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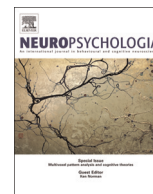
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A unilateral medial frontal cortical lesion impairs trial and error learning without visual control



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ABSTRACT

There is considerable debate regarding the involvement of the medial frontal cortex in motor and cognitive functions. Recent neuroimaging data suggest a fundamental underlying process that links the motor and cognitive roles of the mid-cingulate cortex (MCC), namely the processing of feedback during trial and error learning in the cingulate motor region that is related to the modality of the feedback. These data suggest that the specific motor context of a task may be a critical determinant of how its outcome is processed in the MCC. We assessed a patient before and after surgery for brain tumour removal in the medial frontal cortex, and a group of matched control subjects. Subjects had to find by trial and error the stimulus associated with the correct feedback amongst four or five similar stimuli. Subjects performed the task in two different visuo-motor contexts: with the response pad and hand visible and with no sight of either pad or hand. The patient showed a selective impairment in this task relative to control subjects in the hardest conditions and the impairment was most marked when the response pad and the hand were not visible. The results support a specific role of the medial frontal cortex in the construction of a sensorimotor representation of choices and related feedback by encoding the contingency between an efference copy of the action and its outcome.

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1. Introduction

Despite the frequent implication of the medial frontal cortex (MFC) in several psychiatric diseases, a precise understanding of its role is lacking because of poor understanding of the normal functions of its various subdivisions (Rushworth et al., 2004; Hikosaka and Isoda, 2010; Passingham et al., 2010). Within MFC, both the mid-cingulate cortex (MCC) and the pre-supplementary motor area (pre-SMA) contribute to the analysis of events that indicate a need for adaptation of behaviour in non-routine situations (Rushworth et al., 2004; Amiez et al., 2005, 2006; Nachev, 2006; Rushworth et al., 2007; Amiez and Petrides, 2009; Hikosaka and Isoda, 2010; Passingham et al., 2010; Etkin et al., 2011; Amiez

et al., 2012a; Amiez et al., 2012b; Rushworth et al., 2012; Amiez et al., 2013; Amiez and Petrides, 2014). Specifically, pre-SMA and MCC have been, respectively, associated with monitoring response competition and with error or action outcome processing (Ullsperger and von Cramon, 2001). Indeed, disruption of pre-SMA leads to an inability to inhibit pre-determined movement plans in complex situations (Nachev et al., 2007; Taylor et al., 2007), and pre-SMA activation appears to play a role in timing self-generated movements (Mueller et al., 2007). Concerning the MCC, both monkey and human lesion studies suggest a critical role in guiding voluntary choices based on task value or on the history of actions and their related outcomes (Williams et al., 2004; Amiez et al., 2006; Kennerley et al., 2006; Rudebeck et al., 2008; Wunderlich et al., 2010). Our own investigations in both human subjects and monkeys reveal that MCC is reproducibly activated during feedback time when feedback is relevant for adapting behavioural responses (Amiez et al., 2005; Quilodran et al., 2008; Amiez et al., 2012a, 2012b, 2013). By contrast, no involvement of pre-SMA for feedback processing has been reported in experiments with

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human subjects.

Although the precise roles of both these medial frontal regions (pre-SMA and MCC) remain to be specified, they are clearly both at the interface between cognition and action. Indeed, we recently provided evidence that in the MCC, and specifically the cingulate motor areas (CMAs), there is a conjunction of the processing of motor act and feedback within particular motor domains (Procyk et al., 2014), such that processing of the feedback can be said to be embodied. Based on this research, we hypothesised that processing in the MCC and pre-SMA is necessary to bind together motor action and the resultant feedback in exploratory situations when adapting of behaviour is required. This hypothesis provides a link to an unexpected behavioural deficit in performance monitoring that we observed in a patient with a MFC lesion. The patient was being tested, pre-operatively, in order to map out functional aspects of the MCC region invaded by a tumour occupying the MFC region, using functional Magnetic Resonance Imaging (fMRI). The patient was trained on a performance-monitoring task outside the scanner and then had to perform the same task in the scanner. Although his performance was excellent in the training session, it was very poor in the scanner. It appeared that the only difference between these two conditions was the sensorimotor context in which the task was performed: the subject could not see his hand that was making the motor selection when performing the task in the scanner, but he could when performing the task during training outside the scanner. We hypothesized that this patient had a significant deficit linking action to feedback, in light of our previous work, but that in the training task the patient was visually mediating the action–feedback link to compensate for the impairment. We here report a re-assessment of this patient outside the scanner, which confirmed our initial observations and showed striking long-lasting impairments in performance monitoring, particularly when the movements were not visually controlled.

2. Material and methods

2.1. Participants

2.1.1. Patient

The patient was a right-handed 46-year-old male with 16 years of education who was diagnosed with an infiltrating oligodendroglioma grade II–III located in the MFC in the right hemisphere after experiencing a strange numb sensation on his left arm and left side of his face. He reported that sometimes his “leg goes out of control”. Behavioural and neuropsychological testing was performed a few days before the surgery for brain tumour removal and 2 months after surgery. At the time of testing, the patient was not under medication.

The tumour invaded the MCC and pre-SMA region in the right hemisphere (Fig. 1), rendering this region largely dysfunctional. The post-operative MRI indicates that a portion of the superior frontal gyrus was resected involving both its medial and lateral surfaces. Thus, the MCC (involving parts of areas 24 and 32), the pre-SMA, and area 8B and possibly a small part of area 9 were resected. Note that the primary motor cortex and the SMA were not infiltrated by the tumour and were therefore not surgically resected.

2.1.2. Control subjects

The control group consisted of 9 right-handed subjects (6 females) matching on average the patient's age (42.2 ± 4.3 SD) and years of education (17.9 ± 3.1 SD). Informed, written consent was obtained from the patient and all the other participants according to the institutional guidelines established by the Ethics Committee of the Montreal Neurological Institute and Hospital.

2.2. Neuropsychological testing

The patient completed a battery of neuropsychological tests to evaluate his general level of cognitive functioning pre- and post-operatively. The patient was fluent in English, but his first language was Hebrew and it is possible that his performance on some verbal measures may have underestimated his level of functioning. General intellectual functioning was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The Abstract Word and Abstract Design List Learning Tasks (Jones-Gotman et al., 1997) were used to assess general verbal and nonverbal learning and memory, respectively. Language comprehension was assessed with the Token Test (De Renzi and Vignolo, 1962) and confrontation naming was evaluated with the Boston Naming Test (Kaplan et al., 1983). The Grooved Pegboard Test (Bryden and Roy, 2005) was used to assess fine-motor dexterity and visual-motor coordination. Finally, selective attention and cognitive flexibility were assessed with the Stroop Test (Spreen and Strauss, 1998). Additional tests were administered only post-operatively to investigate further possible deficits in executive functioning. These tests included measures of concept formation and cognitive flexibility (Wisconsin Card Sorting Test, Heaton et al.,

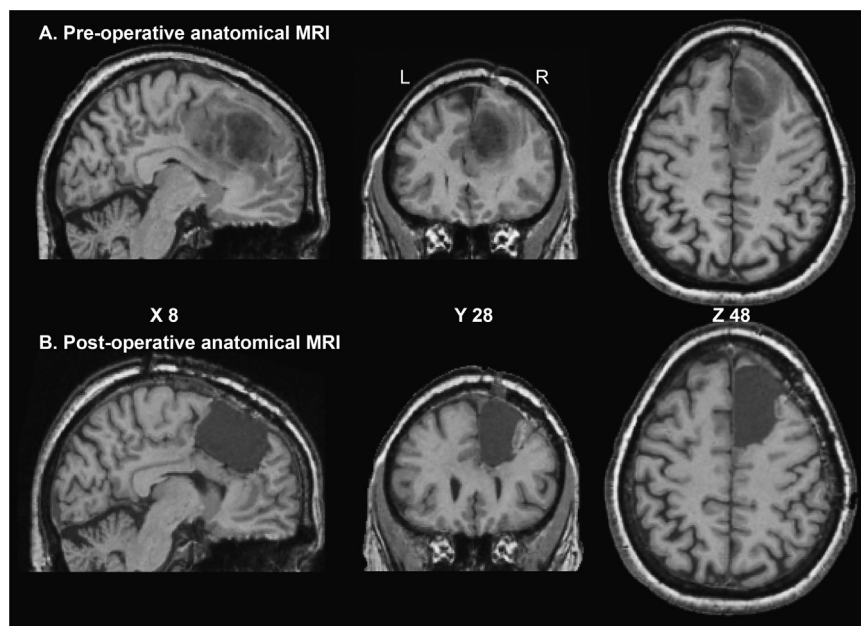


Fig. 1. The pre-operative (A) and post-operative (B) anatomical MRI scan of the patient. The location of the tumour (1 week pre-operatively) and of the surgical excision (2 months post-operatively) are shown on a sagittal view of the right hemisphere (at MNI x coordinate=8), a coronal view (at MNI y coordinate=28), and a horizontal view (at MNI z coordinate=48). Both the pre- and post-operative anatomical MRIs were registered to the MNI standard stereotaxic space. Abbreviations: L, left hemisphere; R, right hemisphere.

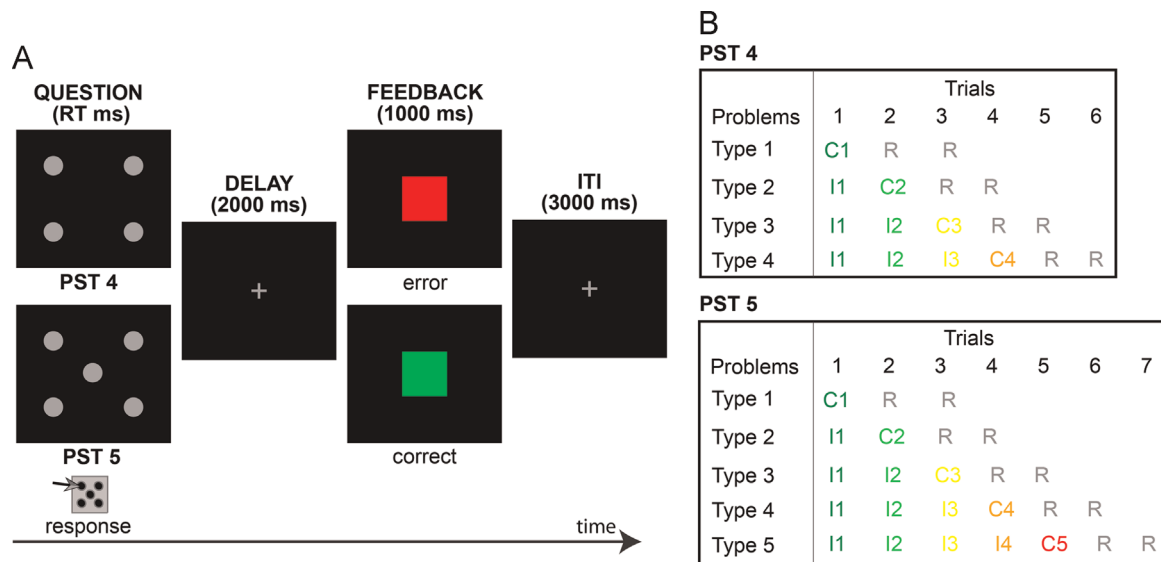


Fig. 2. Behavioural protocol (A) Four (PST4) or five (PST5) grey circles were simultaneously presented on the screen. The subject had to discover by trial and error, on successive trials, which one of the grey circles was associated with a positive feedback (green square), the other ones being associated with a negative feedback (red square). Once the correct grey circle was found, the exploration period ended and the subject had to start the exploitation period by selecting twice the correct stimulus. B. The sequence of feedback for each problem was pre-determined in a pseudo-random design, to vary parametrically the length of the exploration period. Every problem type finishes with the same sequence: a first correct feedback (C), followed by 2 repeated correct feedbacks (R). The problem types vary simply in the number of incorrect feedbacks (I) that are presented prior to the C. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1993), verbal or phonemic fluency (Thurstone's Verbal Fluency Test, [Thurstone and Thurstone, 1949](#)) and nonverbal fluency (The Design Fluency Test, [Jones-Gotman and Milner, 1977](#)).

2.3. Behavioural protocol

2.3.1. Problem-solving task

The patient and control subjects performed a problem-solving task (PST) which assesses the analysis of behavioural feedback in exploratory situations ([Quilodran et al., 2008](#); [Amiez et al., 2012b, 2013](#)). There were two versions of the PST: the "visible" version in which the response selection could be visually controlled (i.e. the response pad and the hand of the subject were on the table) and a "non-visible" version during which the response pad and the subject's hand were hidden under the table and, therefore, the response selection could not be visually controlled. Note that because the patient was right-handed, he performed the task with his right hand (i.e. ipsilateral to the lesion site).

The PST was performed with 4 (PST4) and 5 (PST5) stimuli ([Fig. 2A](#)). The four-stimulus task was performed first followed by the five-stimulus task. Four (or five) identical stimuli were presented on the computer screen and the subject had to select one of them by pressing the corresponding button on a 4-button (or a 5-button) response pad with his right hand. The response pad buttons matched the spatial positions of the four (or five) stimuli that were presented. After each selection on the response pad and a 2 s delay during which the stimulus display was replaced by a fixation cross, a feedback stimulus (a green or a red square) appeared for 1 s on the screen. After a 3 s inter-trial interval with the fixation cross on the screen, the same 4 or 5 stimuli were presented again so that the subject could make another selection.

The subjects had been instructed to discover, by trial-and-error over successive trials, the correct stimulus, namely the one stimulus selection of which resulted in the positive (green square) feedback, the other stimuli leading to error feedback (red square) ([Fig. 2A](#)). The exploration period was defined as the series of choices leading to the first correct selection. After the first correct choice, the exploitation period started during which the subject could select the correct stimulus on two further trials. After the exploitation period, a blue ellipse appeared for 500 ms, informing the subject that the previous set of trials (the combined exploration and exploitation trials) was completed and that now there would be a new correct stimulus that the subject would have to discover, again by trial and error (i.e. a new problem). The same 4 or 5 stimuli were used across the experiment.

Although, to the subjects, the task appeared to be driven by trial and error with a predetermined correct response in each problem, unbeknownst to the subjects it was the sequence of outcomes in a given problem (referred to as problem "type") that was predetermined, such that, regardless of the response of the subject, a set sequence of outcomes would result. These "types" can be seen in [Fig. 2B](#). Every problem type finishes with the same sequence: a correct feedback (C), followed by 2 repeated correct feedbacks (R). The problem types differed in terms of the number of incorrect feedbacks (I) that were provided to stimulus selections prior to the provision of the first correct feedback (C). In PST4, the responses followed by

incorrect feedback varied between 0 and 3 trials before the first correct feedback (C). As such, the exploration period varied in length in a controlled manner, and the exploitation period was always 2 trials long.

Note that these incorrect or correct feedback presentations were independent of the choice of the subject – any sequence of touches would elicit the same pre-determined sequence of feedback – although we observed behaviour demonstrating clear use of the feedback to adapt responses. This approach allowed us to obtain identical numbers of each problem length in a pseudo-random design, and was designed to avoid blocking in perseverative problems and associated frustration from the patient in case he exhibited dysexecutive syndrome after a frontal lesion ([Baddeley and Wilson, 1988](#)).

The key measure was the "correct problem". Optimal performance results from the change in choice after each incorrect feedback during exploration and then the maintenance of the correct choice (i.e. after the first positive feedback) during exploitation. As such, a correct problem contains no repetition of choices that received incorrect feedback in the exploration period, and no response shifts in the exploitation period. Performing a problem in this manner indicates that the subject understands and can use the feedback. Errors in exploration were, therefore, cases of repetition of a response that had been associated with an incorrect feedback earlier in the problem. Errors in exploitation were any deviation from the choice on the first correct (C) trial of that problem.

All testing was carried out, for the patient and control subjects, in two sensorimotor contexts. In the "visible" condition, the subjects could see the response pad and their hand on it clearly in front of them. In the "non-visible" condition, both the hand and the response pad were hidden from view. In most cases the response pad and hand were hidden under the table on the computer table drawer. In each case, the patient and subjects performed about 15 problems of each type in both the visible and non-visible conditions.

The patient was tested both pre- (about one week before surgery) and post-operatively (about 3 months after surgery). Pre-operative testing was carried out in two sessions. In session 1, the subject worked initially in the laboratory in the visible condition, and subsequently worked in the MRI scanner where the hand was not visible during testing (i.e. non-visible condition). Session 2 was added to confirm the hypothesis that the deficit was linked to lack of vision of the hand, and took place 2 days after session 1. In this session, the hand was under the table in the non-visible condition. Post-operatively, the patient performed the visible and non-visible conditions of the PST4 task, as pre-operatively. In addition, in order to further characterize the patient's deficit, he also performed PST5 both in the visible and non-visible conditions. Control subjects performed both the PST4 and the PST5 tasks, in the visible and non-visible conditions.

Note that, in both the visible and non-visible conditions of the task, responses are internally generated since the subject must choose an action that is not triggered by an external stimulus and all stimuli are identical.

2.3.2. Control spatial monitoring tasks

The MCC and the mid-dorsolateral prefrontal cortex (DLPFC) have strong reciprocal connections ([Vogt and Pandya, 1987](#); [Petrides and Pandya, 1999](#)) and there

is functional evidence that they strongly interact during the performance of the PST (Procyk and Goldman-Rakic, 2006; Quilodran et al., 2008; Amiez and Petrides, 2009; Rothe et al., 2011; Amiez et al., 2012a, 2012b). In addition, the DLPFC has been shown to be critically involved in the monitoring of both spatial and non-spatial information in working memory (Petrides, 1996, 2005). Because our spatial problem solving task requires spatial monitoring ability, and because after surgery the patient displayed a significant disconnection between the MCC and the DLPFC in the right hemisphere (Fig. 1B), we tested whether the deficit observed in the PST can be attributed to a spatial monitoring deficit. Hence the patient and control subjects were tested on a spatial version of the self-ordered monitoring task (Petrides, 1996, 2005).

Subjects were presented with 6, 8, 10, 12, 14, 16, and 18 grey squares differing in their spatial position (see Fig. 5A for the version of the task with 6 stimuli) in 6, 8, 10, 12, 14, 16, and 18 successive trials, respectively. These stimuli were presented on sheets of paper. In the first trial, the subject was required to select one of the stimuli by touching it with the index finger of his right hand. Then, the experimenter turned over the next page that displayed the same stimuli. In the following trials, the subject had to select any one of the other stimuli, except for those previously selected. The testing continued like this until all the trials were completed (Petrides, 2005). Each one of the 7 versions of the task was performed three consecutive times. Example performance in the version with 6 stimuli is displayed in Fig. 5A. Note that, in this monitoring task, the subjects could see their responding hand and we did not test the subjects with their hand not being visible.

3. Results

3.1. Neuropsychological testing

No significant differences in performance were observed between the pre- and post-operative neuropsychological assessment on all cognitive measures. The patient had a Full-Scale IQ rating in the average range both pre- and post-operatively (109 and 107, respectively). Similarly, learning and memory for verbal and nonverbal material, language comprehension, selective attention

on the Stroop Test, and cognitive flexibility as assessed with the Stroop Test (pre- and post-operatively) and the Wisconsin Card Sorting Test (post-operatively) were within normal limits. Only confrontation naming was impaired at similar levels pre- and post-operatively. Given that the first language of the patient was not English, the patient's score on this task might have underestimated his verbal abilities. The pre-operative assessment of the patient's manual dexterity using the Grooved Pegboard Test revealed scores within normal limits for the dominant (right) hand with a decline in performance that was below average post-operatively. Impaired performance was observed pre- and post-operatively on the Grooved Pegboard Test for the non-dominant hand, which is consistent with the location of the tumour and resection.

3.2. Performance on the PST

The patient's performance was severely impaired in the non-visible condition compared with the visible condition (Fig. 3A). This deficit was observed pre-operatively in the PST4 and post-operatively in both the PST4 and PST5 ($F(4, 2897)=13.386$, $p < 10^{-5}$, factorial ANOVA with sessions (pre-op PST4, post-op PST4, post-op PST5, control PST4 and control PST5) and position of the hand/pad (visible and non-visible) as factors). Control subjects displayed no difference in performance between the visible and non-visible conditions in either PST4 or PST5 (ns at $p < 0.05$, Newman-Keuls post-hoc analysis), but the patient displayed impaired performance in non-visible as compared with the visible condition ($p < 10^{-4}$). In addition, the patient's pre- and post-operative performance was lower than that of the control subjects in

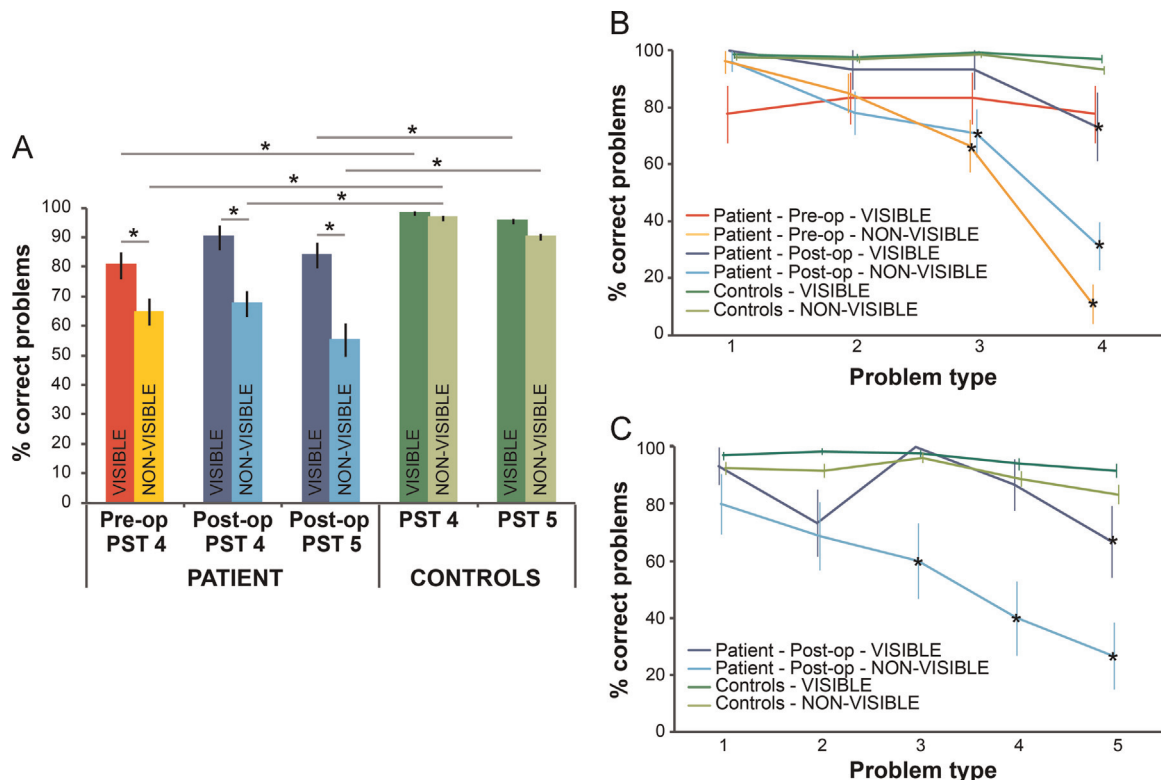


Fig. 3. Performance in the problem solving tasks. A. Global pre-operative and post-operative patient performance as well as control subjects' performance in PST4 and PST5 in visible and non-visible conditions. The patient was mildly impaired when the patient performed the tasks when he could see his hand, and more seriously impaired when he could not see it. B. Performance in the different types of PST4 problem, in both conditions. In the visible condition, control subjects' and the pre-op patient's performance were similar in all problem types. The patient showed a mild impairment post-op in type 4 problems. In the non-visible condition, the patient's performance significantly dropped off both pre- and post-op when the exploratory period was ≥ 3 trials. C. Performance in the different types of PST5 problem in each condition, for controls and the patient post-operatively. As in PST4, the major impairment was noted in the non-visible condition for the patient for the longest exploratory periods. Abbreviations: pre-op, pre-operative; post-op, post-operative; PST, problem solving task.

the non-visible condition ($p < 10^{-4}$) and, to a lesser extent, in the visible condition ($p < 10^{-2}$).

Importantly, this deficit was greater for longer exploration periods (PST4: $F(6, 1408) = 11.023$, $p < 10^{-5}$ (Fig. 3B)), factorial ANOVA with problem types (1, 2, 3, and 4), sessions (pre-op PST4, post-op PST4, and control PST4), and motor context (visible and non-visible as factors); PST5: $F(4, 1455) = 3.4547$, $p < 8 \cdot 10^{-3}$ (Fig. 3C, factorial ANOVA with problem types (1, 2, 3, 4, and 5), sessions (post-op PST5 and control PST5), and motor context (visible and non-visible) as factors). Specifically, in the non-visible condition the patient's performance differed from the control subjects for exploration periods ≥ 3 trials in both the PST4 and PST5 (at $p < 10^{-4}$, Newman–Keuls post-hoc test, Fig. 3C). In the visible condition, a slight drop in the patient's post-operative performance was observed in the longer exploration periods in both PST4 and PST5, as compared to control subjects' performance (i.e. in type 4 PST4 problems and in type 5 PST5 problems, at $p < 0.05$).

We observed that the patient selected less frequently the bottom right button specifically in the non-visible condition of the PST4 task. However, this effect was not observed either in the visible condition of the PST4 task or in the visible and non-visible conditions of the PST5 task. Hence, this fact cannot explain the observed deficits.

To identify the type of errors committed by the controls and the patient, we calculated the average number of errors performed per problem separately for each rank of trial in the exploration period (I and C in Fig. 2B), and also for the exploitation trials (R in Fig. 2B). The patient committed more errors per problem than control subjects in the non-visible versus the visible condition during both the exploration and the exploitation periods of the task ($F(5, 10263) = 11.699$, $p < 10^{-6}$), factorial ANOVA with subject type (i.e. controls and patient), motor condition (visible and non-visible), and trial type (C1/I1, C2/I2, C3/I3, C4/I4, C5 explorative trials, and exploitative trials) (Fig. 4A). Post-hoc analysis revealed that the longer the exploration period, the higher the mean number of errors/problem ($p < 10^{-4}$, Newman–Keuls post-hoc test) made by the patient in the non-visible condition. In the visible condition, the patient committed more errors per problem than control subjects only in the last trials of long exploration periods (i.e. in C4/I4 trials, at $p < 10^{-3}$).

We further assessed the percent of exploratory and exploitative trials in which the optimal strategy was used. In the exploration period, the correct strategy is a “lose-shift” strategy, and the incorrect strategy is a “lose-stay” strategy. In the exploitation period, the correct strategy is a “win-stay” strategy, and the incorrect strategy is a “win-shift” strategy. Data show that the patient is impaired in the ability to select the good strategy in both the exploration and exploitation periods of the task ($F(1, 11165) = 15.451$, $p < 9 \cdot 10^{-5}$, factorial ANOVA with subject type (controls and patient), motor condition (visible and non-visible), and task periods (exploration and exploitation) as factors) (Fig. 4B). This impairment is observed in the visible condition, but is particularly striking in the non-visible condition (at $p < 0.001$, Newman–Keuls post-hoc test).

Interestingly, whereas control subjects reported having detected a few instances of incorrect responses when the feedback was not the expected one (e.g., they had realized that they made an incorrect response but the associated feedback was positive instead of negative; because of the pre-defined feedback delivery), the patient never reported such a detection of mis-match between incorrect responses and the feedback that followed.

3.3. Performance in the spatial monitoring task

The patient's performance on the spatial monitoring task was

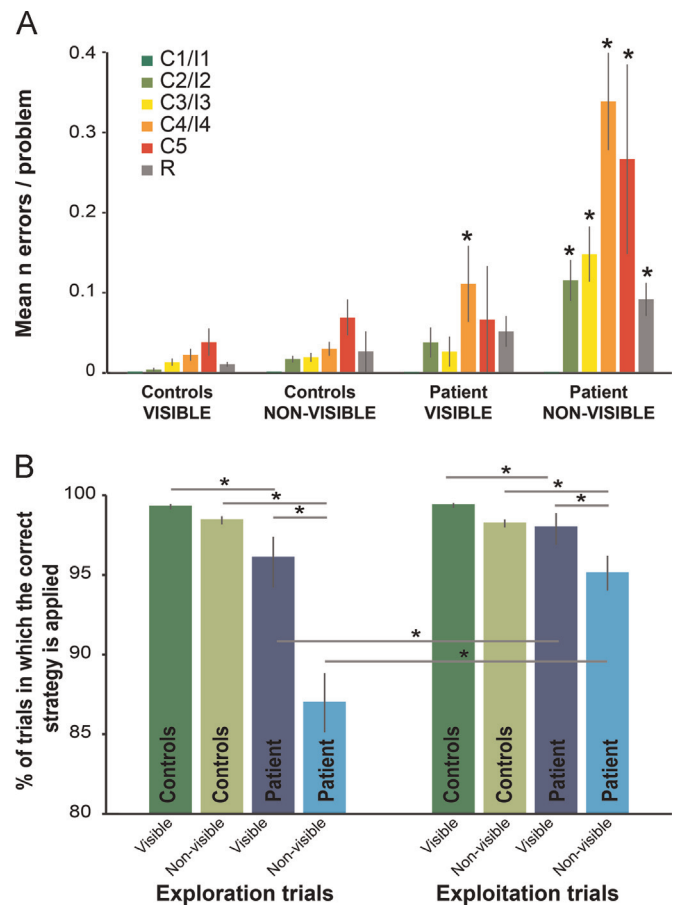


Fig. 4. A. Mean number of errors committed across problem types. The patient makes significantly more errors, particularly in the non-visible condition. B. Percent of trials in which the correct strategy was used in the exploration (i.e. percent of lose-shift strategy) and exploitation periods (i.e. percent of win-stay strategy). Abbreviations: n, number; C, first correct exploration trial, I, incorrect exploration trial, R, repetition trials.

impaired compared with the performance of the control subjects ($F(6, 196) = 7.0664$, $p < 10^{-5}$, factorial ANOVA with patient/subjects and number of stimuli to monitor [6, 8, 10, 12, 14, 16, and 18] as factors) (Fig. 5B). Recall that each one of the 7 difficulty levels of the monitoring task was repeated 3 times. The patient's mean number of errors committed at each difficulty level was significantly greater than those of the control subjects when stimuli were 12 or greater, i.e. performance was impaired on the more difficult versions of the task ($p < 7.10^{-5}$, $p < 2 \cdot 10^{-5}$, and $p < 2 \cdot 10^{-5}$ for 14, 16, and 18 stimuli, respectively).

4. Discussion

A patient with resection of a tumour invading the MFC showed a robust and long-lasting impairment on the performance of a trial and error learning task that required exploration of alternative stimuli to find the correct one. Two important aspects characterized the patient's impairment: (a) it emerged in longer periods of the exploration task, and (b) it was much greater when the motor selection was not visually controlled, both before and after surgery.

The deficit cannot be attributed to a simple motor deficit or inability to map the stimuli on the screen to the corresponding buttons on the response pad, since short exploration periods ($n \leq 2$, Figs. 3B, C and 4A) were performed appropriately even in the non-visible condition. This impairment cannot also be

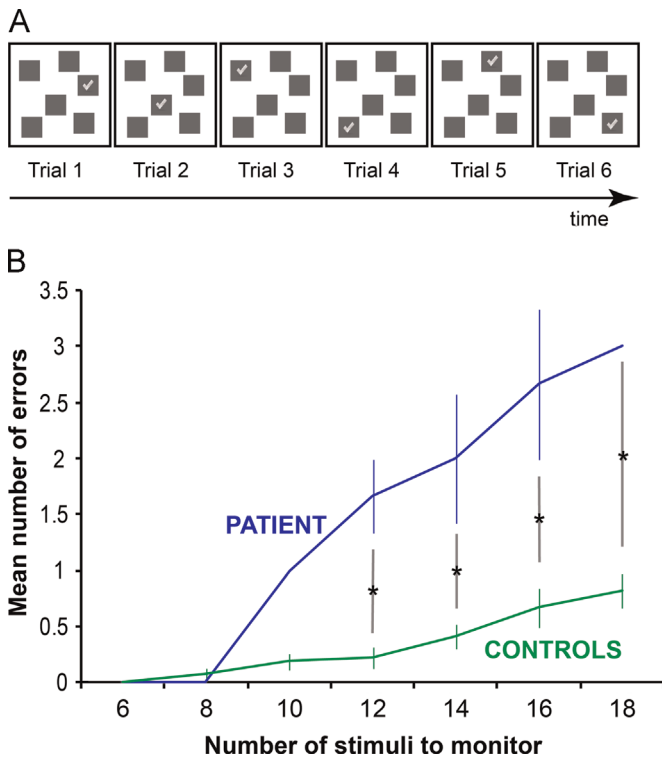


Fig. 5. Behavioural protocol (A), and patient/control subjects' performance in the spatial monitoring task (B). A. The behavioural protocol is displayed for the version with 6 stimuli. Six grey squares are presented on a sheet of paper and the subject selects one of the stimuli and points to it, turns over to the next page where the same stimuli are displayed in order to select another stimulus. On successive trials, the subject can select any one of the previously not chosen stimuli. In the example shown here, each choice of the subject is indicated with a toggle mark, but during testing these marks were not indicated and the subject had to track these choices in working memory. There were 6 trials for this 6 stimulus set. B. Mean number of errors committed in each version of the task, each version being performed three times. Spatial monitoring deficits emerge in the patient when the number of stimuli to monitor is greater than or equal to 12. Bars represent s.e.m. Asterisks represent statistical differences at $p < 0.001$ (post-hoc Newman–Keuls test).

attributed to pure motor deficits or to general attentional or mnemonic deficits as indicated by the normal performance of the patient on the relevant tests of the neuropsychological battery. Finally, the deficit is not secondary to an inability to monitor spatial information in working memory. The patient was only impaired when 12 or more spatial stimuli had to be monitored (Fig. 5) and it should be remembered that only 4 and 5 spatial stimuli were used in the problem solving task (Fig. 4). The lesion of the patient caused major disconnection between the lateral mid-dorsolateral prefrontal region (areas 46 and 9/46) that is known to be critical for the monitoring of information in working memory (Petrides 2005). The LPFC and MCC are strongly interconnected (Sallet et al. 2011) and often display functional synergies (Rothe et al., 2011; Khamassi et al., 2014). In monkeys, performance of the PST is accompanied by activity in both MCC and LPFC that reflects a collaborative role of these regions in a working memory monitoring and response action control loop. One hypothesis of the interaction of these areas is that, during trial and error exploratory behaviour, the MCC processes feedback-related information, transfers this information to the LPFC, which in turn biases decision making (Rothe et al., 2011; Khamassi et al., 2014). One explanation for an absence of deficits in the self-ordered task for less than 5 items and a presence of strong deficits for larger numbers might be the relative absence of load on the monitoring loop for small numbers. Manipulating and ordering choices with a larger number of items might rely more on self-monitoring and

adaptation and thus might be altered by the MCC lesion. Further support that the LPFC and MFC are both involved in the performance of such monitoring is provided by the demonstration of differential impairments targeted with the 2-back task in patients with such lesions (Tsuchida and Fellows, 2009).

Most current theories suggest a role of MCC in adaptive mechanisms. The reinforcement learning theory suggests that an interaction of cingulate motor areas and of the afferent dopaminergic axons produces error signals triggering adaptive decisions (Holroyd and Coles 2002). The conflict theory, recently updated as the Expectancy Violations Theory (EVT) theory, suggests a role for MCC in processing signals used to regulate control functions (Botvinick et al., 2001; Shenhav et al., 2013). The Prediction of Response Outcome (PRO) model emphasises that MCC establishes predictive response-outcome mappings allowing detections of surprising outcomes and adaptation of behaviour (Alexander and Brown 2010). But such theories have been regularly challenged because MCC lesions in humans were rarely associated with convincing deficits of adaptive action. Holroyd and Yeung (2012) have recently argued that such ambiguous results in trial-and-error learning tasks observed after MCC lesions suggest that MCC is not involved in simple reinforcement learning for precise action, but in high level selection of behavioural options, at the level of tasks rather than actions.

Recently however, MCC lesions were shown to induce deficits in the ability to adapt action selection based on feedback, but not in stimulus selection (Camille et al., 2011). Patients with orbito-frontal cortical lesions display the opposite pattern of deficits (Camille et al., 2011). This suggests a specific role for MCC in dealing with the contingencies between actions and outcomes, a conclusion that fits with our observation. However, in our study, the deficits were small when the patient could see his hand for choice selection. This might be explained by differences in protocols. The task used by Camille et al. (2011) required subjects to evaluate the probability of feedback contingencies, whereas the problem solving task is deterministic. Further, Camille et al. (2011) included patients with acute lesions such as ischaemic stroke or aneurysm rupture that would involve more significant frontal disruption including ventromedial frontal function. Patients with acute lesion may therefore have more pronounced deficits than patients with surgical resection of slow growing low-grade tumours.

MCC lesions also alter online error prediction and subsequent correction of erroneous responses (Modirrousta and Fellows, 2008; Wessel et al., 2014). Here we show that such lesions also induce impairments in feedback-based adaptation tasks. Modirrousta and Fellows (2008) reported that patients rated themselves as highly confident just prior to performing false alarms. The patient in our study also reported high confidence in his performance at the end of each session in both the visible and non-visible conditions. This high level of confidence may result from a failure to realise the dissociation between the motor response and the feedback in the task.

The most striking impairment in our study was the effect of the “non-visible” condition in which the hand making the choice was unseen. Appropriate performance in the PST requires the ability to integrate the successive actions and feedback to adapt behaviour properly after errors and after discovery of the correct response (Procyk and Goldman-Rakic, 2006; Quilodran et al., 2008). Several sources of correlative evidence in monkeys and humans suggest that action-feedback contingency processing involves maps in MCC (Procyk et al., 2014). In human fMRI, juice feedback responses co-localise with voluntary tongue motor control to the CMAR (Amiez et al., 2013). In monkeys, neurophysiological responses to juice feedback co-localize with orofacial motor areas in MCC. Hence, MCC processes feedback with specific subdivisions of

CMAr. Although the consequence of this functional overlap remains elusive, we suggest that it might serve to monitor the contingencies of choices and feedback, and to integrate decision/action-related information as internal feedback of behaviour, especially during adaptive behaviour. This would explain the patient's deficit in the non-visible condition by an inability to link the somatosensory feedback of action, or the efference copy, with the contingent performance feedback. The fact that MCC receives information from efference copy is in line with its suggested role in producing the error-related negativity (Holroyd and Coles, 2002), although the specific role of MCC in such a physiological marker is debated (Bonini et al., 2014).

It is important to remember that deficits were observed while the subject used his preferred hand, ipsilateral to the lesioned hemisphere. We did not test the patient with his contralateral hand because the basic motor deficits observed during its use (as assessed with the Pegboard test) might have prevented us from disentangling motor from cognitive deficits in the problem-solving task. It is difficult to predict which cognitive deficits would accompany the use of the contralateral hand given that the impact of the laterality of cingulate motor areas is not known.

The deficit in monitoring the contingency of decision, actions and performance feedback, could be remedied for in the visual context by oculomotor strategies (scanning) that would allow maintaining objective links between actions and performance feedback. The identification of potential compensatory strategies used to solve the task may thus benefit from eye movement recordings in future studies. Hence the impairment is clearly observed at its fullest in the non-visible condition.

The above interpretation must also be associated to the fact that neuronal recordings in MCC show little, if any, information related to the specific action to be made after a particular feedback. On the contrary, data and theory suggest that the outcome of the process in MCC serve the orientation of broad classes of adaptation or strategies (Quilodran et al., 2008; Holroyd and Yeung, 2012). Thus taken together the present data and current knowledge on MCC suggest that feedback from action, outcome, and their contingency are used in MCC to trigger adaptive strategies but not specific corrective action.

In conclusion, the effect of 'non-visible' condition and the effect of search length suggest a combined influence of the lesion on the integration of feedback history and on the binding of action feedback to adapt decisions. The MCC/preSMA lesion induces a deficit in assigning outcomes to specific choices, a function that is naturally performed within the sensorimotor frame of reference. As such, our results support a critical role of the MFC in the construction of a sensorimotor representation combining selection choices and outcomes and in the updating of these representations when choices, modalities, and feedback contingencies change.

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