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Anterior cingulate cortex and cognitive control: Neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex

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Abstract

Whereas neuroimaging studies of healthy subjects have demonstrated an association between the anterior cingulate cortex (ACC) and cognitive control functions, including response monitoring and error detection, lesion studies are sparse and have produced mixed results. Due to largely normal behavioral test results in two patients with medial prefrontal lesions, a hypothesis has been advanced claiming that the ACC is not involved in cognitive operations. In the current study, two comparably rare patients with unilateral lesions to dorsal medial prefrontal cortex (MPFC) encompassing the ACC were assessed with neuropsychological tests as well as Event-Related Potentials in two experimental paradigms known to engage prefrontal cortex (PFC). These included an auditory Novelty Oddball task and a visual Stop-signal task. Both patients performed normally on the Stroop test but showed reduced performance on tests of learning and memory. Moreover, altered attentional control was reflected in a diminished Novelty P3, whereas the posterior P3b to target stimuli was present in both patients. The error-related negativity, which has been hypothesized to be generated in the ACC, was present in both patients, but alterations of inhibitory behavior were observed. Although interpretative caution is generally called for in single

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bandc.2012.07.008>.

case studies, and the fact that the lesions extended outside the ACC, the findings nevertheless suggest a role for MPFC in cognitive control that is not restricted to error monitoring.

Keywords

Anterior cingulate cortex; Prefrontal cortex; Executive function; Event-related potentials; Cognitive control; Novelty P3

1. Introduction

The role of the frontal lobes in top-down controlled information processing has been thoroughly documented (Duncan & Owen, 2000; Knight & Stuss, 2002; Stuss & Alexander, 2000) and there is increasing evidence that executive control is implemented by distributed networks of closely interacting, but anatomically dissociable areas (Stuss & Alexander, 2007). Major functional distinctions are commonly drawn between the dorsolateral, orbital and medial prefrontal cortex (MPFC). While the dorsolateral prefrontal cortex is associated with cognitive executive control and top-down processes (Miller & Desposito, 2005; Voytek & Knight, 2010a), the orbital division plays a major role in control of social and emotional behavior (Knight & Stuss, 2002; Stuss & Levine, 2002). Exploration of the role of MPFC in general, and the anterior cingulate cortex (ACC) in particular, has evoked great interest over the past decade.

The extensive connectivity of the MPFC and ACC with cortical and sub-cortical brain areas puts this region in a key position for top-down modulation of behavior (Devinsky, Morrell, & Vogt, 1995). A functional subdivision in a primarily rostral “affective” and a dorsal “cognitive” division of the ACC has been described (Bush, Luu, & Posner, 2000; Mohanty et al., 2007), although such a dichotomy might represent an oversimplification (Etkin, Egner, & Kalisch, 2011). MPFC is proposed to play a critical role in the operations of the anterior attentional system responsible for the maintenance of an alert state (Posner & Petersen, 1990), and superior MPFC lesions have been shown to affect the capacity for task monitoring and maintenance of stable performance (Shallice, Stuss, Alexander, Picton, & Derksen, 2008). A multitude of proposals regarding the specific role of ACC in executive control have emerged, typically converging on a key role in conflict detection, performance monitoring and response-selection (Alexander & Brown, 2010; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). It has, however, been a challenge to provide a synthesized account of existing data and theoretical proposals (Ridderinkhof, Nieuwenhuis, & Braver, 2007).

Knowledge regarding the role of the ACC in cognitive control has derived largely from neuroimaging studies of healthy subjects (Cabeza & Nyberg, 2000; Carter et al., 1998). The Stroop color-word interference task is the neuropsychological test typically used to measure the ability to override a prepotent response in a cognitive conflict situation (Delis, Kaplan, & Kramer, 2001). ACC activation has been demonstrated during Stroop performance in both Positron Emission Tomography (PET) (Pardo, Pardo, Janer, & Raichle, 1990) and functional Magnetic Resonance Imaging (fMRI) studies (Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004). Involvement of the ACC has also been suggested in long-term

consolidation of memories, as it has been demonstrated that as memory traces are consolidated over time, reduced activity in the hippocampal formation is associated with an increased activity in MPFC in both rodents and humans (Frankland & Bontempi, 2005; Takashima et al., 2007). A role for ACC in attention and reward-based learning has also been suggested in both human and macaque studies (Hayden, Heilbronner, Pearson, & Platt, 2011; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011).

Event-Related Potential (ERP) studies have demonstrated an error-related negativity that peaks over fronto-central electroencephalographic (EEG) recording sites 60–80 ms after an erroneous response (Danielmeier & Ullsperger, 2011; Danielmeier, Wessel, Steinhauser, & Ullsperger, 2009; Edwards, Calhoun, & Kiehl, 2012). The error-related negativity is typically followed by a positive component, the “error-positivity” (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Simons, 2010). EEG source analysis (van Veen & Carter, 2002), magnetoencephalography (Miltner et al., 2003), fMRI (Nieuwenhuis, Schweizer, Mars, Botvinick, & Hajcak, 2007), as well as animal studies (Emeric et al., 2008; Gemba, Sasaki, & Brooks, 1986) have suggested that the error-related negativity is generated in the ACC.

A dynamic relationship between ACC and dorsolateral prefrontal cortex has been proposed in which the main role of the ACC is detection and evaluation of conflict, thus providing input to the top-down attentional dorsolateral system, where the actual stimulus manipulation and attentional maintenance and control is performed (MacDonald, Cohen, Stenger, & Carter, 2000; Walsh, Buonocore, Carter, & Mangun, 2011). The error-related negativity of patients with lateral prefrontal lesions does not differ between erroneous and correct responses as in healthy subjects (Gehring & Knight, 2000), demonstrating a dynamic interaction between the two frontal subregions.

Lesion studies have not uniformly confirmed predictions derived from imaging studies of healthy subjects (Nachev, 2006; Ridderinkhof et al., 2007). One study with a fairly large sample ($N = 8$) demonstrated that patients with rostral ACC lesions failed to modulate performance depending on the level of conflict in a Simon task, and that they did not display the expected slowing of reaction times following errors (post-error slowing) (di Pellegrino, Ciaramelli, & Ladavas, 2007). In five patients with MPFC lesions resulting from aneurysms of the anterior communicating artery, the error-related negativity was absent in most, but not all patients (Stemmer, Segalowitz, Witzke, & Schonle, 2004). In one patient with a left rostral to mid-ACC lesion, a reduced midline errorrelated negativity was demonstrated, whereas stimulus-locked ERPs in successful inhibition trials were normal (Swick & Turken, 2002).

Studies of Stroop performance after ACC damage have also produced mixed results. One patient with a right dorsal ACC lesion displayed normal results for vocal response delivery, whereas manual response delivery was impaired (Turken & Swick, 1999). A later study adding a second person with a left rostral – to mid-ACC lesion (Swick & Jovanovic, 2002) showed reduced accuracy in incongruent trials for the patient with left – but not the one with right-ACC lesion. Stuss, Floden, Alexander, Levine, and Katz (2001) demonstrated an association between bilateral superior MPFC injury and increased error rate as well as

reaction times in the incongruent Stroop-condition, whereas Vendrell and colleagues (Vendrell et al., 1995) found that right LPFC but not ACC injury was associated with an increased error rate.

In summary, controversy remains on the exact role of the ACC in cognition. One hypothesis that is largely based on case-studies of patients with ACC lesions is that the ACC is not involved in cognitive processing per se, but rather plays a role in linking cognitive control processes subserved by other prefrontal regions to autonomic arousal. Fellows and Farah (2005) described 4 patients with dorsal ACC lesions resulting from strokes who displayed normal Stroop and Go/NoGo performance, as well as a normal post-error slowing and performance adjustment after changing task instructions. A patient with a large left frontal lesion that included the ACC had largely normal behavioral performance on a task demanding executive control, but decreased skin conductance response (Naccache et al., 2005). Moreover, Critchley et al. (2003) demonstrated an association between ACC activation and modulation of heart-rate during cognitive and motor-tasks in healthy subjects. In the same paper, three patients with rostral and dorsal ACC-lesions demonstrated blunted autonomic reactions during working-memory performance. Of particular relevance to the current paper is a later publication of neurocognitive functioning in two of the three patients from the Critchley et al. study (Baird et al., 2006). One presented with a unilateral right ACC lesion, with additional right hemisphere frontal involvement, whereas the second patient had bilateral ACC-affected with widespread additional frontal damage. Only minor cognitive impairment was found in a few of the tests of executive functions employed, and prolonged reaction times were seen in attention tasks, although not on the same measures. The findings were taken to support the hypothesis that the ACC does not have a primary role in cognitive control.

Thus, despite extensive interest in the function of the ACC over the past decade, controversy and diverging findings persist. It has both been suggested that the ACC plays a generally vital role in cognitive control (Botvinick et al., 2001; Ridderinkhof et al., 2004; Shallice et al., 2008), that it has a very distinct role in error monitoring (Fan et al., 2007; Pailing & Segalowitz, 2004; Swick & Turken, 2002), and finally that the ACC is actually not involved in cognitive operations (Baird et al., 2006; Critchley et al., 2003). The present study provides neuropsychological, behavioral and electrophysiological data from two patients with unilateral dorsomedial frontal lesions that included the ACC. The lesions were comparable to those presented by Critchley et al. (2003) and Baird et al. (2006) in anatomical location and extent. The main goal was to examine behavioral and electrophysiological indices of neurocognitive functioning following ACC injury. A specific aim was to investigate Baird et al.'s (2006) proposition that the ACC is not involved in cognitive processing. As a distinct role of ACC has been proposed in attentional shifting (Crottaz-Herbette & Menon, 2006), we used an auditory Novelty Oddball task to study novelty and target detection (Polich, 2007; Soltani & Knight, 2000). Additionally, a Stop-signal task allowed investigation of behavioral and neurophysiological correlates of inhibitory control and error monitoring (Aron et al., 2007; Schmajuk, Liotti, Busse, & Woldorff, 2006). In line with existing knowledge of neuropsychological test limited sensitivity to the effect of frontal lobe lesions (Knight & Stuss, 2002; Løvstad et al., in press), it was hypothesized that the neurophysiological measures might reveal signs of

altered information processing not evident in neuropsychological test results. It was predicted that lesion-related alterations of motor-inhibition, error-monitoring and novelty processing would be observed. Of particular interest was whether patients with unilateral ACC lesions would exhibit the error-related negativity and the post-error slowing of reaction times.

2. Methods

2.1. Patients

The patients participated in a research program at Oslo University Hospital investigating the effects of focal frontal lobe lesions. See Fig. 1 for MRI scans depicting the lesions.

Patient 1 is a right-handed male in his mid thirties with 12 years of formal education. He was assessed 20 months after surgical removal of a right frontal low-grade glioma. The lesion included medial, dorsal and rostral ACC (BA 24 and 32), with marginal involvement of BA 25. In addition to involvement of posterior medial frontal cortex (BA 6 and 8), the lesion extended towards polar and ventral prefrontal areas (BA 9 and 10, and to a limited degree BA 46).

Patient 2 is a right-handed male in his thirties who completed 15 years of formal education. A low-grade glioma in the left hemisphere was resected 10 months prior to study inclusion. The lesion predominantly affected rostral, but also medial ACC (BA 24 and 32). Additional damage was seen in BA 9 and 10, as well as corpus callosum, and scarred tissue was observed dorsally along the corpus callosum.

2.2. Controls

Neuropsychological performance of the patients was compared to a healthy control group consisting of 21 persons with a mean age of 42.9 years (SD 11.9) and mean length of formal education of 13.5 years (SD 2.3). The control group consisted of 11 females and 10 males, of whom 20 were right-handed.

2.3. Consent and ethics

Participants gave informed consent to participation. Controls received 500 NOK (approximately 80 USD) for participation in the entire research program (neuropsychological assessment, EEG, structural and functional MRI). The study was approved by the Norwegian Regional Committee for Medical Research Ethics, Region South.

2.4. Measures

2.4.1. Functional outcome and neuropsychological performance—Functional outcome was classified using the Glasgow Outcome Scale Extended (GOS-E) (Wilson, Pettigrew, & Teasdale, 1998), a hierarchical scale in which the patient's overall functional outcome is estimated based on the lowest item score obtained.

Full scale, verbal and performance IQ were established based on all 4 subtests of the Wechsler Abbreviated Scale of Intelligence; Vocabulary, Similarities, Block Design and Matrix Reasoning (WASI; Wechsler, 1999). Digit Span and Letter–Number Sequencing from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997) were included as measures of attention and working memory. Verbal learning and memory was assessed with the California Verbal Learning Test Second Edition (Delis, Kaplan, Kramer, & Ober, 2000). Visuospatial learning and memory was examined with the Brief Visuospatial Memory Test-Revised (Benedict, 1997). The following subtests from the Delis–Kaplan Executive Function System (D–KEFS; Delis et al., 2001) were included: Trail Making Test, Design Fluency, Verbal Fluency, and Color-Word Interference Test (CWI).

2.4.2. Self- and informant report measures—Self-reported symptoms of executive problems in everyday living were assessed with the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A; Roth, Isquith, & Gioia, 2005). A close relative of the patients completed the informant version. The Symptom Checklist 90-Revised (Derogatis, 1994) was used to screen for psychopathology and emotional distress.

2.4.3. Experimental measures—Two experimental tasks were administered along with simultaneous EEG recordings. See Appendix A for a detailed description of EEG recording, experimental tasks, and ERP-analysis.

2.4.3.1. Target and Novelty detection: Target and novelty detection was studied in an auditory Novelty Oddball task where the subjects were instructed to respond with a button press to auditory deviants, while ignoring standard tones as well as rare and unique environmental sounds (Løvstad et al., 2012).

2.4.3.2. Behavioral inhibition and performance monitoring: Behavioral correlates of response inhibition and neurophysiological indices of error processing were studied in a visual Stop-signal task where a button-press was required after presentation of left- or right-pointing arrows, while motor-inhibition was required when the arrows were followed by a visual stop-signal.

2.4.4. Statistical computations—Patient scores on neuropsychological and self-report measures, behavioral data from the experimental tasks, and ERP amplitudes were compared to the mean scores of the control group. In order to reduce the risk of type I errors, *T*-scores with corresponding *p*-values (Bhattacharyya & Johnson, 1997) were computed as recommended by Crawford and Garthwaite (2011). This procedure takes the sample size of the control group into account, thus treating the control group as a statistical sample and not as a true population, as is the case if the common procedure of direct comparison to the standard deviation (SD), confidence intervals or *z*-scores of the control group is followed.

$$t_{n-1} = \frac{X^* - \bar{x}}{S \sqrt{\frac{n+1}{n}}}$$

X^* represents the patient individual score whereas $\bar{x}$ is the mean and s is the standard deviation of the control group. Results are reported with a significance level of .05. However, there is inherent uncertainty associated with the interpretation of and generalization from single case studies. In order to discuss trends in the results, we also report findings at $\alpha = 0.1$ level.

As recommended by Crawford, Garthwaite, and Porter (2010), an index of effect size was computed as an estimate of the average difference in standard deviation units between a case's score and the score of a randomly chosen member of the control group:

$$Z_{CC} = \frac{x - \bar{x}}{S_x}$$

3. Results

3.1. Functional outcome

Patient 1 scored 7 (Lower Good Recovery) and patient 2 scored 8 (Upper Good Recovery) on the GOS-E. Both patients were in full-time paid work at the time of study inclusion. Neither of the patients had any total- or subscale T -scores above 55 on the Symptom Checklist 90-Revised, indicating that they did not display significant psychopathology at the time of assessment.

3.2. Neuropsychological performance

Neuropsychological data for the healthy control group and patients 1 and 2 are reported in Table 1a-e. Patient 1 displayed significantly reduced Verbal IQ, with a tendency towards reduced total IQ, whereas patient 2 had above average IQ, although not significantly different from the control group. The patients tended to differ from the control group on Digit Span forward, but in different directions; patient 1 with a trend towards lower and patient 2 towards higher scores.

On the memory measures, patient 1 showed significantly impaired learning and long term free recall performance on both verbal and visual memory tests, as well as an increased false alarm rate on the Brief Visuospatial Memory Test-Revised (elevated response bias score). Patient 2 tended towards reduced short- and long-term free verbal recall. Given IQ in the high normal range, a short- and long-term verbal recall 1–1.5 SD below the control group mean would not be expected in healthy subjects, thus these results are considered to be of potential clinical interest (Lezak, 1995).

Patient 1 tended towards reduced performance on the switching condition of the Verbal Fluency task (condition 3). Patient 2 displayed a impairment of the Visual Scanning condition of the Trail Making Test (condition 1), and on the Semantic Fluency subtest of the Verbal Fluency task (condition 2). Of note, the Inhibition (corresponding to the traditional Stroop-task) and combined Inhibition and Switching conditions of the Color-Word Interference Test were not impaired in either patient. The patients did not produce more errors than healthy controls on the D-KEFS tasks.

3.3. Self-reported symptoms of executive functioning

Patient 1 did not report executive problems of daily living on the Behavior Rating Inventory of Executive Function (Table 1e), whereas patient 2 tended towards reporting problems with initiation of activity. The informant reports were in line with both patient subjective reports.

3.4. Target and novelty detection – the Novelty Oddball task

Both patients had normal hit rates to targets and normal reaction times (RT) to successfully detected targets (Table 2d). Patient 2 had significantly more false alarms to both novel and standard sounds compared to controls.

The Novelty Oddball ERPs are displayed in Fig. 2, with amplitudes reported in Table 2a-c. The Novelty P3 response could not be confidently identified for either patient (Fig. 2A). Amplitudes of negative polarity were seen over left, right as well as midline frontal electrode groups for both patients, rendering the Novelty P3 diminishment independent of laterality of injury. This finding was significant over midline and both left and right frontal electrode groups with the exception of left frontal site for patient 2 where the findings were at the 0.1 level only. On the other hand, both patients displayed a tendency towards enhanced parietal P3b responses to target stimuli (Fig. 2B). The amplitude enhancement was significant at the 0.1 level for all measurement sites except the right parietal electrode cluster in patient 2. Both patients also displayed a late negative slow wave (NSW) over frontal midline electrodes to novel stimuli that was significantly larger than in the control group. Ipsilateral to the lesion, the NSW enhancement was significant for patient 1 and a trend in the same direction was present for patient 2.

3.5. Motor inhibition and error-monitoring in the Stop-signal task

Both patients had a high success rate to Go-trials (99%) (Table 3e). Patient 1 had longer Go RTs than the controls, resulting in a trend towards prolonged stop-signal delay. The estimated stop-signal reaction time (SSRT) did not differ significantly between patients and controls. However, there was a tendency towards an enhanced rate of successful inhibitions that was significant for patient 1 only and suggestive for patient 2. Interestingly, neither of the patients slowed down after having made a mistake (post-error slowing). For patient 2, the difference between mean RTs in Go-trials following a failed inhibition compared to Go trials preceding the failed inhibition was only 2.8 ms, whereas patient 1 actually speeded up after a failed inhibition by a mean of 8.5 ms. In comparison, the control group slowed down by a mean of 28.9 ms (SD 41.9). The lack of post-error slowing in the two patients did, however, not turn out as significant, due to the large variability within the control group.

As in the novelty oddball task, both patients displayed a clear target (Go)-related parietal P3b (Fig. 3A). Interestingly, both patients had an error-related negativity with a subsequent error-positivity following failed inhibitions (Fig. 3B). In patient 1, the error-related negativity was identifiable over both hemispheres as well as midline central electrodes. Amplitudes seemed enlarged over midline and right hemisphere (ipsilateral to lesion) sites, although this effect did not turn out as significant. Patient 2, on the other hand, displayed a normal error-related negativity over the left hemisphere (ipsilateral to lesion) only and a significantly diminished error-related negativity over midline and right hemisphere

electrodes. The error-positivity was present over all sites for both patients, with a significant enhancement over the lesioned hemisphere for patient 1. Response-locked ERPs to correct responses are shown in Fig. 3C, with corresponding amplitudes in Table 3d, illustrating that successful Go-trials did not elicit a negative deflection resembling the error-related negativity neither in the control group nor the patients.

4. Discussion

The contribution of dorsomedial PFC in distributed cognitive control networks remains poorly understood. This case study examined neuropsychological, behavioral, and electrophysiological indices of cognitive control following ACC injury, with a specific aim to investigate the claim set forth by Baird et al. (2006) that the ACC is not involved in cognitive processing.

In summary, performance on the Color-Word Interference Test, the D-KEFS version of the traditional Stroop task, was normal in both patients, whereas scores on memory tasks were reduced. As hypothesized, alterations of electrophysiological responses were observed. The Novelty P3 response was diminished bilaterally, whereas the target-related posterior P3b was present in both patients. Interestingly, both patients displayed the error-related negativity to failed stop-signal inhibitions, although the results varied in that patient 1 demonstrated an error-related negativity over the left hemisphere only, while patient 2 tended to have increased amplitudes over midline electrodes and ipsilateral to lesion. There were also indications of altered behavioral adjustment in the Stop-signal paradigm, as the patients did not show the expected post-error slowing.

4.1. Neuropsychological findings

Stuss et al. (2001) found that bilateral lesions of the MPFC were associated with impaired Stroop performance. As the two patients in this study had unilateral lesions, we cannot confirm this finding, but the unaffected performance indicates that a bilaterally intact ACC is not critical for normal performance on the Stroop task. It is also of potential significance that we only administered a verbal Stroop task, while Turken and Swick (1999) found that manual, but not verbal response delivery was affected by a right dorsal ACC lesion.

Of interest are the learning and memory scores of the patients. PFC damage particularly affects strategic aspects of memory and learning, as part of a broader cognitive impairment associated with problems in controlling extraneous or irrelevant information processing (Shimamura, 1995). Ventromedial PFC has been found to be of particular relevance for long-term consolidation of memories, with a main role being to ensure that irrelevant information from limbic structures does not interfere with the long-term consolidation of memory traces (Nieuwenhuis & Takashima, 2011). Of note, the region discussed by Nieuwenhuis and Takashima is more orbital than those presented in the current study. Also, memory consolidation as such was not studied beyond a 1 h time frame in this study. However, the reduced learning, and tendency towards false positive responses for patient 1, and the trend towards similar findings in patient 2, give preliminary support to a role of ACC in learning and long-term memory retrieval.

Patient 1 had a reduced Verbal IQ, resulting in a trend towards affected total IQ. Note that the IQ of patient 1 was 100, which is a normal result according to normative data. Verbal IQ in the lower normal range could reflect premorbid level of functioning, precluding strong conclusions. In general, studies exploring the effect of PFC lesions on IQ have yielded mixed results (Anderson, Jacobs, & Harvey, 2005; Tranel, Manzel, & Anderson, 2008).

Patient 2 reported a tendency towards initiation problems on the Behavior Rating Inventory of Executive Function, in line with a particular role of superior MPFC in drive and motivation (Bonelli & Cummings, 2007; Stuss, Binns, Murphy, & Alexander, 2002). Except from this suggestive finding, however, the BRIEF-A scores were normal. The adult version of the Behavior Rating Inventory of Executive Function has not been studied extensively in patient populations, and there is a need to demonstrate the questionnaire's sensitivity to the effects of focal frontal lesions. In patients with lateral and orbital frontal lesions, we have found weak correlations between the Behavior Rating Inventory of Executive Function and cognitive measures, but very strong correlations ($r = .64 - .98$) with Symptom Checklist 90-Revised, giving rise to concern about the scale's specificity with regard to executive dysfunction (Løvstad et al., 2012).

4.2. Effects of ACC lesions on neurophysiological indices of attentional control

4.2.1. The role of the ACC in target and novelty detection—Electrophysiological studies of target and novelty detection typically apply variants of the oddball paradigm, where infrequently occurring target stimuli will elicit a parietally distributed P3b, indexing attentional resource allocation, while salient distractor stimuli are associated with the earlier and more frontally distributed P3a, or Novelty P3, associated with the orienting response (for comprehensive reviews, see Polich, 2007 and Soltani & Knight, 2000). Studies of the role of ACC in target and novelty detection have given somewhat mixed results, indicating possible ACC involvement in both target and novelty detection. Whereas studies employing EEG-source analysis have suggested a distinct role of the ACC in novelty detection (Dien, Spencer, & Donchin, 2003; Lee et al., 2007), an fMRI study of the auditory oddball task demonstrated ACC-involvement to task-relevant target stimuli only (Kiehl, Laurens, Duty, Forster, & Liddle, 2001). In a combined ERP and fMRI study of a two-tone auditory oddball paradigm, it was found that target stimuli activated the supramarginal gyrus, thalamus and ACC (Menon, Ford, Lim, Glover, & Pfefferbaum, 1997). An association between ACC activation and the P3a has been demonstrated, suggesting that ACC plays a role in facilitating attentional shifting (Crottaz-Herbette & Menon, 2006). Strobel et al. (2008) found that whereas both EEG-source analysis and fMRI-data indicated target-related involvement of MPFC including the ACC, MPFC-activation to novel events was found in the fMRI-data only. Finally, compelling evidence for the role of ACC in generation of the Novelty P3 response has come from intracranial recordings in patients undergoing surgery for intractable epilepsy (Halgren, Marinkovic, & Chauvel, 1998).

In the current study, hit rates and RTs to target stimuli were normal in both patients. Electrophysiologically, however, bilateral abolishment of the frontal Novelty P3 response was observed for both patients. Earlier lesion studies have demonstrated that DLPFC as well as OFC lesions result in Novelty P3 attenuation (Daffner et al., 2000; Daffner et al., 2003;

Knight & Scabini, 1998; Løvstad et al., 2012). Thus, this study confirms the role of PFC in generation of the Novelty P3 response, and interestingly suggests that novelty detection is supported by distributed prefrontal networks where all three major subdivisions constitute necessary components.

The posterior P3b to target stimuli was present bilaterally in both patients. On visual inspection, the parietal P3b to targets seemed enhanced in both experiments, but this turned out as significant at the 0.1 level in the Novelty Oddball experiment only, calling for caution in interpretation of the findings. Presence of the posterior P3b to target stimuli does not preclude a role of the ACC in target detection, but shows that normal target detection can take place despite unilateral ACC-damage. The finding is in accord with existing knowledge that intact PFC functions are necessary for normal novelty but not target detection (Daffner et al., 2003; Knight & Scabini, 1998; Løvstad et al., 2012).

Deviant stimuli can generate a frontally distributed negative slow wave (NSW) (Näätänen, 1992; Spencer, Dien, & Donchin, 2001) that has been linked to level of mental processing (Ritter & Ruchkin, 1992; Ruchkin, Canoune, Johnson, & Ritter, 1995). An enhanced frontal midline NSW was seen to novel stimuli over midline electrodes, with a tendency towards the same finding ipsilateral to the lesion in both patients. Enhanced frontal NSW has been reported by our group after LPFC lesions (Løvstad et al., 2012). In the patients with ACC injury the negative deflection had a somewhat earlier onset, but the findings could nevertheless indicate that MPFC as well as LPFC lesions can result in enhanced processing of task-irrelevant deviant stimuli, confirming a role in controlled attention.

4.2.2. The effect of ACC lesions on the error-related negativity and motor-inhibition—

Although generation of the error-related negativity and the subsequent error-positivity has been intimately linked to the ACC (Bush et al., 2000), only a few studies have explored the ERP effect of lesions to this area. Stemmer et al. (2004) and Swick and Turken (2002) found indications of reduction of the error-related negativity. Likewise, Hogan and coworkers (Hogan, Vargha-Khadem, Saunders, Kirkham, & Baldeweg, 2006) found attenuated error-related negativity but not error-positivity changes in patients with frontal white matter lesions due to sickle-cell disease. The findings were interpreted as indexing the result of damaged white matter connections between the medial and lateral PFC.

Interestingly, the reduction of error-related negativity amplitude was found in both unilateral and bilateral lesions, suggesting that unilateral ACC-affection is sufficient to attenuate the error-related negativity.

In the present study, both patients displayed the error-related negativity. However, the ERP-findings in the Stop-signal task were more variable than in the novelty oddball task, as error-related negativity was only clearly present over the left (i.e. lesioned) hemisphere in patient 2, whereas patient 1 tended to have increased error-related negativity and error-positivity amplitudes over midline electrodes and ipsilateral to the lesion. The most important aspect of the finding is, however, that unilateral damage to the ACC and surrounding MPFC tissue is not necessarily associated with abolishment of the error-related negativity.

Behaviorally, the control group displayed a clear post-error slowing of 29 ms. The variability within the control group was large however, rendering the lack of post-error slowing in patients non-significant. Patient 1 deviated from controls by having longer Go RTs. Inhibitory speed (estimated in the Stop-signal reaction time) was not altered in either patient, whereas inhibitory success rates tended to be enhanced. The Stop-signal paradigm involves an inherent competition between a speeded response to the GO-stimulus and inhibiting this response after a stop-signal (Logan, Cowan, & Davis, 1984). The current experiment contained individually tailored Stop-Signal Delays aiming at establishing a 50% inhibitory success-rate. This was achieved for controls but not patients, indicating a lesion-related alteration of the speed-accuracy trade-off. Theoretically, the stair-case adjustment of task difficulty might break down due to reduced psychomotor speed in the patients. This is probably not the case here, however. Although patient 1 did have prolonged RT to successful GO trials, this was neither the case in the Novelty Oddball task nor in the speeded neuropsychological measures. This indicates that the reaction time difference does not reflect generally reduced psychomotor speed but a change in speed-accuracy trade-off. Stop-signal task performance can be affected by factors such as inter-trial interval and task instructions. In this study, speeded RT was stressed, as the subjects were instructed to respond as fast and accurately as possible, and explicitly instructed to not slow down and wait for a stop-signal. We are not aware of other patient studies showing that the staircase adjustment of task difficulty did not work as well for the patients as for controls. A recent study by Bonnelle et al. (2012) showed slowed stop signal reaction times, but not altered inhibitory success rates in TBI patients, confirming findings from e.g. Rieger, Gauggel, and Burmeister (2003), in patients with frontal lobe and basal ganglia lesions and Floden and Stuss (2006), where it was demonstrated that right posterior MPF lesions were associated with longer stop-signal reaction times. Prolonged stop signal reaction times have also been demonstrated in rats with orbitofrontal lesions (Eagle et al., 2008). Krämer, Solbakk, and Fund (2012), however, did not find altered SSRTs or inhibition rates in patients with lateral PFC lesions. Thus, the literature is inconsistent on this issue, and our findings do not confirm altered stop-signal reaction times after PFC lesions. On the other hand, we are not aware of other studies including only patients with medial prefrontal lesions, thus our findings could be specific to lesion site. The findings should be considered preliminary, but all in all we find that two potential interpretations seem plausible; either that the patients chose a deliberate strategy of waiting, thus increasing inhibitory success, or that the patients tendency to wait does not reflect an explicit choice, but rather is secondary to a more general reduction in drive and motivation.

4.3. Specific cognitive control problems or motivation and energization?

It has been suggested that the ACC does not play a crucial role in cognition per se, but is involved in associating executive functioning with activation of the autonomic nervous system (Baird et al., 2006; Critchley et al., 2003). This is in line with the well-established knowledge that lesions to MPFC can result in clinically reduced drive and internally motivated behavior (Holroyd & Yeung, 2012). Examples of this are transcortical motor aphasia, characterized by limited spontaneous speech despite normal repetition, articulation, and auditory comprehension (Alexander, 2006; Freedman, Alexander, & Naeser, 1984), and akinetic mutism (Bonelli & Cummings, 2007), where the patients display wakefulness but

serious apathy and lack of behavioral and emotional spontaneity. The current study did not include measures of autonomic activation, precluding examination of this issue. One could however argue that the language impairments seen in patient 1 with reduced verbal IQ, verbal memory and tendency towards reduced verbal fluency, could reflect motivational aspects of language rather than distinct cognitive deficits. On the other hand, this would not explain why only long-term and not short-term free recall would be affected, which would be more easily accounted for by a long-term memory consolidation problem as suggested by Nieuwenhuis and Takashima (2011). Regarding the electrophysiological findings, it could be hypothesized that abolishment of the Novelty P3, a tendency towards increased P3b, increased negative slow wave, and absence of post-error slowing all could reflect altered inhibitory control, and that inhibitory control is indirectly related to initiation through facilitation of internally generated behaviors. On the other hand, such an explanation would lead to an expected impairment on the Stroop-task, which we did not observe. Also, the presence of both the error-related negativity and the following error-positivity to failed inhibitions does not fit with this understanding. The lack of post-error slowing in the patients, could indicate that patients do not process the emotional significance of errors and thus do not slow down after an error is made. While the P3 indexes attentional resource allocation, it also covaries with biological arousal states (Polich & Kok, 1995). Thus, the tendency towards increased P3b amplitudes in the ACC patients could therefore indicate increased and not decreased arousal levels, as would be predicted by a underlying motivational deficit.

In summary, we find that the lesion-related effects are not easily attributed solely to changes in autonomic arousal as would be predicted by Critchley et al. (2003). The findings indicate presence of differentiated cognitive lesion-related changes. However, the role of MPFC in motivation and initiation is well-documented, and it cannot be ruled out that motivational changes contribute to some of the findings.

4.4. Methodological considerations

One must exercise caution when interpreting results from single cases, and bear in mind that both patients, as in most other ACC-lesion studies, suffered additional frontal damage. Spontaneous injuries to the ACC are typically caused by tumors or strokes, and will almost always result in damage to surrounding structures (Devinsky et al., 1995; Nachev, 2006). Although the lesions presented here did not extend to orbital cortex nor to the most lateral parts of prefrontal cortex, additional white matter damage is expected to cause disruption of functional networks in which the MPFC participates. Caution should generally be used in interpreting any functional localization arguments (Voytek & Knight, 2010b), especially in lesion studies where recovery may have occurred (Voytek, Soltani, Pickard, Kishiyama, & Knight, 2012; Voytek et al., 2010). Therefore, the study does not allow for strict localization of functions (Posner et al., 1988). On the other hand, case studies are potentially of great theoretical interest. Nachev (2006) calls for caution in drawing strong theoretical conclusions based on correlational imaging evidence derived from healthy subjects, and notes that establishing necessity of an areas participation in cognitive processes requires studies examining loss of function. He also notes that even a small number of studies

showing absence of deficit despite damage to a specific area represents important knowledge.

It is well known that although patients with prefrontal injury typically perform worse than healthy controls on neuropsychological tests, the results are often within normal limits (Alvarez & Emory, 2006), and that patients with frontal lobe injury can have devastating problems of everyday living despite normal neuropsychological test profiles (Knight & Stuss, 2002). Assessment of patients with prefrontal injury can be substantially improved by using an integrative methodological approach where traditional cognitive measures are supplemented by experimental measures and functional neuroimaging techniques (Stuss & Levine, 2002; Zald & Andreotti, 2010). Inclusion of a healthy comparison group in all measures including neuropsychological tests, as well as application of experimental behavioral and electrophysiological measures thus poses a strength of this study.

5. Conclusions

Although the role of the MPFC, and specifically the ACC, in cognitive operations has attracted substantial interest over the past decade, consensus has not been established. In this study, neuropsychological, behavioral and electrophysiological functioning was explored in two patients with MPFC damage including the ACC. Learning and memory was affected in both patients, but the Stroop-task was insensitive to unilateral ACC damage. It was also demonstrated that whereas unilateral ACC damage seemed to be sufficient to result in bilateral extinction of the Novelty P3, it did not diminish the posterior target-related P3b. Contrary to what would be predicted from theories about ACC as generator of the error-related negativity, this ERP component was observed in both patients. Thus, while unilateral ACC damage does not seem to be sufficient to abolish the error-related negativity, the effect of bilateral lesions could not be explored in the present study. Behaviorally, however, they showed signs of altered error processing as inhibition tended to be enhanced and they did not slow down after having made an error.

Although the findings should be considered suggestive and we acknowledge that motivational changes might contribute to the results, this study allows for two broad conclusions; (1) claims that the ACC is irrelevant to cognitive control functions were not confirmed, and (2) the findings indicate that the MPFC is involved in various cognitive control tasks rather than being limited to specific cognitive operations such as error detection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(A) Patient 1

(B) Patient 2

Fig. 1.
MRI scans of (A) patient 1, illustrating unilateral right medial prefrontal lesion, (B) patient 1, illustrating unilateral left medial prefrontal lesion.

Fig. 2.
ERP in novelty oddball task. (A) frontal novelty P3, (B) frontal ERP to standards (C) parietal P3b to target for controls (black), and Acc patients (1 = blue, 2 = red).

Fig. 3.

Stop signal task ERP's controls (black) and ACC patients (1 = blue, 2 = red). (A) parietal P3 to successful GO (GO P3), (B) response-locked error related negativity (ERN) over central electrodes, and (C) response-locked correct related negativity (CRN) over central electrodes.

Table 1

Comparison between healthy controls and patients 1 & 2 on neuropsychological measures and the BRIEF-A.

	Control	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2
	Mean (SD)			t-Values		Effect size (Z_{cc})	
<i>(a) WASI & WAIS-III subtests</i>							
Total IQ	112.76 (8.65)	100	121	-1.5*	0.9	-1.5	0.95
Verbal IQ	108.76 (8.77)	92	115	-1.8**	0.7	-1.9	0.71
Performance IQ	113.24 (8.99)	109	123	-0.46	1.06	-0.47	1.09
Digit span total	16.76 (3.95)	11	20	-1.4*	0.8	-1.46	0.82
- Digit span forward	6.1 (1.37)	4	8	-1.5*	1.36*	-0.80	1.39
- Digit span backward	5.38 (1.2)	4	5	-1.1	-0.31	-1.15	-0.32
Letter-number sequencing	11.95 (2.64)	10	14	-0.72	0.76	-0.74	0.78
<i>(b) California verbal learning test – II</i>							
Total learning trial 1–5	54.10 (9.76)	36	49	-1.82**	-0.51	-1.85	-0.52
Short term free recall	11.48 (3.47)	10	7	-0.42	-1.27*	-0.43	-1.29
Short term recall interf. list	6.62 (3.12)	4	7	-0.82	0.12	-0.84	0.12
Long term free recall	12.43 (3.03)	7	8	-1.76**	-1.43*	-1.79	-1.46
<i>(c) Brief visuospatial memory test – Revised</i>							
Total learning trial 1–3	25.05 (3.07)	19	23	-1.93**	-0.65	-1.97	-0.67
Learning	5.48 (2.01)	4	5	-0.72	-0.23	-0.73	-0.24
Delayed recall	10.67 (1.06)	10	10	-0.62	-0.62	-0.63	-0.63
Percentage recall	98.3 (6)	125	100	4.36***	0.28	4.43	0.28
Recognition hits	5.8 (.4)	6	6	0.49	0.49	0.47	0.47
Recognition discrimination	5.8 (1.3)	6	6	0.15	0.15	0.32	0.32
Response bias	.5 (.1)	.05	.5	-4.5***	0	-4.0	0.0
<i>(d) Delis–Kaplan executive function system</i>							
TMT 1	20.52 (3.75)	21	28	0.13	6.33***	0.13	2.0
TMT 2	32.38 (9.73)	32	28	-0.04	0.44	-0.04	0.45
TMT 3	32.19 (11.30)	34	31	0.16	-0.10	0.16	-0.11
TMT 4	71.29 (21.09)	79	57	0.36	-0.67	0.37	-0.68
TMT 5	24.67 (10.60)	18	18	-0.62	-0.62	-0.63	-0.63
Design Fluency 1	9.95 (2.89)	9	12	-0.32	0.69	-0.33	0.71
Design Fluency 2	11.52 (3.89)	15	14	0.88	0.64	0.90	0.64
Design Fluency 3	10.24 (2.72)	12	12	0.64	0.64	0.65	0.65
Verbal Fluency 1	44.81 (10.44)	43	45	-0.17	0.02	-0.17	0.02
Verbal Fluency 2	50.43 (10.39)	46	72	-0.42	2.03**	-0.43	2.08
Verbal Fluency 3	14.52 (2.60)	11	15	-1.33*	0.18	-1.36	0.18
Verbal Fluency 3 correct switches	13.81 (2.38)	12	14	-0.74	0.08	-0.76	5.8
CWI – Color naming	29.38 (4.48)	30	28	0.14	-0.30	0.14	-0.31

	Control	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2
	Mean (SD)			t-Values		Effect size (Z_{cc})	
CWI – Word Reading	22.43 (3.51)	21	23	−0.40	0.16	−0.41	0.16
CWI – Inhibition	51.10(10.73)	42	45	−0.83	−0.56	−0.85	−0.57
CWI – Inhibition/switching	60.48 (13.69)	50	55	−0.75	−0.39	−0.77	−0.4
<i>(e) Behavior rating inventory of executive function – Adult version – self report form</i>							
Global executive composite (GEC)	42.9 (9.24)	35	40	−0.83	−0.31	−0.86	−0.31
Metacognition index (MI)	44.05 (8.61)	37	44	−0.80	−0	−0.82	−0.01
Initiate	43.86 (7.23)	37	54	−0.93	1.38*	−0.95	1.40
Working memory	45.81 (7.53)	39	46	−0.89	0.02	−0.90	0.03
Plan/organize	44.38 (7.14)	42	44	−0.33	−0.05	−0.33	−0.05
Task monitor	46.29 (10.22)	37	42	−0.89	−0.41	−0.91	−0.42
Organization of materials	44.9 (10.03)	37	37	−0.77	−0.77	−0.79	−0.79
Behavioral regulation index (BRI)	42.48 (9.1)	37	41	−0.59	−0.16	−0.60	−0.16
Inhibit	43.67 (9.13)	37	43	−0.72	−0.07	−0.73	−0.07
Shift	43.81 (6.19)	39	43	−0.76	−0.13	−0.78	−0.13
Emotional control	44.43 (8.65)	41	38	−0.39	−0.73	−0.40	−0.74
Self-monitor	42.76 (9.14)	37	37	−0.62	−0.62	−0.63	−0.63

*
 $p < .1$.

**
 $p < .05$.

 $p < .025$.

Table 2

Novelty Oddball. ERP amplitudes for controls (Mean(SD)) and patient 1 and 2; a) Novelty P3, b) Frontal negative slow wave, c) P3b to target, and d) Behavioral data.

	Control	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2
	Mean (SD)			<i>t</i> -Values		Effect size (<i>Z</i> _{cc})	
<i>ERP amplitudes</i>							
<i>(a) Novelty P3 (mean amplitude 270–400 ms)</i>							
Frontal left	1.51 (1.77)	–2.37	–1.26	–2.13**	–1.52*	–2.19	–1.56
Frontal midline	2.19 (1.55)	–6.95	–4.06	–5.71***	–3.91***	–5.90	–4.03
Frontal right	2.01 (1.67)	–7.07	–1.94	–5.28***	–2.30***	–5.44	–2.37
<i>(b) Frontal negative slow wave to Novels (mean amplitude 400–600 ms)</i>							
Frontal left	–0.87 (1.29)	–1.14	–3.13	–0.20	–1.70*	–0.21	–1.75
Frontal midline	–1.23 (1.02)	–4.94	–4.51	–3.53***	–3.12***	–3.64	–3.22
Frontal right	–1.05 (1.16)	–7.29	–1.93	–5.24***	–0.74	–5.38	–0.76
<i>(c) P3b to target (mean amplitude 300–500 ms)</i>							
Parietal left	2.03 (1.27)	4.19	3.98	1.65*	1.49*	1.7	1.54
Parietal midline	2.94 (2.15)	6.16	5.90	1.46*	1.34*	1.50	1.38
Parietal right	2.33 (1.85)	5.31	4.50	1.56*	1.13	1.61	1.17
<i>(d) Behavioral data</i>							
Hit rate target (%)	99.7 (0.9)	100	100	0.32	0.32	0.33	0.33
<i>False alarms (%)</i>							
Standard	0.6 (0.3)	0.4	1.8	–0.65	3.87***	–0.67	4
Novel	1.2 (2.3)	0	3.3	–0.51	0.89	–0.52	0.91
RT target (ms)	382 (66.2)	387	372	0.07	–0.15	0.08	–0.15

* $p < .1$.

** $p < .05$.

*** $p < .025$.

Table 3

Stop-Signal Task. ERP amplitudes for controls (Mean(SD)) and patient 1 and 2; a) GO P3, b) Response locked ERPs to failed inhibitions; ERN, c) Response locked error related positivity to failed inhibitions; Pe, d) Response locked ERPs to successful GO, and e) Behavioral data.

	Control	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2
	Mean (SD)			t-Values		Effect size (Z_{cc})	
<i>ERP amplitudes</i>							
<i>(a) Successful GO P3 (parietal mean amplitudes 300–500 ms)</i>							
Parietal left	1.03 (1.78)	0.63	1.37	−0.22	0.18	−0.22	0.19
Parietal midline	2.16 (2.92)	3.33	3.34	0.39	0.14	0.40	0.40
Parietal right	1.22 (1.99)	2.38	2.16	0.61	0.45	0.58	0.47
<i>(b) Response locked error related negativity to failed inhibitions; ERN (mean amplitudes 50–100 ms)</i>							
Central left	−2.44 (1.34)	−3.73	−0.91	−0.93	1.1	−0.97	1.14
Central midline	−3.48 (2.39)	−6.30	0.26	−1.13	1.5*	−1.18	1.35
Central right	−2.03 (2.06)	−3.90	0.91	−0.87	1.37*	−0.91	1.43
<i>(c) Response locked error related positivity to failed inhibitions; Pe (mean amplitudes 250–400 ms)</i>							
Central left	2.05 (1.70)	1.61	1.78	−0.25	−0.15	−0.26	−0.16
Central midline	3.90 (3.11)	8.12	4.22	1.32	0.1	1.36	0.10
Central right	1.91 (2.17)	10.03	2.68	3.63***	0.34	3.74	0.35
<i>(d) Response locked correct response negativity; CRN to successful GO trials (mean amplitudes 50–100 ms)</i>							
Central left	−0.8 (1.19)	−1.59	−0.19	−0.64	0.5	−0.66	0.51
Central midline	−0.19 (1.72)	−0.52	1.22	−0.19	0.80	−0.19	0.82
Central right	0.3 (1.11)	−0.12	1.33	−0.37	0.9	−0.38	0.93
<i>(e) Behavioral data</i>							
RT successful GO trials (ms)	616.65 (141.72)	886.2	704.56	1.83**	0.60	1.9	0.62
Stop-signal reaction time (SSRT)	179.09 (22.81)	155.54	157.91	−1.0	−0.9	−1.42	−1.03
Stop-signal delay	436.06 (100.19)	609	498.09	1.68*	0.60	1.73	0.62
Successful GO (%)	93.34 (6.26)	98.93	98.57	0.86	0.80	0.89	0.84
Successful inhibitions (%)	47.34(11.43)	70.8	64.17	1.99**	1.42*	2.35	1.47
Post error slowing #	28.87 (41.87)	−8.5	2.8	−0.86	−0.6	−0.89	−0.62

* $p < .1$.

** $p < .05$.

*** $p < .025$.