulus interval of either 200 or 900 ms. All stimuli subtended a 5º visual angle and were matched in their mean luminance. The background luminance was 0.4 foot lamberts and the stimuli were 5.2 foot lamberts.

Subjects were instructed to fixate a central yellow crosshair and press a button upon detection of a target as fast as possible. Subjects responded with their right hand except for three patients with motor weakness, who responded with the hand ipsilateral to their lesioned hemisphere. Throughout the task subjects sat in a comfortable chair in a sound attenuated recording chamber 1.6 meters from a video monitor. Thus, subjects were required to continuously allocate attention across their entire visual field. This bifield visual attention task was intended to minimize the possibility of differential effort or arousal between visual hemifields that could arise in a blocked design. Importantly, a bilateral stimulus display prevented patients with unilateral brain damage from using their intact PFC to compensate for their deficits. The uncertainty associated with this bilateral stimulus display effectively added 1 bit of information across all other task conditions

(i.e., probability of left field display= probability of right field display= 0.5), and considerably improved the sensitivity of our behavioral and brain measures to unilateral PFC damage (cf., Barcelo and others 2000; Knight 1997; Yago and others 2004).

The data were gathered in two separate 1-hour sessions consisting of 12 blocks of about 150 stimuli each in order to lessen fatigue. Sessions were run several days apart. Contextual predictability was manipulated between sessions, by varying the temporal contingency of novel-to-target pairings. In one session (unpredictable context; Fig. 3a), only 20% of novel stimuli were followed by a target. In the other session (predictable context; Fig. 3b), all novel stimuli were followed by a target. The order of administration of each condition was counterbalanced across subjects. The same task goal was made explicit in both conditions through a fixed set of instructions, and subjects were never informed about the temporal contingency between novels and targets. A short training block ensured that the subject understood this simple detection task. The training block was a typical oddball task with 20% target and 80% standard stimuli, and without novel distracters. The actual recording session consisted of 12 blocks, each lasting about 4 minutes. Subjects took a brief rest after each block (Barcelo and others 2000).

A hit was defined as a correct button press 300-800 ms following a target. Failure to respond in that window was computed as a miss. Both reaction times (in milliseconds) and accuracy of responses were submitted to analysis. The ANOVAs for behavioral data followed a 2 x 2 x 2 x 2 design, with Group as the between-subjects factor and Temporal Context (unpredictable *versus* predictable), Distracter type (standard *versus* novel), and Visual field (ipsi/left *versus* contra/right) as the repeated measures factors. Preliminary behavioral analyses of old controls and patients revealed inhibition rather than facilitation of target discriminations for cued target locations as early as 200 ms post-cue onset. Early facilitatory and inhibitory processes converge around 200 ms post-cue onset, making it difficult to extricate the relative contribution of each process to brain physiology and behavior. For these reasons, and in order to minimize contamination from overlapping ERP activity from the previous trial, only data from long 900 ms ISIs was analyzed and reported in this study.

ERP Recordings and Analyses

Brain electrical activity was recorded from tin electrodes placed at 19 scalp sites (Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) according to the 10-20 system. The electrooculogram (EOG) was measured with electrodes attached to the left and right canthi of both eyes, as well as beneath and above the outer edge of the left eye. Electrode impedances were kept below 5 kΩ. All sites were referenced to linked mastoids. The EEG was amplified (band pass: 0.1-100 Hz), digitized (256 Hz/channel), and stored in a PC for off-line analysis. The averaging epoch was 1024 ms including a 200 ms baseline. Trials were automatically rejected from further analysis on the basis of blinks, EMG artifacts in the scalp channels (peak to peak amplitude 80 μV), or lateral eye movements as monitored in the horizontal EOG. The mean rejection rate was 14.8% versus 14.6% for left versus right hemifield target trials, with no significant differences between patients and controls. Behavioral and electrophysiological performance were comparable for left and right lesioned prefrontal patients, hence results are reported for stimuli delivered in the visual field ipsilateral (IPSI) or contralateral (CONTRA) to the lesion. For example, TOi refers to the averaged ERP data from the T5 electrode for left prefrontal lesions, combined with data from the T6 electrode from right prefrontal lesions. Similarly, Fti equals F7 for left lesions averaged with F8 electrode data from

right lesions. Ipsilesion ERP data were compared to left hemisphere ERP data from controls, and vice versa. Although no significant differences were noted between left and right lesioned patients, power considerations due to the size of the groups precluded any definitive statement about hemispheric laterality effects.

Mean amplitudes of several components of the visual brain potential were obtained relative to a 200 ms prestimulus baseline for each of the three stimulus types used in the study (standards, novels, and targets). Early latency extrastriate ERP components were measured in windows of 110-155 ms for the P1 and 190-210 ms for the N1 components. These sensory ERPs showed anomalies over extrastriate regions ipsilateral to PFC lesions (cf., Barcelo and others 2000), but were not influenced by manipulations of contextual predictability. Here we report only those brain responses that were sensitive to the experimental manipulation of contextual information (i.e., ERPs to unpredictive *versus* predictive novel events; Fig. 5). Novelty-related ERPs were measured in time windows of 230-255 ms for the P2, 340-370 ms for the N2, and 460-490 ms for the novelty P3 components. Target-related ERPs were measured in windows of 340-370 ms for the N2, and 560-600 ms for the P3b components. Peak latencies for these components were also computed relative to stimulus onset. Mean amplitude voltages were also measured in windows of 50 ms from 0 to 700 ms for the analysis of abnormal frontal negativities observed in response to predictive novels (Fig. 5).

Statistical tests of hypotheses about brain activation were performed separately for novel and target events, since they convey information about qualitatively distinct component processes. In either case, the ANOVAs for physiological data followed a 2 x 2 x 2 x 2 x 4 design, with Group as the between-subjects factor, and Temporal Context (unpredictable *versus* predictable), Distracter type (standard *versus* novel), Visual field (ipsi/left *versus* contra/right), and Electrode (Fpz, Fz, Cz, Pz) as the repeated measures factors. Normal long latency ERPs to novels and targets were generally symmetrical and did not show any significant differences across hemispheres. Following predictions from the guided activation model, inter-hemispheric asymmetries in the ability to represent novel and familiar information at the lesioned and intact PFC of patients were assessed at two fronto-temporal electrodes (F7/F8) with the following ANOVA design: Hemisphere (ipsilesional, contralesional) and Stimulus type (Novel, Target). Finally, amplitude values were normalized in order to assess the scalp distribution of voltages from relevant ERP components independent from their source strength. Vector length was defined as the square root of the sum of squared difference wave amplitudes over all locations, calculated separately for each group, event type and visual hemifield of stimulus display. In those contrasts with more than one degree of freedom, significance levels are reported using the uncorrected degrees of freedom. Greenhouse-Geisser corrections were performed when appropriate and corrected probability values are given.

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Appendix

The bifield visual discrimination task comprised one instructed task-set with one-forced responses (r1) to visual targets, and no responses (r0) to standard and novel distracters. From an information theoretical approach, the response entropy, h(R), generated by any stimulus (S) in our task can be estimated as:

$h(R) = I(R,S) + I(R_{Next}, S)$, where

h(R) = response entropy associated with a stimulus;

I(R, S) = information conveyed by a stimulus about its associated response (i.e., a measure of 'sensorimotor control'; Koechlin and Summerfield 2007);

$I(R_{Next}, S)$ = information conveyed by a stimulus about the response to the next stimulus (i.e., a measure of 'contextual control'; Koechlin and others 2003).

In order to compute the information conveyed by a novel stimulus for sensory and contextual control in our visual discrimination task (see Fig. 1), we have:

$$h(R) = I(r0, Novel) + I(R_{Next}, Novel)$$

1. SENSORIMOTOR CONTROL: Unpredictive and predictive novel and standard events conveyed the same amount of sensory information for response selection (logarithms are in base 2; conditional and joint probabilities are listed in Table A1 below):

For unpredictive novels (uNovel):

$I(r0, uNovel) = \log(0.10) - \log(0.80*0.10) = -\log(0.80) = 0.32$ bits

For predictive novels (pNovel):

$I(r0, pNovel) = \log(0.10) - \log(0.80*0.10) = -\log(0.80) = 0.32$ bits

For unpredictive standards (uStandard):

$I(r0, uStandard) = \log(0.70) - \log(0.80*0.70) = -\log(0.80) = 0.32$ bits

For predictive standards (pStandard):

$I(r0, pStandard) = \log(0.70) - \log(0.80*0.70) = -\log(0.80) = 0.32$ bits

For unpredictable targets (uTarget):

$I(r1, uTarget) = \log(0.20) - \log(0.20*0.20) = -\log(0.20) = 2.32$ bits

For predictable targets (pTarget):

$I(r1, pTarget) = \log(0.20) - \log(0.20*0.20) = -\log(0.20) = 2.32$ bits

Table A1. *A priori* marginal, conditional, and joint probabilities between stimuli and responses in the unpredictable and predictable context conditions of the visual target discrimination task (i.e., 'sensorimotor control' after Koechlin and Summerfield 2007).

UNPREDICTABLE	CONDITIONAL *P*(R|S)		JOINT *P*(R,S)	
Marginal P	*r0*	*r1*	*r0*	*r1*
uTarget (*P* = 0.2)	0.00	1.00	0.00	0.20
uNovel (*P* = 0.1)	1.00	0.00	0.10	0.00
uStandard (*P* = 0.7)	1.00	0.00	0.70	0.00
PREDICTABLE	CONDITIONAL *P*(R|S)		JOINT *P*(R,S)	
Marginal P	*r0*	*r1*	*r0*	*r1*
pTarget (*P* = 0.2)	0.00	1.00	0.00	0.20
pNovel (*P* = 0.1)	1.00	0.00	0.10	0.00
pStandard (*P* = 0.7)	1.00	0.00	0.70	0.00

2. CONTEXTUAL CONTROL: While unpredictive novels did not inform about the next target response, predictive novels conveyed a large amount of contextual information for the selection of the next target response (logarithms are in base 2; conditional and joint probabilities are listed in Table A2 below):

Contextual information for unpredictive novels (uNovel):

$I(r1_{\text{Next Target}}, \text{uNovel}) = \log(0.02) - \log(0.20*0.10) = 0.00$ bits

Contextual information for predictive novels (pNovel):

$I(r1_{\text{Next Target}}, \text{pNovel}) = \log(0.10) - \log(0.20*0.10) = -\log(0.20) = 2.34$ bits

Table A2. *A priori* marginal, conditional, and joint probabilities between contextually related S1-S2 stimuli under unpredictable and predictable target conditions in the visual discrimination task (i.e., 'contextual control' after Koechlin and others 2003).

UNPREDICTABLE	**CONDITIONAL P(S2|S1)**			**JOINT P(S1,S2)**		
Marginal P	$Target_{S2}$	$Novel_{S2}$	Std_{S2}	$Target_{S2}$	$Novel_{S2}$	Std_{S2}
uTarget_{S1} ($P = 0.2$)	0.00	0.00	1.00	0.00	0.00	0.20
uNovel_{S1} ($P = 0.1$)	0.20	0.00	0.80	0.02	0.00	0.08
uStandard_{S1} ($P = 0.7$)	0.26	0.14	0.60	0.18	0.10	0.42
PREDICTABLE	**CONDITIONAL P(S2|S1)**			**JOINT P(S1,S2)**		
Marginal P	$Target_{S2}$	$Novel_{S2}$	Std_{S2}	$Target_{S2}$	$Novel_{S2}$	Std_{S2}
pTarget_{S1} ($P = 0.2$)	0.00	0.00	1.00	0.00	0.00	0.20
pNovel_{S1} ($P = 0.1$)	1.00	0.00	0.00	0.10	0.00	0.00
pStandard_{S1} ($P = 0.7$)	0.14	0.14	0.72	0.10	0.10	0.50

Note. S1 and S2 denote stimuli in the present and the next trials, respectively.

3. MUTUAL INFORMATION (or 'information transmission'; Miller, 1956) between different task events and their corresponding multimodal sensorimotor representations in Fig. 1 (marginal and joint probabilities are listed in Table A3 below):

Visual representations	***Subordinate multimodal representations***			***Superordinate multimodal representations*** [¥]	
Task Events	*s2 – r1*	*s1 – r0*	*sx – r0*	*Chunk I*	*Chunk II*
Target	2.32	0.00	0.00	0.15	0.00
Standard	0.00	0.51	0.00	0.15	0.00
Novel	0.00	0.00	3.32	0.00	3.32

[¥] If only chunk I was assumed, all cells will equal 0 bits at this level of representation.

Table A3. *A priori* marginal and joint probabilities between task stimuli and their corresponding multimodal sensorimotor representations in Fig. 1.

Visual representations	***Subordinate multimodal representations***			***Superordinate multimodal representations***	
Task Events	*s2 – r1*	*s1 – r0*	*sx – r0*	*Chunk I*	*Chunk II*
Target ($P = 0.2$)	0.20	0.00	0.00	0.20	0.00
Standard ($P = 0.7$)	0.00	0.70	0.00	0.70	0.00
Novel ($P = 0.1$)	0.00	0.00	0.10	0.00	0.10