Executive functions after focal lesions to the lateral, orbital and medial subdivisions of the prefrontal cortex - neuropsychological, behavioral and electrophysiological findings

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Marianne Løvstad, Nesodden, June 20th 2012

Abbreviations

ABI – Acquired brain injury
ACC – anterior cingulate cortex
ACcd – anterior cingulate cognitive division
ACad – anterior cingulate affective division
AD – Alzheimers disease
ADHD –Attention Deficit Hyperactivity Disorder
BA – Brodmann area
BOLD – blood oxygen level dependent
BVMT-R – Brief Visuospatial Memory Test-Revised
BRIEF-A – Behavior Rating Inventory of Executive Function - Adult version
CE – central executive
CT – Computer Tomography
CVA – cerebrovascular accident
CVLT-II – the California Verbal Learning Test - Second Edition
CWI – Colour-Word Interference Test
DAI – diffuse axonal injury
D-KEFS – Delis-Kaplan Executive Function System
DLPFC – dorsolateral prefrontal cortex
EF – executive functions
ERP – event-related potentials
fMRI – functional Magnetic Resonance Imaging
GOS-E – Glasgow Outcome Scale - Extended
LGG – low grade glioma
LPFC – lateral prefrontal cortex
MD – Major depression
MRI – Magnetic Resonance Imaging
OCD – Obsessive Compulsive Disorder
OCI-R – Obsessive-Compulsive Inventory Revised
OFC – orbitofrontal cortex
PD – Parkinsons disease
PFC – prefrontal cortex
RT – reaction time
SAH – subarachnoid haemorrhage
SAS – Supervisory Attention System
SCL-90-R – Symptom Checklist 90 Revised
SMA – supplementary motor area
TBI – traumatic brain injury
TMT – Trail Making Test
ToM – Theory of Mind
VMPFC – ventromedial prefrontal cortex
WAIS-III – Wechsler Adult Intelligence Scale - Third Edition
WASI – Wechsler Abbreviated Scale of Intelligence
WCST – Wisconsin Card Sorting Test

General Summary

Executive functions (EF) ensure goal-directed behavior and flexible adaptation to changing environmental requirements. EF enable us to plan and anticipate future events, with the capacity to control and distribute attentional resources being an important part of normal EF. Executive deficit is common following acquired brain injury and results in problems with higher-order control over thoughts, emotions and behavior. Presence of executive problems complicates the rehabilitation process and has negative impact on long-term outcome.

Executive control is mediated by distributed but anatomically dissociable neural networks where the prefrontal cortex (PFC) plays an important role. Three main frontal-subcortical circuits involving the lateral (LPFC), orbital (OFC), and medial (MPFC) subdivisions of PFC have been suggested. Each neurocircuitry is thought to subserve partly different functions. Whereas LPFC is primarily associated with cognitive aspects of EF, OFC is related to emotional self-regulation. The MPFC is involved in motivation and energization, and is suggested to play a role in detection and monitoring of cognitive conflict.

Debate persists with regard to the level of regional specificity and functional fractionation within PFC. It has been argued that EF is subserved by distinct and dissociable functions with specific anatomical substrates, but also that the key feature distinguishing the PFC is the high level of flexibility and adaptability across sensory modalities and cognitive domains. Progress in revealing the neural underpinnings of EF requires a high level of conceptual and anatomical specificity. It has been suggested that future developments will be dependent upon research that combines knowledge and methodological approaches from clinical neuropsychology, neurology, cognitive neuroscience and modern imaging techniques.

A main aim of the current study was to examine distinct cognitive control functions associated with the three main subdivisions of the PFC. To this end, a neurocognitive, electrophysiological and lesion study approach was adopted. Patients with focal lesions to one of the three subdivisions of PFC were included and assessed with neuropsychological behavioral tests as well as a questionnaire measure of executive functions in every-day living. Electrophysiological indices of attentional control following focal PFC lesions were also studied with event-related potentials (ERPs) in two experimental tasks. An auditory Novelty

Oddball task allowed investigation of novelty and target processing, while a Stop-Signal Task (SST) provided information about motor inhibition and error-monitoring.

In Paper I, novelty and target processing was compared in patients with OFC and LPFC lesions and healthy controls. In **paper II**, neurocognitive functioning and self- and informant reported executive problems in everyday living were explored in patients with OFC and LPFC lesions. In **paper III,** the effect of unilateral MPFC damage including the anterior cingulate cortex (ACC) was investigated in two patients who were assessed with neuropsychological and questionnaire measures as well as ERPs in the Novelty Oddball and SST tasks.

The findings reported in paper II largely confirmed our hypothesis that LPFC damage is particularly prone to cause cognitive executive deficit with reductions on tasks demanding sustained mental effort, working memory, response inhibition, and mental switching, while OFC injury is more strongly associated with self-reported dysexecutive symptoms in everyday living. The findings confirmed a functional dissociation between LPFC and OFC.

Paper I and III on the other hand, showed that lesions to all three subdivisions of PFC resulted in altered processing of unexpected novel events, indexed by attenuation of the frontal Novelty P3 response. The findings extend current knowledge in suggesting that not only LPFC, as shown in previous studies, but OFC as swell as MPFC play a role in novelty processing. The studies therefore confirm a role of PFC in novelty processing, but do not lend strong support for a high degree of regional specificity within PFC. Target detection seems not to be critically dependent upon the PFC, as the target-related parietal P3b was normal after lesions to both OFC, LPFC and MPFC.

The results in paper III did not confirm suggestions that the ACC is not involved in cognitive control, as the two patients displayed learning and memory deficit as well as an abolished Novelty P3. Interestingly, the error-related negativity (ERN) was however present in both patients, indicating that error detection can occur despite unilateral ACC lesion. In summary, the findings from the three studies lend support both to theories that highlight functional and anatomical specificity of distinct control functions within the PFC, as well as theories that emphasize adaptive, supramodal properties of the frontal lobes in complex tasks.

List of papers

This thesis is based on the following papers which are referred to in the text by their Roman numbers I – III.

Paper I

Løvstad, M., Funderud, I., Lindgren, M., Endestad, T., Due-Tønnessen, P., Meling, T.R., Voytek, B., Knight, R.T., & Solbakk, A.K. (2012). Contribution of subregions of human frontal cortex to novelty processing. *Journal of Cognitive Neuroscience,* 24(2), 378-395.

Paper II

Løvstad, M., Funderud, I., Endestad, T., Due-Tønnessen, P., Meling, T.R., Lindgren, M., Knight, R.T., & Solbakk, A.K. (in press). Executive functions after orbital or lateral prefrontal lesions: Neuropsychological profiles and self-reported executive functions in everyday living. *Brain Injury.*

Paper III

Løvstad, M., Funderud, I., Meling, T., Krämer, U.M., Voytek B., Due-Tønnessen, P., Endestad, T, Lindgren, M., Knight, R.T., & Solbakk, A.K (2012). Anterior cingulate cortex and cognitive control: Neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex. *Brain and Cognition, 80,* 237-249.

Introduction

In 1949, the Nobel price in medicine was awarded to Antonio Caetano de Abreu Freire Egas Moniz "for his discovery of the therapeutic value of leucotomy in certain psychoses". In the award ceremony speech, professor Herbert Olivecrona from the Royal Caroline Institute in Sweden said: *"Frontal leucotomy, despite certain limitations of the operative method, must be considered one of the most important discoveries ever made in psychiatric therapy, because through its use a great number of suffering people and total invalids have recovered and have been socially rehabilitated."*
(http://www.nobelprize.org/nobel_prizes/medicine/laureates/1949/).

Three years earlier, Wilder G. Penfield delivered the Ferrier lecture in London. He argued for highly specialized functional areas in the cerebral cortex. However, in relation to the frontal lobes, he drew the following conclusion: ''*Complete removal of the frontal cortex on one side back to, but not including, the precentral gyrus and Broca's speech area, produces surprisingly little interference with the intellectual capacity and behavior of the individual''* (Penfield, 1947). In accord with this, the frontal lobes were often denoted as "silent".

Much has happened since these statements were made. To the notion that some parts of the brain should be considered to be largely without functional value, Devinsky (2005) commented:*"...false view that many brain areas go unused and that certain cortical or subcortical regions and white matter tracts have little functional value. These myths reflected bias as well as the insensitivity of clinical and neuroscientific tools, not brain function" (p. 385).* It is no longer disputed whether the frontal lobes are dispensable, rather it is uniformly accepted that the PFC subserves complex mental capacities related to cognition, emotion and motivation, and extensive scientific effort has been invested in solving the "riddle of the frontal lobes" (Stuss & Alexander, 2007). A PubMed entry with the search term "frontal lobe" was performed in January 2012, giving 55 622 hits. Of these, almost exactly half (27 388) were from the last 10 years. When entering the term "executive functions", 7 388 hits came up, whereof 6 431 were from the last decade.

Modern techniques for imaging of ongoing brain activation have contributed vastly to improved cognitive models of the brain, and helped disentangle the functional and anatomical

substructures of the PFC. One specific challenge regarding the PFC and EF lies in the seeming contrast between theories emphasizing that 1) elementary cognitive operations are strictly localized, while at the same time, 2) even simple tasks require orchestration of performance in distributed brain areas (Posner, Petersen, Fox, & Raichle, 1988).

The work presented in this thesis forms part of the effort to enhance our understanding of frontal lobe functioning, its functional subdivisions, as well as the methodological challenges faced when trying to describe the effect of damage to this part of the brain. In this introduction, the current status of knowledge regarding development, functional anatomical distinctions, cognitive theories, as well as assessment issues related to the PFC and EF will be summarized. It will be argued that the human capacity to control attention is a core executive capacity, and that scientific progress will depend upon the degree to which we achieve clarity of concepts and understand their neural underpinnings (Stuss & Knight, 2002; Stuss, 2011).

Executive functions

The human capacity to maintain an overarching control over mental states and behavior relies on multiple, distributed and dynamically cooperating brain networks (Stuss & Alexander, 2000). When top-down control over mental processes breaks down, the information processing system is rendered inflexible and increasingly stimulus-bound (Fernandez-Duque, Baird, & Posner, 2000). There is not consensus on a single definition of this process, but the common denominator is top-down controlled processes, thereof terms such as ”executive functions”, ”cognitive control”, ”self-regulation”, ”emotional regulation”, and ”metacognition”. In the following, the global term executive functions (EF) will be used when discussing this general capacity.

In the International Neuropsychological Society dictionary of neuropsychology, EF is defined as the *“cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands. Executive function includes the ability to plan and anticipate outcomes (cognitive flexibility) and to direct attentional resources to meet the demands of nonroutine events.”* (INS dictionary of neuropsychology, 1999, p. 64).

Other definitions of EF emphasize distinct aspects of controlled information processing. Braver, Cohen and Barch point to the very central role of **selective attention and inhibitory processes** in EF: *”…to flexibly adapt behavior to the demands of particular tasks by*

facilitating processing of task-relevant information over other sources of competing information and by inhibiting habitual or otherwise prepotent responses that are inappropriate to the task" (Braver, Cohen, & Barch, 2002). The following definition highlights the requirement of **flexible adaptation** to contextual factors: *"...the ability to use or change behavioral rules in a dynamic fashion on the basis of advance information or feedback derived from monitoring ongoing behavior.*" (Kok, Ridderinkhof, & Ullsperger, 2006). **Online monitoring** of cognition and behavior is a key feature of this characterization of EF: "… *involves the ability to monitor and control the information processing necessary to produce voluntary action."* (Fernandez-Duque, Baird, & Posner, 2000). Stuss and Levine pinpoint the **top-down control** from the frontal lobes: *"...are high-level cognitive functions that are involved in the control and direction of lower-level functions"* (Stuss & Levine, 2002). Yet others point to the important aspect of **temporal integration and working memory** in executive control. Flexible adaptation of behavior requires an integrated *representation of past events* (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006) combined with *anticipation of future possibilities* (Brunia, 1999). These aspects of top-down cognitive control collectively subserve goal-directed behavior, and are mediated by distributed neural networks that include the frontal lobes.

The frontal lobes – anatomical delineations and developmental features

Prefrontal cortex

The prefrontal cortex (PFC) comprises 25-33% of the human cortex (Stuss & Benson, 1986) and has extensive reciprocal connections to other cortical and subcortical areas, placing it in a core position in executive control networks (Petrides & Pandya, 2002). Each frontal lobe can be visualized as a pyramid with a base at the level of the central sulcus, and the apex at the frontal pole, with the three external surfaces forming the lateral, medial and orbital walls (Mesulam, 2002). In primates, the frontal cortex is limited posteriorly by the central sulcus. Anterior to the central sulcus is the motor and premotor cortex (Brodman areas 4 and 6). The term PFC is usually applied to the part of the frontal cortex that is anterior to the premotor cortex (Petrides & Pandya, 2002). See figure 1 for Brodmann areas of the human brain.

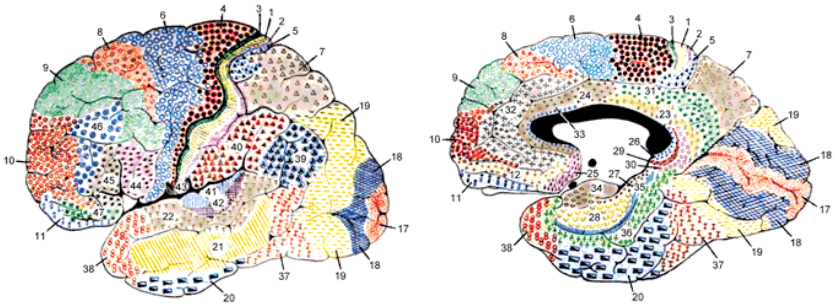

Figure 1. Brodmann areas (BA) of the human brain. Prefrontal cortex includes BA 8, 9, 10, 11, 12, 24, 25, 32, 44, 45, 46, and 47.

Developmental features

The PFC is not fully developed in humans until early adulthood, with a normal course of maturation consisting of an increase in *grey matter* in early childhood followed by a reduction of grey matter in later childhood and adolescence (Nelson & Guyer, 2011; O'Donnell, Noseworthy, Levine, & Dennis, 2005). Along with the temporal lobes and caudate nucleus, the frontal lobes mature late, and within the frontal lobes there is a maturational gradient along the posterior-anterior axis (Gogtay et al.; 2004; Lenroot, et al., 2007). As for grey matter volume, *synaptic density* matures along an inverted U-curve, with synapse elimination, or pruning, continuing into late adolescence (Casey, Giedd, & Thomas, 2000; Giedd & Rapoport, 2010; Huttenlocher & Dabholkar, 1997; Toga, Thompson, & Sowell, 2006). M*yelination*, the development of fatty tissue surrounding neuronal axons, does not follow the inverse U-curve, but increases linearly throughout childhood and into the third decade of life (Giedd & Rapoport, 2010; Nelson & Guyer, 2011; Toga, Thompson, & Sowell, 2006). Newer insights suggest that myelin not only supports speeded signal transmission, but also modulates timing and synchrony of neuronal firing patterns, thus participating actively to create functional networks in the brain (Fields & Stevens-Graham, 2002). Whereas it is a common conception that the human PFC is proportionally larger than in other species, it has been shown that relative to total brain size, the human PFC is not larger than that of the great apes (Semendeferi, Lu, Schenker, & Damasio, 2002). Rather, it is suggested that the specifically human cognitive capacities associated with PFC-functioning, might be due to rich interconnectivity rather than a relative increase in volume (Semendeferi, Lu, Schenker, & Damasio, 2002).

Sensitive periods in the development of the PFC have been suggested (Nelson & Guyer, 2011). Anderson et al. (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999) demonstrated profound social deficit in two adults who acquired injury to the PFC at age 3 and 15 months of age. Both ”grew into” their problems through late childhood and adolescence, with an outcome that was poorer than patients who acquired comparable lesions in adulthood. This adheres well with new knowledge of the effect of pediatric traumatic brain injury (TBI). The traditional belief that the immature pediatric brain had plasticity on its side, and thus that childhood TBI had a more favorable outcome than adult injury, has proven to be a myth. On the contrary, the immature pediatric brain seems to be particularly vulnerable to injury. A combination of low age (i.e. < 7-8 yrs) and serious TBI results in particularly poor outcome, with problems in higher-order cognitive skills becoming evident over time (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2005; Taylor & Alden, 1997). It has even been suggested that childhood sexual abuse during adolescence (age 14-16) results in lower PFC volume, (Andersen, et al., 2008).

In summary, the PFC and the complex interconnections subserving EF are both evolutionary and developmentally amongst the latest functions to be established, they are specific to humans, and seem to be highly vulnerable to adverse neurological and psychological impact.

Anatomical and functional networks in PFC

Five anatomical and functional frontal-subcortical circuits have been identified (Alexander, DeLong, & Strick, 1986), where distinct regions of PFC form part of structural networks involving the basal ganglia and thalamus. Two of these are associated with motor execution and will not be emphasized. The three other circuits are, closely connected to executive control functions: **1)** The **dorsolateral**, **2)** the **orbitofrontal,** and **3)** the **anterior cingulate** circuits (Bonelli & Cummings, 2007; Tekin & Cummings, 2002). All three networks share connections within the same structures; including the cerebral cortex, striatum, globus pallidus and substantia nigra, as well as thalamus. Within each network there is a direct and an indirect pathway, the latter including the subthalamic nucleus (Alexander, Crutcher, & DeLong, 1990). The relative relations within the circuits are preserved through the relay structures, as dorsolateral PFC projects to the dorsolateral part of the caudate nucleus, the orbitofrontal cortex (OFC) projects to the ventral caudate/ventral striatum, and the anterior cingulate cortex projects to the medial striatum/nucleus accumbens region (Saint-Cyr, Bronstein, & Cummings, 2002). The circuits constitute both ”closed” and ”open” loops, as they remain segregated anatomically throughout

the circuits, but also receive projections and project to regions outside of the frontal-subcortical circuits, thus constituting an important way of information integration, (Bonelli & Cummings, 2007).

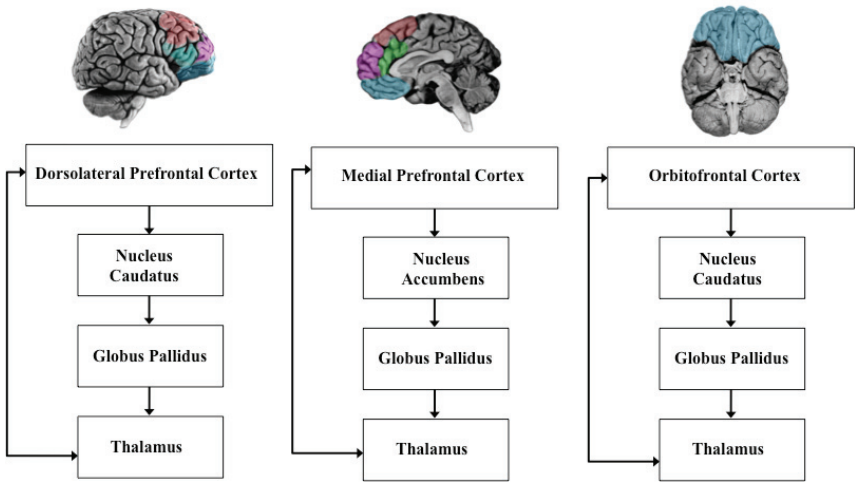

Figure 3. Frontal-subcortical networks (Adapted from Bonelli & Cummings, 2007).

Note that the dorsolateral and orbital circuits coincide with patient subgroups in paper I and II, while the role of the medial PFC is discussed in paper III. Recent developments point towards the polar region of PFC as an area of interest in the integration of executive control functions (Stuss, 2007), and this will be mentioned as a fourth subdivision of PFC.

1) The dorsolateral prefrontal circuit – cognitive executive control

DLPFC (BA 9, 10 & 46) is evolutionary part of the archicortical trend originating in the hippocampus. Association areas of the parietal and temporal lobes are also closely interacting areas (Saint-Cyr, Bronstein, & Cummings, 2002). The frontal-subcortical circuit is closed by mediodorsal thalamus connecting back to DLPFC (Giguere & Goldman-Rakic, 1988).

The DLPFC circuit mediates cognitive EF, defined as "high-level cognitive functions, involved in the control and direction of lower level, more automatic functions" (Stuss, 2007). Much of what is known about EF in neuropsychological studies is based on patients with primarily DLPFC damage (Goldman-Rakic, 1996; Petrides & Milner, 1982; Stuss & Benson, 1984). DLPFC is associated with complex cognition such as controlled attention, working memory, strategic memory, conceptual reasoning, anticipation, goal selection, planning, sequencing, monitoring and use of feedback in task performance (Bonelli & Cummings, 2007; Royall, et al.,

2002). Mechanisms of controlled attention are associated with the DLPFC along with dorsal anterior cingulate cortex (ACC) (Corbetta, Patel, & Shulman, 2008; Posner & Petersen, 1990). Commonly used neuropsychological tests of cognitive executive control are more sensitive to DLPFC injury compared to injury to the orbital and ventral parts of the PFC (Stuss, 2007).

Cognitive executive deficit can be observed after a wide array of neurological conditions, both acquired brain injury (TBI, tumors and cerebrovascular accidents (CVA)), developmental disturbances (Attention Deficit/Hyperactivity Disorder (ADHD), Tourette´s syndrome) as well as neurodegenerative diseases (Alzheimers (AD), Parkinsons (PD) and Huntingtons disease (HD)). Cognitive executive problems are also found to be core symptoms in various psychiatric conditions, such as schizophrenia, bipolar disorder and obsessive-compulsive disorder (Bonelli & Cummings, 2007; Goldberg & Chengappa, 2009; Heinrichs & Zakzanis, 1998).

2) The orbitofrontal circuit – decision-making and self-regulation

The OFC (BA 10, 11 & 47) is the neocortical representation of the limbic system and phylogenetically the oldest part of PFC (Kringelbach & Rolls, 2004). Significant individual anatomical variations have been described in the human OFC (Kringelbach & Rolls, 2004). The OFC receives input from all sensory modalities, resulting in this area being one of he most polymodal regions of the brain (Kringelbach & Rolls, 2004). The OFC subserves establishment of multimodal stimulus-reinforcement association learning, and plays an important role in controlling and correcting reward- and punishment-related behavior (Rolls, 2004). OFC damage affects the ability to utilize environmental cues to predict future rewarding or aversive events and choose appropriate responses in the context of changing reinforcement contingencies (Hampshire, Chaudhry, Owen, & Roberts, 2012; Koenigs & Tranel, 2006; Stuss & Levine, 2002). Thus, OFC is involved in self-regulation in situations where cognitive analysis, habit or environmental cues are not sufficient to determine the most adaptive response (Stuss, 2007), with emotional and social dysregulation, poor interpersonal functioning and occupational problems being hallmarks of symptoms after OFC damage (Burgess, Alderman, Volle, Benoit, & Gilbert, 2009; Bonelli & Cummings, 2007; Zald & Andreotti, 2010). A recent study confirmed the role of OFC in emotionally driven attentional control, as patients with OFC lesions displayed both reduced electrophysiological responses to emotional distractors, and increased responses to target stimuli which were preceded by emotionally laden stimuli (Hartikainen, Ogawa & Knight, 2012). A major theory of OFC functioning is the “somatic marker hypothesis” (Bechara, Damasio, & Damasio, 2000; Damasio, 1994; Damasio, 1995), which points to the role of

emotional activation in decision-making, and how physiological activation patterns learned in previous situations will help bias and speed decision-making in novel contexts. Popularly speaking, the "somatic marker hypothesis" explains "gut-feeling", and addresses why patients with normal IQ and seemingly normal cognitive executive functioning make bad decisions in everyday living.

Lesions to the OFC can result from various conditions, such as closed and/or open head injury, surgical excisions of tumors or epiletogenic tissue. Strokes affecting the anterior and middle cerebral artery can result in OFC damage (Tatu, Moulin, Bogousslavsky, & Duvernoy, 1998), and aneurysms of the anterior communicating artery (ACom) are among the most common causes of damage to the posterior OFC (Zald & Andreotti, 2010). The frontal variant of fronto-temporal dementia can also result in profound OFC-degeneration (Lu, Khanlou, & Cummings, 2006).

3) The anterior cingulate circuit – energizing and task monitoring

The ACC forms part of the brain´s limbic system, and encompasses BA 24, 32, and 25 (Bush, Luu, & Posner, 2000). Neurons in BA 24 project to the ventral striatum, which includes the ventromedial caudate, ventral putamen, nucleus accumbens, and olfactory tubercle, collectively termed the limbic striatum. The ventral striatum and accumbens also receive inputs from the amygdala, and establish extensive output to the limbic midbrain. Thus, the so-called emotional circuits of the brain can directly influence autonomic and motor centers involved in expression of motivated behaviors and emotion, without passing through cortical relays (Bonelli & Cummings, 2007; Saint-Cyr, et al., 2002). Cognitive and emotional information is mainly processed in separate subsystems of the ACC; the dorsal cognitive division (ACcd), and the rostral-ventral affective division (ACad) (Bush, Luu, & Posner, 2000; Bush et al., 1998; Vogt, Nimchinsky, Vogt, & Hof, 1995; Whalen, et al., 1998), although it has been argued that the clear-cut dichotomy between the cognitive and affective divisions of the ACC might be overly simplistic, as the dorsal ACC is involved in emotional processing as well, particularly negative emotions (Etkin, Egner, & Kalisch, 2011). The Stroop task is the neuropsychological test typically considered to measure the ability to override a prepotent response (Delis, Kaplan, & Kramer, 2001), and ACC-activation has been demonstrated during Stroop performance (Matthews, Paulus, Simmons, Nelesen, & Dimsdale, 2004; Pardo, Pardo, Janer, & Raichle, 1990). Medial PFC (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 attributing energy or effort to attentionally demanding tasks (Stuss & Alexander, 2007).

Theories regarding the role of ACC in cognitive control typically converge on a key role in performance monitoring, conflict detection, and response-selection (Alexander & Brown, 2010; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter, et al., 1998; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). A dynamic relationship between ACC and DLPFC 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 system of DLPFC, where the actual stimulus manipulation and attentional maintenance and control is performed (Gehring & Knight, 2000; MacDonald, Cohen, Stenger, & Carter, 2000; van Veen & Carter, 2006; Walsh, Buonocore, Carter, & Mangun, 2011). Paper III provides an overview of this issue.

Bilateral lesions to the ACC circuit, including subcortical structures, can cause akinetic mutism, a clinical state characterized by wakefulness but serious apathy and lack of behavioral and emotional spontaneity (Bonelli & Cummings, 2007; Mega & Cohenour, 1997). Focal lesions to the ACC are rare, as spontaneous lesions of the ACC, such as tumors or strokes, typically involve neighboring areas (Devinsky, Morrell, & Vogt, 1995). Damage to the ACC can however come about after various etiologies such as TBI, CVA (ACom aneurysms), and tumors. Apathy is also common in degenerative dementias such as AD, HD, and PD (Tekin & Cummings, 2002).

4) The frontal polar region - metacognition

Although the polar frontal region (BA 9, 10 & 11) is not one of the originally described frontal-subcortical circuits, this area is mentioned, as it has been proposed to play a crucial role in integration of cognitive control and self-regulation. This results in a capacity for high-level abstract reasoning (Badre & D'Esposito, 2007; Koechlin & Summerfield, 2007) as well as self-awareness; the upholding of a metacognitive representation of one´s own mental states, beliefs, attitudes and experiences. The latter is a prerequisite for realistic assessments of ourselves in relation to the outer world, including the inner states of other people (Stuss & Levine, 2002). The polar frontal areas are from an evolutionary perspective, the newest part of PFC (Cicerone, Levin, Malec, Stuss, & Whyte, 2006). A hierachical model of information processing in the PFC has been suggested, where executive control is proposed to be hierarchically organized along the anterior–posterior axis of the lateral PFC (LPFC) (Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Koechlin, Corrado, Pietrini, & Grafman, 2000; Koechlin, Ody, & Kouneiher, 2003;

Koechlin & Summerfield, 2007). Sensorimotor cortex is postulated to deal with tasks where actions are defined by the external stimulus itself, while posterior LPFC will be engaged in tasks where the immediate environment provides contextual signals to guide action selection. Anterior divisions of LPFC will be activated when a discrete past event defines a new set of rules for action selection, while the most anterior LPFC is activated when action needs to be selected among several past cues during multiple task performance (Koechlin & Summerfield, 2007). More recently, it has been argued that the dimension of primary interest along the posterior-anterior axis is not the nature of the cues in the external environment, but the level of cognitive abstraction required (Badre & D'Esposito, 2007; Badre, Hoffman, Cooney, & D'Esposito, 2009).

In summary, the PFC is not an undifferentiated anatomical or functional entity. The anatomical networks described here represent a simplification, but provide a conceptual framework for understanding prefrontal functioning that is evolutionary, anatomically, functionally and clinically useful. See figure 4 for a gross summary of subregions of primary interest:

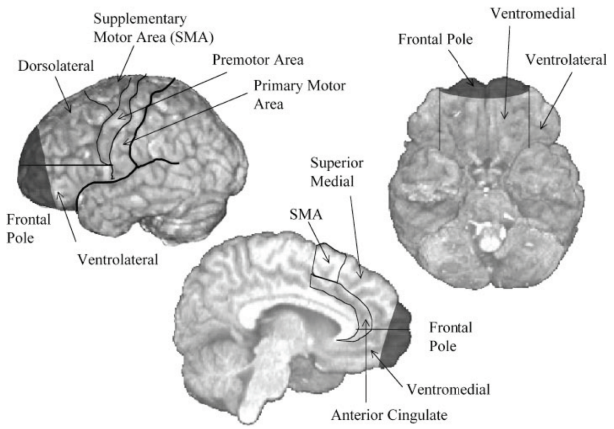

Figure 4. Major functional subdivisions of the human frontal lobes (Stuss & Levine, 2002, p. 408. Reprinted with permission).

Core cognitive domains in executive functioning – attention and inhibition

As the PFC deals with information from all other brain areas, it is involved in top-down modulation of all cognitive functions. However, some cognitive processes lie at the heart of cognitive control, and are of particular relevance to this thesis. This is the capacity to control allocation of attentional resources, and the ability to inhibit some thoughts, emotions and behaviors in favor of others. Thus, in the following, theoretical and empirical issues relating to

1) controlled attention, and 2) inhibition, will be discussed. Although presented separately, inhibition and attention are closely related cognitive constructs.

Controlled attention and the PFC

"Everyone knows what attention is. It is the taking possession by the mind in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought... It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrained state which in French is called distraction." (James, 1890, pp. 403-404)

Attention is a limited-capacity phenomenon. It can be described along several dimensions, such as degree of automaticity vs. conscious control. It can be directed towards action, thoughts or percepts, and be focused towards one aspect of the environment or shared amongst several (Shallice, Stuss, Alexander, Picton, & Derkzen, 2008). Three principles for attentional functioning were noted by Posner and Petersen (1990): 1) attention systems of the brain are *anatomically separate* from other cognitive functions even though attention interacts with other cognitive domains, 2) attention is carried out by a *distributed network* of brain areas. Thus, attention is neither carried out in one specific area, nor is it an undifferentiated property of the whole brain, and finally, 3) the areas involved in attention can be separated from each other and *described in cognitive terms* (Posner & Petersen, 1990). Three attention systems were proposed; 1) alerting, 2) orienting, and 3) executive attention. Alerting is related to tonic maintenance of an alert state and phasic responses to warning signals. Automatic and voluntary orienting is involved in the selection of information among multiple sensory inputs, while executive attention involves detecting and resolving conflict in order to control thoughts or behaviors (Fan, et al., 2009; Posner & Petersen, 1990; Rothbart & Posner, 2005). The Attention Network Test is a task designed to disentangle the three dimensions of attention (Fan, McCandliss, Sommer, Raz, & Posner, 2002), which has contributed in validating the three networks and their functional neuroanatomy (Fan, et al., 2009; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Fan & Posner, 2004; Posner & Rothbart, 2007). Figure 5 displays the functional neuroanatomy of the alerting, orienting and executive attentional networks.

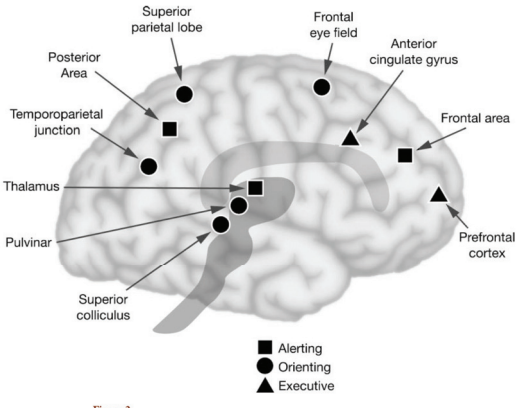

Figure 5. Functional neuroanatomy of the alerting, orienting and executive attention networks. From Posner & Rothbart, 2007, p. 6. Reprinted with permission.

The executive attention network involves PFC, particularly the dorsal ACC and ventrolateral PFC (Fan, et al., 2005), confirming a dynamic interplay between ACC and LPFC in tasks involving cognitive conflict and attention (Bush, et al., 2000; Gehring & Knight, 2000; MacDonald, et al., 2000; Walsh, et al., 2011). Petersen and Posner (2012) recently reviewed empirical and theoretical developments since their 1990-review, and suggested two independent executive attentional control networks. The cingulo-opercular system is linked to the ACC and anterior insular cortex, and deals with stable background task-set maintenance across trials, while a fronto-parietal control network deals with task switching and initiation, and ensures behavioral adjustment within trials.

Theories of executive attention

Influential theories of executive attention are the Supervisory Attentional System (SAS) (Norman & Shallice, 1986) and the Central Executive (CE) in working memory (Baddeley & Hitch, 1974).

The Central Executive in working memory. In contrast to earlier and more static short-term memory models (Atkinson & Shiffrin, 1971), Baddeley and Hitch (1974) presented a model of working memory that incorporated an account of attentional control. Working memory was postulated to consist of two temporary storage systems; the phonological loop and the visuo-spatial sketchpad, whereas the Central Executive (CE) represented a limited-capacity system capable of both storage and manipulation of information (Baddeley, 1996, 2002). Three distinct

tasks for the CE have later been described; dual-task performance, task switching and active retrieval from memory storage (episodic buffer). Baddeley avoided referring to anatomical structures (Baddeley, 1996, 2002), and proposed that the term "frontal lobe syndrome" should be replaced by the functional term "dysexecutive syndrome" (Baddeley & Wilson, 1988).

Supervisory Attention System. The SAS model also incorporated control mechanisms in proposing two attentional concepts; 1) the Contention Scheduling System, dealing with routine operations, and 2) the Supervisory Attention System, called into action in non-routine situations (Norman & Shallice, 1986). The PFC was believed to be the area of interest for the SAS. However, in its first version, the model relied heavily on concepts derived from the field of Artificial Intelligence (AI), and was underspecified as to the cognitive content of the SAS as well as its neural underpinnings. The model has been specified further in later work (Shallice, 2002; Shallice & Burgess, 1996), where 4 subsystems are described; a) the modulation of contention scheduling, b) monitoring/checking, c) retrieval of relevant memory traces, and d) intentionality. Anatomical localizations in the PFC were suggested, with the four systems originating in the left VLPFC (a), right VLPFC (b & c), and BA 10 (d). Schallice (2002) concluded very similarly to Posner and Peterson (1990): 1) specific control processes come into play in non-routine situations, 2) non-routine processing is performed by distinct and separable cognitive systems, and 3) there is a neuroanatomical correlate to these systems.

Fractionated networks of executive attention

Stuss and colleagues have provided considerable evidence from studies of patients with PFC lesions that supports fractionation of the anterior attention networks (Alexander, 2005; Alexander & Stuss, 2000; Alexander, Stuss, & Fansabedian, 2003; Alexander, Stuss, Picton, Shallice, & Gillingham, 2007; Stuss, 2011; Stuss, et al., 1998; Stuss, et al., 2005; Stuss & Benson, 1984, 1986; Stuss, Binns, Murphy, & Alexander, 2002; Stuss, et al., 2001; Stuss, Floden, Alexander, Levine, & Katz, 2001; Stuss & Levine, 2002; Stuss, Shallice, Alexander, & Picton, 1995). With the SAS as a theoretical starting point, Stuss and colleagues stated: *"If we are correct that there is no central executive, neither can there be a dysexecutive syndrome. The frontal lobes (in anatomical terms) or the supervisory system (in cognitive terms) do not function (in psychological terms) as a simple (inexplicable) homunculus" (Stuss, et al., 1995,* p. 206).

Three distinct attentional control systems with identifiable anatomical substrates have been suggested: 1) energizing, 2) task setting, and 3) monitoring (Stuss & Alexander, 2007).

Energizing *refers to initiating and sustaining a response,* by which performance maintenance over long periods of time is ensured. Superior medial (SM) prefrontal lesions are associated with altered energization in tasks requiring simple reaction times (RT), choice RT, sustained preparation to respond, verbal fluency and Stroop tasks (Stuss & Alexander, 2007). The ACC, as well as supplementary motor area (SMA) and the preSMA also contribute, with a dominant role for the right hemisphere. The energizing network is highly similar to the cingulo-opercular system proposed by Petersen and Posner (2012).

Task setting *refers to the ability to set a stimulus-response relationship.* This includes initial learning, and implies the suppression of irrelevant behaviors in specific stimulus contexts. This is related to flexible adaptation of behavior in the face of changing stimulus-response contingencies. Stuss and Alexander (2007) review studies demonstrating that patients with lesions to the left lateral PFC are impaired on initial trials of attentional RT-tasks as well as on a verbal Stroop task, set-loss in the Wisconsin Card Sorting Task (WCST), and "false positive" responses in verbal memory and Go/NoGo tasks. This system is closely associated with the fronto-parietal control network described by Petersen and Posner (2012).

The third control system; ***monitoring****, refers to the checking of task performance over time.* It ensures "quality control" and behavioral adjustment, and is related to processes such as adequate timing of behavior, anticipation of future events, error detection and discrepancies between behavioral responses and the external reality. Stuss and Alexander (2007) summarize that the right lateral PFC seems to be of particular relevance for monitoring.

Stuss and coworkers attempted to establish empirically justified subcomponents within the overall concept of controlled attention. This does not, however, imply independent processes, as they will be recruited in a flexible manner, and cooperate with each other as well as with posterior regions (Stuss & Alexander, 2007). Stuss and Alexander (2007) claimed that the concepts of energizing, task setting and monitoring are sufficient to explain phenomena traditionally explained as a result of inhibition. They stated that while inhibition clearly exists at a neurobiological and neurochemical level, its justification as an important psychological construct should be questioned and explored.

The frontal lobes and inhibition

Inhibition relates to "*the process of suppressing or restraining an action, sensation, feeling, thought or desire"* (Hooker & Knight, 2002). At a neuronal/neurochemical level, the dynamic balance between facilitation and inhibition of signal transmission is a basic characteristic of the central nervous system, and not a localized function. Miller and Cohen (2001) placed the interplay between facilitation and inhibition at the core of all information processing in stating that information processing in the brain is fundamentally competitive: Different pathways, carrying different sources of information, compete for expression in behavior, and the winners are those with the strongest sources of support.

At the **cognitive level**, inhibition is closely related to selective attention (Kok, 1999). It is associated with the selection of goal-relevant information as well as contextually appropriate responses, in parallel with the suppression of irrelevant information and prepotent but inappropriate response tendencies. This dynamic balance between excitation and inhibition results in optimization of the signal-to-noise ratio in the information processing stream (Brunia, 1999). The theory of dynamic filtering proposes that the PFC establishes executive orchestration of signals in various brain areas through a filtering mechanism that inhibits some signals and maintains activation of others (Shimamura, 2000), again placing inhibition and selective attention at the heart of executive control. Examples of the extensive number of experimental paradigms and psychological methods used to study cognitive aspects of inhibition are presented in Kok (1999).

At the **affective level**, inhibition is closely related to impulsivity, decision-making and behavioral regulation. Within the somatic marker hypothesis (Damasio, 1995), reasoning and decision-making in the personal and social domain is proposed to be intimately connected to the dynamic regulation of affective stimuli with the ventromedial OFC in a particular position to do so. Shimamura likewise said that although the model of dynamic filtering was established to account for cognition and memory, it is as well suited to understand the executive control of emotion (Shimamura, 2000).

Particularly paper I, but also paper III explore the effect of frontal lobe injury to the balance between detecting and responding to task-relevant target information and orienting towards and processing of irrelevant but salient distracting stimuli. A thorough review of electrophysiological studies of target and novelty processing of auditory stimuli can be found in the introduction and

discussion of paper I. The neuroanatomical basis for conflict detection, error monitoring and response inhibition is dealt with in paper III. The neuropsychology of cognitive inhibitory control is discussed in paper II.

The neuropsychology and assessment of EF

Executive deficit is common following acquired brain injury as well as a wide range of psychiatric and degenerative diseases and is a potent negative predictor for long-term outcome (Bonelli & Cummings, 2007; Draper & Ponsford, 2008; Goldberg, Andrews, & Hobbs, 2009; Heinrichs & Zakzanis, 1998; Levine, Katz, Dade, & Black, 2002). Concluding about the presence of executive problems and their relation to the brain poses one of the most common and at the same time most challenging issues raised in clinical neuropsychological practice. There is no "gold standard" against which presumed EF deficit can be measured. Royall and colleagues (2002) noted three reasons why this may not be achievable; 1) since the PFC constitutes such a large part of the brain, it is unlikely that any one measure would be able to cover its functions, 2) the anatomy of the PFC suggests that subcortical lesions would affect EF, and 3) since the essence of EF is to influence lower level functions on a superordinate level, it is a challenge to obtain measures that distinguish between a deficit in top-down control over the function, and the function itself.

Psychometric properties of tests are typically described in relation to their reliability, validity and diagnostic utility (sensitivity and specificity). The latter question relates to whether a measure in question is sensitive enough to detect true cases of PFC damage, and specific enough to reject cases with no PFC damage (Zald, 2002). There is a need for diagnostic tools that not only differentiate between healthy controls and patients with PFC damage, but also differentiate between patients with PFC damage and those with lesions to other parts of the brain, and finally, between lesions to different frontal subsystems. A great challenge in relation to EF assessment, is that many tests considered "frontal" have weak evidence for their relationship to the frontal lobes. Additionally, anatomical validity studies have typically not explored different regions within the frontal lobes (Stuss, 2007). Finally, given the multifactorial nature of any test aiming at detecting deficit in complex higher-order functions, patients might fail the same test for different reasons and due to lesions in different parts of the brain (Knight & Stuss, 2002).

Assessment of cognitive executive dysfunction

Much of what is known about neuropsychology and executive functions is derived from patients with DLPFC lesions (Stuss & Benson, 1984), and neuropsychological test measures will typically be more sensitive to the effect of DLPFC compared to OFC lesions (Jurado & Rosselli, 2007; Knight & Stuss, 2002; Levine, Katz, Dade, & Black, 2002; Zald, 2002; Zald & Andreotti, 2010). In the following, a brief review of the functions that are typically tested in relation to cognitive EF will be described. The topic is also covered in paper II.

Tests of **controlled speeded language production** (verbal fluency) are commonly used, as phonemic fluency has been shown to be associated with lesions to left DLPFC, and not right DLPFC nor OFC (Stuss, et al., 1998). Semantic fluency is typically normal after PFC injury (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). However, bilateral posterior medial lesions as well as parietal lesions may also result in impaired function (Stuss, et al., 1998), and imaging studies have confirmed that a network involving left DLPFC, posterior medial PFC and parietal cortex is involved in word generation (Cabeza & Nyberg, 2000).

Frontal lobe lesions typically do not result in classical amnesia, but affect **strategic aspects of memory and learning**, as part of a broader impairment associated with reduced control over irrelevant information. Deficit is most pronounced when performance depends upon self-initiated encoding and organization, as on tests of free recall. Also, tests involving extensive search and retrieval processes, such as tests of **source memory** and **metamemory**, are susceptible to PFC lesions (Shimamura, 1995). Word list learning tasks are typically included in neuropsychological assessments, and problems with encoding, retrieval as well as recognition and organizational aspects of learning have been shown to be associated with lesions to PFC (Baldo, Delis, Kramer, & Shimamura, 2002), particularly left DLPFC (Alexander, et al., 2003). Medial PFC is associated with the **consolidation of long-term memory** (Nieuwenhuis & Takashima, 2011). See paper III for a discussion.

Tests of **working memory functions** are typically denoted as “frontal lobe tests”; as PFC is involved in any task requiring short-term retention and manipulation of information that is no longer accessible in the environment (D'Esposito, Postle, & Rypma, 2000). Examples of common working memory tests are Digit Span Backwards and Letter-Number Sequencing (WAIS-III; Wechsler, 1997), as well as the Paced Serial Addition test (PASAT; Gronwall,

1977). Lesion studies have confirmed a role of DLPFC in the Letter-Number Sequencing task (Stuss, et al., 2001; Yochim, Baldo, Nelson, & Delis, 2007).

Related to working memory are tasks requiring **task set and attentional switching**, such as the Wisconsin Card Sorting test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993) and switching conditions of Trail Making tests (Delis et al., 2001). The WCST is widely considered a frontal lobe test, and not unjustified, as both monkey (Buckley, et al., 2009) and human (Stuss, et al., 2000) studies have confirmed an association between PFC and WCST-performance. However, the WCST also relies on multiple cognitive functions, and it seems that while DLPFC lesions affect extra-dimensional task setting, ventral PFC lesions result in loss of task set (Stuss, et al., 2000). The WCST can also be affected by posterior brain lesions (Anderson, Damasio, Jones, & Tranel, 1991). The switching condition of the Trail Making Test is likewise often cited as a "frontal lobe test", although it is multifactorial in that it also tests for mental speed and visual search (Stuss & Levine, 2002).

Selective attention. As noted, the Stroop task is commonly used to assess inhibition in cognitive conflict situations, and Stroop-performance is associated with activation of medial PFC and the ACC (Matthews, et al., 2004; Pardo, et al., 1990). Stuss et al. (2001) reported that deficient performance on the color naming condition of the Stroop test was associated with left DLPFC injury, whereas impaired performance on the incongruent/inhibition condition was associated with lesions to superior medial PFC. The close cooperation between DLPFC and MPFC is indicated in another lesion study where impairment was seen after right DLPFC lesions (Vendrell, et al., 1995). OFC damage, on the other hand, does not result in diminished Stroop-performance (Alvarez & Emory, 2006).

The capacity for **sustained attention** in dull, repetitive tasks is associated with top-down modulation of endogenous arousal (Levine, Katz, et al., 2002). In tasks with low level of cognitive demand or conflict, a right lateralized frontoparietal network has been identified where LPFC is involved together with superior parietal cortex (Corbetta, et al., 2008; Pardo, Fox, & Raichle, 1991; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). In neuropsychological practice, this is typically assessed with continuous performance tasks (e.g. Conners, 2002).

Assessment of self-regulatory dysfunction

Despite largely normal test results, patients with lesions to the orbital (OFC) or orbitomedial PFC (OMPFC) can have devastating problems in everyday functioning, with profound impairment in occupational, leisure, social and emotional functioning (Knight & Stuss, 2002; Levine, Katz, et al., 2002; Zald, 2002; Zald & Andreotti, 2010). A study of patients with neurodegenerative disease demonstrated this double dissociation as OFC volume predicted behavioral regulation, whereas DLPFC volume predicted performance on tests of EF (Krueger, et al., 2011). Levine and colleagues used the term **self-regulatory disorder (SRD)** for the cluster of symptoms exhibited by patients with injury to OMPFC, defined as "*the inability to hold a representation of the self on-line and to use this self-related information to inhibit inappropriate responses"* (Levine et al., 2002). SRD will be most prominent in unstructured environments, in contrast to the well-structured context of a neuropsychological examination.

There is no "gold standard" for measuring the effects of OMPFC dysfunction. Some measures originating in experimental research traditions have shown to be quite sensitive to OMPFC functions, while the challenge for clinicians is that they typically lack a sound normative basis (Zald & Andreotti, 2010). Zald and Andreotti (2010) propose 5 functional domains of relevance to OMPFC which will be outlined briefly in the following, with representative examples of measures within each functional category.

1) Learning and adapting to changing reinforcement contingencies

Tasks related to alternation of task-set combined with changes in reward contingencies tap into this function; such as Object Alternation (OA) tasks where a subject is e.g. asked to select the object that was not chosen in a prior trial. OA performance is related to the phenomenon of perseveration and is impaired in both monkeys (Mishkin & Manning, 1978) and humans with OMPFC lesions (Fujiwara, Schwartz, Gao, Black, & Levine, 2008). In reversal learning tasks, subjects learn the association between originally neutral stimuli and their rewarding or punishing value, and are subsequently required to inhibit selection of previously rewarded stimuli when rules are reversed. Reward-based learning has been associated with OFC (Berlin, Rolls, & Kischka, 2004; Elliott & Deakin, 2005; Hampshire & Owen, 2006), and it seems to be the value-/reward aspects of the tasks that are associated with OFC, as OFC lesions do not result in perseverative errors on the WCST, where the rule-reversal is of a cognitive nature (Stuss, et al., 2000).

2) Decision-making/gambling tasks

Observation of poor and risky decision-making in patients with OFC lesions has precipitated development of reward-based decision-making tasks, such as the Iowa Gambling task (Bechara, Damasio, Damasio, & Anderson, 1994). Subjects draw cards from decks whereof some lead to high short-term but low long-term monetary gain and others to lower short-term but higher long-term gain. Patients with VMPFC lesions tend to make risky decisions based on short-term considerations (Bechara, et al., 2000; Bechara, Damasio, Damasio, & Lee, 1999; Bechara, Damasio, Tranel, & Anderson, 1998), and it seems that the right VMPFC is of particular relevance (Tranel, Bechara, & Denburg, 2002).

3) Social processing

Efforts have been made to establish measures that are sensitive to the social sequelae of PFC injury. These range from tests of basic emotional perception to complex social processing. An example of the former is "Reading the Mind in the Eyes test" (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), where subjects are asked to infer the emotional state of a depicted face where only the eyes and surrounding facial area is visible. Aspergers syndrome and autism is associated with impaired performance (Baron-Cohen, et al., 1997; Baron-Cohen, et al., 2001). Impaired interpretation of facial expression has also been shown to be reduced in patients with VMPFC lesions (Blair & Cipolotti, 2000; Heberlein, Padon, Gillihan, Farah, & Fellows, 2008). Assessing complex social cognition involves examining Theory of Mind (ToM); the ability to make inferences regarding the mental states of others, and "faux-pas" situations which involves interpretation of social blunders. These functions have been shown to be associated with PFC and VMPFC in particular (Lough, et al., 2006; Shamay-Tsoory, Tomer, Berger, Goldsher, & Aharon-Peretz, 2005).

4) Olfactory functioning

The olfactory bulbs are located above the olfactory sulcus adjacent to the gyrus rectus in OFC, and the OFC receives extensive olfactory projections (Gottfried & Zald, 2005). Loss of smell is most common with lesions to the olfactory nerve, while smell distortions are associated with damage to the secondary olfactory cortex (Zald & Andreotti, 2010). Smell disturbances might be among the most sensitive and specific measures of OFC dysfunction (Jones-Gotman & Zatorre, 1988). The University of Pennsylvania Smell Identification Test (Jones-Gotman & Zatorre, 1988) includes normative data.

5) Memory

Confabulations have been defined as "falsification of memory occurring in clear consciousness in association with an organically derived amnesia" (Berlyne, 1972). Confabulations are characterized by an inability to adapt thought and behavior to ongoing reality, leading patients to act according to presently inappropriate memories (Schnider, 2003). Confabulation and personality change is a common sequelae of ruptured aneurysms of the anterior communicating (ACom) artery (Alexander & Freedman, 1984). OFC is also involved in retrieval of autobiographical episodic memory (Brand & Markowitsch, 2006; Fujii, et al., 2004). The Autobiographical Interview was designed to capture deficits in autobiographical memory (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002).

Executive functions in everyday living – interview and questionnaire data.

As symptoms of PFC damage are often not detected in formal assessments, efforts have been made to establish measures with predictive value in relation to everyday functioning (Gioia & Isquith, 2004; Gioia, Kenworthy, & Isquith, 2010). To this end, structured interviews and questionnaires allowing collection of both self-report and informant data have been developed. Several questionnaires are in clinical use, although availability of normative data and descriptions of the psychometric properties of the scales vary (see Malloy & Grace, 2005; Zald & Andreotti, 2010 for reviews). One rating scale that aims at distinguishing between distinct aspects of EF, is The Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) (Roth, Isquith, & Gioia, 2005). See paper II for a discussion of the BRIEF-A in relation to prefrontal subsystems and behavioral measures.

Summary - assessment of executive function

While some neuropsychological tests are sensitive to PFC dysfunction, they are typically also sensitive to injury in other brain regions, and the anatomical specificity within PFC is low. Additionally, while patients with frontal lobe injury typically perform worse than healthy controls, the results are often within normal limits (Alvarez & Emory, 2006), further complicating clinical conclusions in individual patients. Finally, the tests reviewed here almost exclusively seem to be sensitive to the cognitive EF subserved by lateral and medial PFC.

Diagnosing executive deficit represents one of the most complex assessment issues for clinical neuropsychologists. Dysexecutive symptoms can occur after a wide range of conditions, not necessarily due to structural brain injury (Goldberg & Chengappa, 2009; Heinrichs & Zakzanis,

1998). On the other hand, dysexecutive symptoms following acquired brain injury can be devastating, but not detected in formal neuropsychological evaluations (Royall, et al., 2002). There is thus substantial risk of both over- and underdiagnosing organicity of symptoms.

In order to improve assessment, an integrational approach to clinical examination and research is needed. Zald and Andreotti (2010) noted the potential of integrating frontal-specific and neuropsychiatric rating scales as well as experimentally derived measures. They also emphasize the need to develop standardized versions of these measures along with normative data, and that this, combined with advances in neuroimaging and neurophysiology have the potential to increase our understanding of PFC functioning, particularly of the OMPFC.

The electrophysiology of attentional control

An "Event-Related Potential" – ERP – is an electrical change recorded from the brain in association with an occurrence in the external environment or within the brain (Picton, Lins, & Scherg, 1995). Human ERPs are most often recorded from the scalp, but intracranial recordings are also performed (Flinker, Chang, Barbaro, Berger, & Knight, 2011; Halgren, Marinkovic, & Chauvel, 1998). ERP is based on continuous electroencephalographical (EEG) recordings, where the ERP represents small perturbations of spontaneous electrical activity that are time-locked to a definable event. Signals are averaged across repeated stimulus presentations in order to eliminate the background EEG activity, thus producing a measure of the stimulus-specific processing (Näätänen, 1992). The resulting ERP curve contains a rich record of information-processing events distributed in the temporal as well as the spatial domain (Reinvang, 1999). ERPs are recorded on individual electrodes of varying numbers, placed according to a standardized system, see Figure 6.

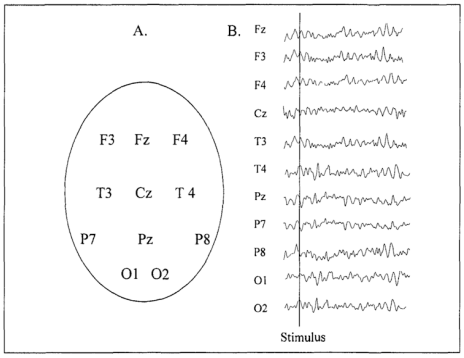

Figure 6. Properties of electroencephalography (EEG) and derivation of event-related potentials (ERPs). (A) Electrodes are placed on the skull in locations defined by the International 10-20 system (F = frontal, T = temporal, C = central, P = parietal, O = occipital; odd numbers = left side, even numbers = right side, z = midline; increasing numbers indicate increased distance from midline). A simplified array of 11 electrodes is shown, whereas up to 128 electrodes or more can be used in studies with dense placements. (B) EEG activity is recorded and amplified from different electrodes while a stimulus is

presented. For the clinician to bring out an ERP component of the EEG, averaging over repeated stimulus presentations is necessary, with the stimulus onset defining the point of temporal coordination of events (Reinvang, 1999). Reprinted with permission.

ERPs represent activity over large neuronal groups, and only cerebral activity that is sufficiently synchronized to create electrical fields measurable on the scalp will be detectable. Also, any recording at a given scalp site represents the summed activity of temporally converging activity, which nonetheless might represent separate and distinct underlying cognitive processes in need of disentanglement. Thus, although the electrode density affects the potential for anatomical localization of activity, and topographical interpretations can and are typically made, the basis for detailed anatomical localization of activity is limited compared to other imaging techniques, such as fMRI. On the other hand, the temporal resolution of the ERP-method is excellent and offers the opportunity to observe dynamics of stages of information processing at the millisecond level. ERP-components are typically described along a temporal continuum and according to their polarity. ERPs have traditionally been termed "endogenous" or "exogenous", where endogenous components have largely been considered to be determined by physical stimulus characteristics, while the exogenous components have been interpreted as being cognitively mediated (Picton, et al., 1995). The endogenous-exogenous dimension generally follows a temporal order, with the earlier ERP components being less cognitively mediated than the later ones. This distinction is, however, not absolute. The findings of paper II illustrate that also the early and largely stimulus-driven ERP components are subject to cognitively mediated top-down control from the frontal lobes (Friedman, Cycowicz, & Dziobek, 2003; Knight, Hillyard, Woods, & Neville, 1980; Kok, 2000).

Given sound and theoretically well-informed experimental paradigms, the ERP-method provides a spatio-temporal representation of the flow of information processing during stimulus processing and task execution, and is of particular promise in the study of attentional dynamics (Näätänen, 1992). By need of brevity, only the most common ERP-components associated with automatic and controlled attention will be mentioned, according to their temporal order:

N1 and P2 occur within the first 200 ms after stimulus onset, and are considered to reflect sensory processing. However, these early potentials may provide valuable indications that early processing is normal or impaired in more complex tasks. Additionally, early ERP components can be modulated by top-down processes and be affected by frontal lobe injury

(Knight et al., 1980). In a review of the sparse P2 literature, it was noted that the P2 seems to be influenced by both stimulus and task characteristics as it is elicited by both attended and unattended stimuli, but tends to display larger amplitudes in unattended conditions (Crowley & Colrain, 2004; Näätänen, 1992). The **Mismatch Negativity (MMN)** is a negative deflection elicited by rare deviant stimuli. The MMN is related to automatic deviance detection and is considered to reflect early attention selection in interaction with sensory traces (Näätänen, 1992).

N2 and P3 are mainly endogenous cognitive potentials, as they are more influenced by psychological variables of stimulus probability and task relevance than by sensory dimensions of the stimuli. N2 shows variation in topography and amplitude with changing sensory modality, whereas P3 is supramodal with a more stable topographic distribution (Reinvang, 1999). The P3 has been extensively studied. Tasks requiring allocation of attentional resources will elicit the central-parietal positive P3-component 3-500 ms after stimulus presentation. It is typically elicited by a to-be-responded-to (target) stimulus that occurs within a train of frequent standard tones that are to be ignored. The P3 is assumed to reflect an information processing cascade when attentional and memory mechanisms are engaged. If the task is supplemented with a salient distractor that is to be ignored, the novelty P3, or the P3a, is elicited (Squires, Squires, & Hillyard, 1975). It has a more frontal distribution than the P3b, it occurs earlier, it habituates easily and is related to the orienting response. The novelty P3 is observed across modalities, and is associated with PFC function (Polich, 2007; Soltani & Knight, 2000).

N2 and P3 can be followed by a negative deflection (**negative slow wave -NSW**). In language tasks, a posterior negativity (N400) is seen when the stimulus deviates from the semantic context (Kutas & Hillyard, 1980). Deviant stimuli can generate a frontally distributed NSW (Dien, Spencer, & Donchin, 2004; Näätänen, 1992) that has been discussed in relation to the orienting response and is typically observed in **Contingent Negative Variation (CNV)** paradigms where an initial stimulus (S1) signals that the second and imperative stimulus (S2) will follow (Walter, 1964). The frontal NSW is sensitive to task load, aspects of encoding and retrieval from long-term memory, and working memory (Ruchkin, Canoune, Johnson, & Ritter, 1995). Current theories typically link the frontal NSW to the level of mental processing (Ritter & Ruchkin, 1992; Ruchkin, et al., 1995).

Several ERP-components are associated with inhibition: (1) the frontal **N200**, (2) the **NoGo-**

P3, (3) the **Error Related Negativity (ERN)** and 4) the **"error-positivity" (Pe)**. In Go–NoGo and Stop-signal tasks, the N200, as well as the NoGo P3 have been proposed to index inhibitory control processes generated in the PFC, as both components have greater amplitudes for NoGo relative to Go trials (Kok, 1986; Pliszka, et al., 2007; Pliszka, Liotti, & Woldorff, 2000; Schmajuk, Liotti, Busse, & Woldorff, 2006), and the N200 is larger in successful compared to failed inhibition trials (Schmajuk, et al., 2006). The response-locked ERN peaks over fronto-central recording sites 60-80 ms after an error (Danielmeier & Ullsperger, 2011; Danielmeier, Wessel, Steinhauser, & Ullsperger, 2009; Edwards, Calhoun, & Kiehl, 2012), and is followed by the Pe (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Simons, 2010). A close link has been postulated between the ERN and the ACC (Emeric, et al., 2008; Gemba, Sasaki, & Brooks, 1986; Miltner, et al., 2003; Nieuwenhuis, Schweizer, Mars, Botvinick, & Hajcak, 2007; van Veen & Carter, 2002)

The effect of prefrontal lesions to the N1-P2 complex, the frontal Novelty P3, the target-related parietal P3b, as well as NSW, ERN and Pe is discussed at length in papers I and III.

Main research objectives

There is emerging consensus that EF is not unitary, but is a set of interrelated capacities resulting from activity in anatomically and functionally independent, but interrelated networks subserved by widespread brain regions where the PFC plays a central role (Stuss & Alexander, 2007). A vast amount of research has demonstrated that a distinction between the lateral, orbital, and medial subdivisions of the PFC are of relevance on an evolutionary, anatomical as well as a functional level (Bonelli & Cummings, 2007; Stuss, 2007; Stuss & Alexander, 2007; Stuss & Levine, 2002). However, a striking aspect of PFC function is its supramodal flexibility, which is a key factor in facilitation of adaptive behavior in the face of changing stimuli and task demands. It has therefore been questioned whether an approach concerned with linking specific functions to distinct PFC areas is fruitful (Duncan & Miller, 2002).

Control over limited attentional resources is a prerequisite for the human capacity for task initiation and maintenance as well as task switching, placing the concept of attentional control at the heart of EF (Petersen & Posner, 2012; Stuss & Alexander, 2007). It is a clinical challenge that patients with executive dysfunction can perform normally on formal cognitive assessments, but experience devastating problems in everyday living, resulting in compromised social relations, vocational problems and reduced quality of life (Zald & Andreotti, 2010). Making progress in understanding the neural underpinnings of EF requires a high level of conceptual precision along with a broad methodological approach where traditional neuropsychological behavioral measures are supplemented with rating scales as well as experimentally derived measures and modern neuroimaging techniques (Knight & Stuss, 2002; Zald & Andreotti, 2010). This thesis forms part of a larger research program which has undertaken a cognitive neuroscience approach, and where methodological integration has been aimed for. A lesion study approach was chosen, as lesion studies complement correlative neuroimaging methods with the opportunity to establish causal relationships (Nachev, 2006), as they can help detect what regions are *necessary* for optimal task performance, and not only *associated* with it. A patient cohort with isolated structural damage to subregions of PFC has thus been established.

The main research objectives of this work were:

1) to investigate the **validity of the lateral, orbital and medial subdivisons of PFC** (Bonelli & Cummings, 2007). Regional functional specificity was studied across a wide range of cognitive tasks**,** with a primary interest in aspects of **controlled attention** and the degree to which performance on these tasks is subserved by distinct anatomical regions within PFC (Petersen & Posner, 2012). Executive attention was explored with neuropsychological and questionnaire measures. Furthermore, electrophysiological correlates of attentional processes such as novelty and target detection, as well as error monitoring, were investigated.

2) to explore the additive value of applying various **methodological approaches** ranging from questionnaires of everyday living, behaviorally-based neuropsychological tests, experimental tasks and ERP in detecting executive impairment following lesions to subdivisions of the PFC.

Methods

Participants, methods and measures applied in papers I-III are summarized in table 1.

Table 1. Participants and methods included in papers I, II and III.

	Paper I	Paper II	Paper III
Participants			
OFC lesion	n=13	n=14	
LPFC lesion	n=6	n=10	
MPFC lesion			n=2
Healthy controls	n=15	n=21	Novelty oddball = 14 Stop-signal task = 15 Neuropsychology = 21
Experimental tasks			
Novelty oddball	X		X
Stop-signal task			X
ERP components			
N1	X		
P2	X		
N2	X		
P3b	X		X
Novelty P3	X		X
NSW	X		X
Error-related negativity (ERN)			X
Error positivity (EP)			X
Correct response negativity (CRN)			X
Go P3			X
Questionnaires			
CAGE	X	X	X
Edinburgh Handedness Inventory	X	X	X
Glasgow Outcome Scale Extended (GOSE)	X	X	X
Obsessive-Compulsive Inventory Revised (OCI-R)	X		
Symptom Checklist 90 Revised (SCL-90-R)	X	X	X
Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A)		X	X
Neuropsychological tests			
WASI (all 4 subtests)	X	X	X
Digit Span and Letter-Number Sequencing (WAIS-III)	X	X	X
Memory; CVLT-II & BVMT-R		X	X
D-KEFS (Trail Making Test, Design Fluency, Verbal Fluency, Color-Word Interference Test)	X	X	X

Participants

The patients included in the study were recruited from Oslo University Hospital, Sunnaas Rehabilitation Hospital and colleague referrals. Criteria for inclusion were: 1) age between 18

and 65 years; 2) focal prefrontal injury, with no extra-frontal damage; 3) injury sustained at least 6 months prior to study; 4) capability of simple motor response delivery in the experimental tasks.

Exclusion criteria were: 1) premorbid neurological injury or disease affecting the central nervous system; 2) serious premorbid or ongoing psychiatric disturbance (schizophrenia, bipolar disorder, personality disorder); 3) history of substance abuse/dependence requiring treatment; 4) profound vision or hearing loss; 5) pronounced aphasia (impeding communication) or spatial neglect; and 6) IQ below 85.

Potential participants were identified through inspection of medical journals and indication of PFC lesions. All tumor patients were referred by the neurosurgeon in the research group (T. Meling). After informed consent to participate in the study was given, pre-existing MRI and/or computer tomography (CT) scans were reviewed to establish lesion location. Those with focal prefrontal lesions, who adhered to the inclusion but not the exclusion criteria, were included in the study. In the larger research project, there has been a continuous on-going inclusion process. However, by the time data collection for all three papers included in this thesis was finalized, 35 patients had been included in the study sample, whereof 2 patients are included in paper III only due to the involvement of the ACC. Originally, this small subgroup consisted of three patients, but one was excluded due to uncertainty about lesion extent in addition to the patient being heavily medicated with both anti-epileptic drugs and sedatives for pain relief.

Paper I

By the time data collection for paper I was finalized, a total of 28 patients had been included. Of these, two TBI patients did not display positive prefrontal lesion on the MRI scans obtained at study inclusion, despite description of such lesions in the acute phase in their medical journals. One patient was excluded due to a very large PFC lesion that extended broadly into both LPFC and OFC, thus not possible to place into an anatomical subgroup. One TBI patient was furthermore excluded due to evidence of subcortical damage, and two were not included in the paper due to suspected ACC-involvement. Two patients were excluded due to excessive alpha rythm in the EEG. Thus, in paper I, a total of 19 patients were included, with 13 in an OFC group, and the remaining six in the LPFC group.

Paper II

When data analysis was performed for paper II, an additional six patients had been recruited, whereof two were excluded due to extensive tumor invasion into the corpus callosum. Of the remaining 25, one was excluded from paper II due to marginal lesion size. This resulted in 24 patients being included in paper II, whereof 14 in the OFC and ten in the LPFC group.

Paper III

Two patients were not included in paper I and II due to extensive unilateral medial PFC damage involving the ACC. These two patients are presented as case studies in paper III along with healthy control group comparisons.

Of note, a total of four patients with TBI were included, nine with meningeomas and the remaining 14 had low grade gliomas (LGG). All patients with tumors had gone through surgical tumor resection. None of the patients had received radiation therapy, while one patient in the LPFC group had undergone chemotherapy.

A control group was established that was matched to the patient groups by age and level of formal education. Two of the originally 23 healthy controls were excluded due to abnormal structural MRI scans, leaving 21 controls in paper II and III. In paper I, five controls were excluded due to a combination of technical issues related to EEG-recordings and excessive EEG artifacts.

Procedures

Neuropsychological test measures and questionnaires

All participants underwent a neuropsychological examination. The assessment included a custom-made questionnaire securing relevant demographic information as well as premorbid and current medical status.

The following neuropsychological test measures were applied:

Computations of full scale, verbal and performance IQ were based on the four subtests of the *Wechsler Abbreviated Scale of Intelligence* (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 working memory. Verbal learning and

memory was assessed with the *California Verbal Learning Test Second Edition* (CVLT-II; Delis, Kaplan, Kramer, & Ober, 2000). Visuospatial learning and memory was examined with the *Brief Visuospatial Memory Test-Revised* (BVMT-R; Benedict, 1997). The following subtests from the *Delis-Kaplan Executive Function System* (D-KEFS; Delis, et al., 2001) were included: Trail Making Test (TMT), Design Fluency, Verbal Fluency and Colour-Word Interference Test (CWI).

The following questionnaires were included:

Screening of alcohol and drug use was performed with the *CAGE*-questionnaire (Ewing, 1984), while handedness was assessed with the *Edinburgh Handedness Inventory* (Oldfield, 1971). The functional outcome of the patients was classified with the *Glasgow Outcome Scale Extended* (GOS-E; Wilson, Pettigrew, & Teasdale, 1998; Røe et al., 2008), which is a hierarchical scale where overall rating is based on the lowest outcome indicated. Screening of emotional distress was performed using the *Symptom Checklist 90 Revised* (SCL-90-R; Derogatis, 1994). 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 filled out the informant version of the questionnaire. Presence of obsessive-compulsive symptoms was explored using the *Obsessive-Compulsive Inventory Revised* (OCI-R; Foa et al., 2002).

Experimental tasks

Detailed descriptions of the experimental paradigms can be found in the methods section of Paper I and Appendix A of paper III.

Target and Novelty detection was examined in a three-tone auditory novelty oddball task (paper I and III). Subjects were presented with 70 % designated standard tones (1000 Hz) to be ignored, and 15 % target tones that differed from standards in pitch (1500 Hz). Interspersed were also 15 % perceptually salient and meaningful unique distractor sounds (e.g. dog barks, door slams, laughter). Subjects were instructed to make a button press to target tones and ignore all other sounds.

Behavioral inhibition and performance monitoring was examined in a Stop-Signal Task (paper III) where subjects were instructed to make a right button press after seeing an arrow pointing towards the right and a left button press following left-pointing arrows. In 43 % of

the trials, a stop-signal prompted the subjects to not press the button after all (stop-signal). Approximately equal distribution between successful and failed inhibitions was ensured through individually tailoring inhibitory difficulty (see Appendix A in paper III).

Although results are not reported in this thesis, is should be mentioned that all participants completed a **Contingent Negative Variation (CNV)** paradigm using both ERP and fMRI, allowing investigation of anticipatory attention, as well as a Stop-signal task adopted for fMRI. Papers discussing the role of PFC in anticipatory attention and motor preparation in healthy subjects (Funderud et al., 2011) and patients with LPFC and OFC lesions (Funderud et al., 2010) are under preparation. Preliminary data showing ERP-correlates of motor inhibition and error monitoring has also been presented (Solbakk et al., 2011).

EEG-recordings

All EEG-data were acquired using a 128-channel HydroCel Geodesic Sensor Net and Net Amps 300 amplifier (Electrical Geodesics, Eugene, OR). Detailed descriptions of EEG recording, data preprocessing and strategies for ERP-analysis can be found in the methods section of Paper I and Appendix A of paper III.

MRI lesion reconstruction

Structural MRI scans of patients and healthy controls were obtained after study inclusion using a 3 Tesla Philips scanner at the Interventional Center at Oslo University Hospital - Rikshospitalet. Lesion reconstructions were established by drawing the lesion outlines in MRIcron (Rorden & Brett, 2000). As lesion volume might be underestimated reconstructions are based on T2 images, lesions were reconstructed on Fluid attenuation inversion recovery (FLAIR) images, with T2 images available for comparison. Each MRI volume contained 160 slices, resulting in good spatial resolution. The lesion reconstructions were transferred to a normalized space as the T1 image of each subject was coregistered to a reference T1 image (the Colin-brain; Collins, et al., 1998), using the Statistical Parametric Mapping software (SPM.5; http://www.fil.ion.ucl.ac.uk/spm). Individual FLAIR images were coregistered to the normalized T1 image. The resulting transformation parameters were then applied to the lesion mask, ensuring alignment of the T1, FLAIR, and lesion mask. Overlays of standardized lesion reconstructions were established using MRIcron, which also provided information about lesion volume, affected Brodmann areas (BA), as well as estimated lesion size within each BA. Consensus was established on the accuracy of lesion reconstructions, with the

neuroradiologist, neurologist and neurosurgeon in the research group (authors P. Due-Tønnessen, R. T. Knight, and T. Meling) playing important advisory roles.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 and 18.0 (SPSS Inc.). ERP-data was analyzed using repeated measures analysis of variance (ANOVA), and demographic, psychometric and performance data with One-Way ANOVA, in both cases with Group (Control, OFC and LPFC) as between-subjects factor. In cases of significant differences between patient groups, lesion volume was entered as a covariate in an ANCOVA. In paper II, effect size was computed using partial eta-squared. Relationships between measures were explored with Pearson two-tailed correlation coefficients. Results are reported with a significance level of $\leq .05$. In the case study (paper III), T-scores, p-values and effect sizes were established as recommended by Crawford and Garthwaite (2011) and Crawford, Garthwaite, and Porter (2010). Details are provided in the methods sections of papers I-III.

Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics, Region South and was conducted in agreement with the Helsinki declaration. All patients and controls gave informed consent to participation. There were no cases were doubt was raised concerning the patients´ ability to deliver truly informed consent. Research involving persons with cognitive deficit requires a high level of awareness of whether the cognitive impairment might affect the patients´ ability to communicate reactions along the way, and ultimately, a wish to retract from the study. The project manager, A.K. Solbakk, and M. Løvstad are both experienced neuropsychologists and were jointly responsible for patient communication. The patients in this study had all sustained serious disease and most were living with chronic sequelae, whereof many with prognostic uncertainty. Many of the patients had not received neuropsychological assessment and/or rehabilitation efforts before study participation. All patients (along with relatives if wished for) were offered information about the results of their neuropsychological examination. When needed, a neuropsychological report was written. In some cases, referral for further follow-up was recommended to the patients MD. In two of 23 cases, abnormalities were discovered on the MRI scans of asymptomatic healthy controls. In these cases, the neurologist and neurosurgeon in the research team assessed the images, and the patients were provided with medical follow-up at the Department of Neurology or Department of Neurosurgery at Oslo University Hospital, Rikshospitalet. Further, Solbakk and Løvstad met with these participants to ensure their psychological well-being.

Summary of papers

Paper I - Contribution of subregions of human frontal cortex to novelty processing.

Background: Novelty detection is related to the orienting response, enabling redirection of attention toward salient new stimuli. The frontally distributed Novelty P3 and negative slow wave (NSW) have been proposed to represent neurophysiological markers of the orienting response. Lesions to the LPFC have been shown to result in attenuated Novelty P3, whereas knowledge about the role of the human OFC in novelty processing is sparse.
Methods: Novelty processing was compared in patients with lesions centered in orbitofrontal (OFC; N = 13) or lateral prefrontal cortex (LPFC; N = 6), and 19 healthy controls. An auditory novelty oddball Event-Related Potentials (ERP) paradigm was applied with environmental sounds serving as task-irrelevant novel stimuli.
Hypothesis: LPFC lesions were expected to result in reduced Novelty P3 amplitudes, while the extant literature did not allow for strong predictions about the effects of OFC lesions. A second objective was to examine the effect of OFC or LPFC lesions to other aspects of Novelty processing, such as the NSW.
Main findings: Lesions to both LPFC and OFC resulted in reduced frontal Novelty P3 responses. The posterior P3b to targets was unaffected in patients with lesions in either location. LPFC patients displayed an enhanced sustained NSW to novel sounds not observed in OFC patients, while both patient groups had an enhanced NSW to targets. Behavioral performance on the task was comparable between patients and controls.
Conclusions: The findings suggested a key role of both LPFC and OFC in novelty processing. Unaffected P3b in both patient groups indicates intact posterior target detection mechanisms. Enhanced NSW to novel sounds in the LPFC patients suggests prolonged resource allocation to task-irrelevant stimuli. However, the normal behavioral results in patients indicate that the enhanced NSW to targets may index an increased resource allocation enabling normal performance. The study suggests partly shared and partly differential contributions to the cognitive subcomponents of novelty processing following LPFC and OFC lesions.

Paper II - Executive functions after orbital or lateral prefrontal lesions: Neuropsychological profiles and self-reported executive functions in everyday living.

Background: While the dorsolateral PFC is primarily associated with cognitive executive functions (EF), injury to the orbitofrontal cortex (OFC) is more strongly associated with altered self-regulatory behavior, resulting in poor interpersonal and occupational functioning.
Methods: The study examined the effects of chronic focal lesions to lateral prefrontal cortex (LPFC; N=10) or OFC (N=14) compared to healthy controls (N=21). Neuropsychological tests with emphasis on measures of cognitive EF were administered along with the Behavior Rating Inventory of Executive Function (BRIEF-A), and a psychiatric screening instrument, the Symptom Checklist 90 Revised (SCL-90-R).
Hypothesis: Impaired EF after LPFC injury was expected to be detectable with neuropsychological measures of EF. It was explored whether the BRIEF-A would aid in identifying problem areas due to prefrontal injury in general and self-regulatory deficit after OFC damage in particular. The relationship between neuropsychological measures, EF in everyday living and emotional distress was examined. In accord with previous studies, a weak association was expected between the BRIEF-A and performance measures of EF.
Main findings: The LPFC group differed from controls on neuropsychological tests of sustained mental effort, response inhibition, working memory and mental switching, while the BRIEF-A provided clinically important information on deficits in everyday life in the OFC group compared to the LPFC group. Correlations between neuropsychological test results and BRIEF-A were weak, while the BRIEF-A correlated strongly with a general index of emotional distress.
Conclusions: The study demonstrated that LPFC damage is particularly prone to cause cognitive executive deficit, while OFC injury is more strongly associated with self-reported dysexecutive symptoms in everyday living. The study illustrates the challenge of identifying executive deficit in individual patients and the lack of strong anatomical specificity of the currently employed methods. There is a need for an integrative methodological approach where standard testing batteries are supplemented with neuropsychiatric and frontal-specific rating scales.

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

Background: Theories on the role of anterior cingulate cortex (ACC) in cognition typically converge on a key role in conflict detection, performance monitoring and response-selection. Empirical findings are largely derived from neuroimaging studies of healthy subjects, while lesion studies are sparse and have produced mixed results. A hypothesis has been advanced claiming that the ACC is not involved in cognitive operations (Baird et al., 2006).
Methods: Neuropsychological, behavioral and electrophysiological data from two patients with unilateral lesions to dorsomedial prefrontal cortex (MPFC) that encompassed the ACC are presented. An auditory Novelty Oddball task was used to study novelty and target detection, while a Stop-Signal task (SST) allowed investigation of behavioral and neurophysiological correlates of inhibitory control and error monitoring.
Hypothesis: The proposition that ACC is not involved in cognitive processing was investigated. Neurophysiological measures were expected to reveal altered motor-inhibition, error-monitoring and novelty processing not evident in neuropsychological test results. It was of particular interest to investigate whether unilateral ACC lesions would affect the error-related negativity (ERN) evoked potential and the post-error slowing (PES) of reaction times.
Main findings: Both patients performed normally on the Stroop test but showed impaired learning and memory. Altered attentional control was reflected in a diminished Novelty P3, whereas the posterior P3b to target stimuli was present in both patients. The ERN was seen in both patients, but alterations of inhibitory behavior were observed as inhibition rates were enhanced and the patients did not slow down after having made an error.
Conclusions: Memory impairment was seen in both patients, while performance on the Stroop-task was unaffected. Whereas unilateral ACC damage resulted in bilateral extinction of the Novelty P3, the posterior target-related P3b was preserved. Unilateral ACC damage was not sufficient to abolish the ERN, although the effect of bilateral lesions remains unknown. This study allows for two broad suggestive conclusions; 1) claims that the ACC is irrelevant to cognitive control functions were not confirmed, and 2) the MPFC seems to be involved in various cognitive control tasks rather than being limited to specific cognitive operations such as error detection.

Discussion

The main aims of this study were to explore distinct cognitive control functions associated with the three major cognitive subdivisions of PFC; the lateral, the orbital and the medial PFC (Bonelli & Cummings, 2007). The research project has had a major focus on controlled attention as a key construct underlying EF (Petersen & Posner, 2012; Stuss, 2011). As neuropsychological assessment of EF is highly challenging, it was also a goal to examine the effect of PFC lesions with a wide array of measures, and study their relative utility in revealing lesion-related change.

Fractionation and integration of cognitive control

A core notion throughout this work is that distinct subdivisions of PFC interact with posterior cortical and subcortical brain structures in executing top-down control. Somewhat in contrast to this is the "adaptive neural coding" model of Duncan and Miller (2002), which highlights the capacity of PFC to promote flexible, adaptive behavior in the face of varying stimulus types and task demands. The authors suggested that it might not be very fruitful in future research to strive for an understanding of the specialization of frontal subsystems, and further conclude that their "*approach implies that it is difficult, or perhaps fruitless, to search for different roles for different regions, since there is substantial flexibility of neural properties. The prefrontal region is perhaps best viewed as a "general computational resource", freely adapting to solve many quite different cognitive problems*" (Duncan & Miller, 2002, p. 289).

In the following it will be discussed to what degree the three studies in this thesis support a model of regional functional specificity within PFC.

Regional specificity in novelty and target processing?

Novelty detection – the novelty P3

Patients with frontal lobe injury often fail to adapt efficiently to changed environmental requirements (Stuss & Levine, 2002). Coping with change is important, as failure to detect and respond to salient changes in our surroundings can be fatal. Detecting novel events is related to the orienting response (Sokolov, 1963), enabling the redirection of attention toward a new stimulus. After having detected a novel event, we need to evaluate the significance of the change and to decide whether action is called for. If the novel event is considered irrelevant, we also need to reorient our attention back to the task at hand. The novelty oddball paradigm is well suited to study this process, as it requires controlled direction of attentional

resources in order to detect, evaluate and process salient distractors as well as maintain focus towards target stimuli. Earlier studies of patients with focal brain lesions have provided a strong case for anatomical network specificity in novelty detection. Knight and Scabini (1998) summarized several studies showing that focal lesions to the LPFC and the temporoparietal junction result in reduced Novelty P3 amplitudes in both visual, auditory and somatosensory tasks, whereas parietal lesions do not. LPFC lesions also diminish the memory advantage normally associated with novel material (Kishiyama, Yonelinas, & Knight, 2009). The role of OFC in novelty processing has not been as well documented, although two studies have reported enhanced P3 amplitudes after OFC damage (Rule, Shimamura & Knight, 2002; Kaipio et al., 1999). In paper I, the main finding was that lesions to OFC as well as LPFC result in diminishment of the frontal Novelty P3. We suggest in paper I that the discrepancy between our findings and the Kaipio, et al., 1999 and Rule, Shimamura, and Knight, 2002 studies could partly be due to variations in lesion location, study design, P3 scalp distribution and sample size, but also that the P3-enhancement seen after OFC lesions might be associated with the use of emotionally laden stimuli.

An interesting finding in paper III was that the two patients with MPFC lesions displayed an abolishment of the Novelty P3. Thus, paper I and III extend current knowledge in suggesting that not only LPFC, but OFC as well as MPFC play a role in novelty processing. The findings suggest that all three major subdivisions of the PFC form necessary anatomical substrates for normal novelty processing. The studies therefore confirm a role of PFC in novelty processing, but do not lend strong support for a high degree of regional specificity within PFC.

Target detection – the P3b

The parietally maximal P3b component is associated with voluntary target detection (Soltani & Knight, 2000), which in oddball tasks is elicited by a to be responded to (target) stimulus that occurs within a train of frequent standard tones that are to be ignored. The P3b is thought to reflect an information processing cascade when attentional and memory mechanisms are engaged. It has also been suggested to index rapid neural inhibition of on-going activity to facilitate transmission of stimulus/task information from frontal (P3a) to temporal–parietal (P3b) locations (Polich, 2007). Electrophysiological studies of patients with focal brain lesions have indicated that normal target-related P3bs can occur despite lesions to PFC as well as superior parietal cortex, while injury to the temporoparietal junction will result in reduced amplitudes (Daffner et al., 2000; Daffner et al., 2003; Knight & Scabini, 1998). The results in

both paper I and III confirm this, in that both the OFC and LPFC group as well as the two MPFC patients clearly presented with a parietal P3b to targets. Thus, the findings of this study suggest that normal target detection can take place despite PFC lesions and irrespective of lesion location.

Negative slow wave (NSW)

Deviant stimuli can generate a frontal NSW (Spencer, Dien, & Donchin, 2001; Näätänen, 1992), which is sensitive to task load, aspects of encoding and retrieval from long-term memory and working memory (Ruchkinet al., 1995). Although some debate persists regarding the specific cognitive operations indexed by frontal NSW, current theories link it to the level of mental processing (Ruchkin et al., 1995; Ritter & Ruchkin, 1992). In contrast to the Novelty P3 and P3b, the NSW did show a differentiated anatomical pattern. Both OFC and LPFC patients displayed enhanced NSW to target deviants. Increased NSW amplitudes were associated with longer RTs in the healthy control group. In earlier studies, similar findings have been interpreted as indicating that slow waves are related to task demand (Roth, Ford, & Kopell, 1978). Thus, enhanced NSW in patients with PFC injury might index an abnormal allocation of "mental effort" to the deviant stimuli in order to cope efficiently with the task (Voytek et al., 2010). Only the LPFC group, however, showed an additionally enhanced and prolonged NSW to novel sounds, an effect we hypothesized might index extended processing of task-irrelevant sounds. Clinically, this effect could be a neural mechanism underlying the attentional distractibility typically observed in patients with LPFC damage. Of interest, the NSW to novel stimuli was enhanced following MPFC as well (paper III), confirming the interplay between LPFC and MPFC in attentional control (MacDonald et al., 2000; Walsh et al., 2011).

Regional specificity in error monitoring?

Inhibition of a motor response that is already initiated but no longer adequate, and noticing when the effort to do so has not succeeded, are important aspects of cognitive control. A long line of research suggests involvement of PFC in inhibitory motor control (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Ramautar, Kok, & Ridderinkhof, 2006; Rubia et al., 2001; Schmajuk, Liotti, Busse, & Woldorff, 2006; Swick, Ashley, & Turken, 2008), and current theories place the MPFC and ACC in particular in a key position with regard to conflict detection and error

monitoring (Alexander & Brown, 2010; Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; Ridderinkhof et al., 2004). On the other hand, it has also been suggested that the ACC actually is not involved in cognitive control as such, but rather plays a role in linking cognitive control processes subserved by other prefrontal regions to autonomic arousal (Baird et al., 2006; Critchley et al., 2003; Fellows & Farah, 2005; Naccache et al., 2005). In paper III, a main aim was to explore the proposition that MPFC does not play a role in cognitive control, and to study the electrophysiological effect of unilateral MPFC damage on error monitoring. A main finding was that both patients with MPFC lesions presented with an ERN and a Pe, considered key ERP indices of error processing. A factor precluding strong conclusions about anatomical specificity was that both lesions were unilateral, as we cannot exclude the possibility that the intact ACC compensated for the injured hemisphere. Had the same result occured following bilateral ACC-injury, it would have made a strong case against the necessity of ACC involvement in error processing. Preliminary results from our group indicate that OFC lesions result in reduced ERN, supporting that error monitoring is subserved by a network involving several subregions of PFC (Solbakk et al., 2011). Both patients in paper III displayed other signs of cognitive control deficit, such as affected memory and learning and abolishment of the Novelty response. This was taken to indicate that the MPFC including the ACC 1) plays a role in cognitive control and 2) it´s role is not limited to error monitoring.

Dissociable anatomical substrates of cognitive EF and EF in everyday living?

It is known that commonly used neuropsychological tests of cognitive executive control are more sensitive to DLPFC injury compared to injury to the ventral parts of the PFC (Stuss, 2007). Capturing the consequences of OFC lesions in formal assessments poses a great challenge and highlights the need for standardized measures with predictive value in relation to everyday functioning (Alvarez & Emory, 2006; Gioia & Isquith, 2004). One such measure is the Behavior Rating Inventory of Executive Functions (BRIEF), which aims at identifying executive problems in everyday living (Roth, Isquith, & Gioia, 2005). An association between focal frontal lobe injury and BRIEF scores has been demonstrated in children (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002; Anderson, Jacobs & Harvey, 2005), but similar studies have not been conducted in relation to the adult version (BRIEF-A). The findings reported in paper II largely confirmed our hypothesis that LPFC damage is particularly prone to cause cognitive executive deficit with reductions on tasks demanding sustained mental effort, working memory, response inhibition, and mental switching, while

OFC injury is more strongly associated with self-reported dysexecutive symptoms in everyday living. We also found that the color naming and inhibition conditions of the Stroop task (D-KEFS; CWI) are particularly vulnerable to LPFC damage.

In summary, the study confirmed a functional dissociation between LPFC and OFC. On the other hand, it also confirmed earlier findings showing that while patients with frontal lobe injury typically perform worse than healthy controls, the results are often within normal limits (Alvarez & Emory, 2006), demonstrating the complexity of diagnosing executive dysfunction in individual patients. Also, the lack of covariation between BRIEF-A and neuropsychological measures could indicate that it actually is measuring other aspects of EF than test performance measures. However, the very high correlations found between BRIEF-A and psychological symptoms of distress (SCL-90-R) suggest specificity issues. More lesion studies using the BRIEF-A are clearly warranted before firm conclusions regarding functional and anatomical specificity can be made.

Escaping the homunculus – Reconciling the dispute

Taken together, the findings reported in paper I-III are equivocal with regard to the issue of fractionation of EF. The findings suggest that OFC, LPFC and MPFC lesions have a partly shared and partly differential effect on the cascade of cognitive processes involved in novelty and target processing. Exploring the role of MPFC did not confirm claims that this region is not involved in cognition, neither could we confirm a highly limited role in error monitoring. We did, however, confirm that neuropsychological measures are more apt to detect LPFC lesions than OFC damage. Thus, our findings gave support both to functional specialization and anatomical specificity (Stuss, 2011), as well as to the notion of adaptive and anatomically widespread functional networks (Duncan & Miller, 2002).

In a comment to Duncan and Miller, Stuss (2006) replied that the prefrontal adaptability model does not address *how* the PFC selects or discards information or even what select and discard means in neural terms. Likewise, Botvinick and colleagues (2001) noted that most theories of cognitive control have focused exclusively on the nature of the influence exerted by control, while little is yet known about how the intervention of control processes is itself brought about. They further stated that any theory about cognitive control will need to address issues related to recruitment, modulation, and disengagement of control processes, that is: 1) How does the system “know” that control must be recruited?, 2) Once control processes are

activated, what is the mechanism for online modulation and adjustment, e.g. as task demands vary?, and 3) When and how are control mechanisms withdrawn, e.g. as initially difficult tasks become automated?

In striving to answer these questions, the notion of a homunculus, an ultimate "controller" is tempting. For example, the designated role of ACC in conflict detection and conflict monitoring, is highly relevant to all three questions above. Nachev (2006) noted that the idea of a general conflict monitor could lead to an infinite regress: How is conflict between conflict-detecting cells to be monitored? Further, early theories of executive attention designated terms for this final control mechanism, e.g. the "Central Executive" and "Supervisory Attention System". Baddeley recognized the risk of the Central Executive becoming the "little person in the head who does all the tasks that can not currently be explained by the model" (Baddeley, 2002, p. 246). Likewise, the recent designation of polar frontal areas as the anatomical site where cognitive executive control and self-regulatory processes are integrated (Badre & D'Esposito, 2007; Koechlin & Summerfield, 2007), risks defining this area as the place where "it all comes together". It is by no means my intention to discard theories of the role of ACC in conflict detection or the polar areas in integration of cognition and emotion, but to illustrate a general theoretical point that it can be challenging to establish theories of EF without postulating a "final control centre".

More than two decades ago, Posner, Petersen, Fox, and Raichle (1988) noted that the combination of refined theories of cognition and modern techniques for imaging of ongoing mental processing had resulted in improved models of brain function. They hypothesized that 1) elementary operations that form the basis of cognitive analysis of human tasks are strictly localized, while at the same time, 2) even simple tasks require orchestration of performance in distributed brain areas. In line with this, Mesulam (1990) noted that a one-to-one correspondence among anatomical site, neural computation, and complex behavior will not be anticipated within a distributed-networks model of cognition. In an attempt to reconcile the different theoretical accounts of integration and specialization within PFC, Stuss argued that the controversy between the fractionation and general adaptability roles of the frontal lobes is a false debate, in concluding that *"there are fractionated processes (anatomically and functionally separable domain general processes not related to any particular knowledge domain) within the frontal regions. Some appear to maintain a fair degree of regional specificity, others appear to be more "adaptable." Within the frontal lobes there are networks*

of frontal processes that work together as required by a specific task demand. These frontal processes also interact with posterior brain regions, either in a top-down, or bottom-up, fashion. It is important to investigate how networks are both locally segregated and functionally integrated. Perhaps the more adaptable the network, the higher its segregation and integration. This complexity may be the true importance of the frontal lobes" (Stuss, 2006; p. 269). Of relevance to this argument is the finding that during normal human development, two parallel processes seem to be at work; cognitive task execution activates gradually more focal brain areas, while at the same time, connectivity seems to increase from focal towards global resting state activation patterns (Rothbart, Sheese, Rueda, & Posner, 2011; Kelly & Garavan, 2005; Fair et al., 2009). Rothbart et al. (2011) postulate that as computations become more focal as fewer neurons are needed to carry them out, and as fewer areas are activated, more global connections are used to connect them. Thus, the seeming paradox between increased focality and increased distribution may imply both more efficient processing and more complex networks being engaged, thus demonstrating the fine-tuned interplay between fractionated specificity and distributed connectivity. In a review of imaging studies of executive control, Duncan and Owen (2000) concluded that the neuroimaging literature had contributed in demonstrating functional specialization within PFC. As importantly, however, was the demonstration that the same PFC-regions tend to be activated across a wide range of tasks requiring EF, that is mid-dorsolateral, mid-ventrolateral and dorsal ACC, again demonstrating that both fractionation and integration of functions characterizes the PFC.

The usefulness of broad methodological approaches in assessment of EF

A second main aim of this study was to explore the relative ability of different methodological approaches ranging from questionnaires of everyday living, behaviorally based neuropsychological tests, experimental tasks and ERPs in detecting executive impairment following lesions to subdivisions of the PFC. This question is both related to the sensitivity of different measures to executive deficit, but also to the fact that measures at different levels of analysis will shed light over distinct aspects of EF. For example, while electrophysiological methods might elucidate the temporal and neural characteristics of a given process, neuropsychological tests display consequences within cognitive domains, while questionnaires like the BRIEF-A show how this affects the every day life of patients.

Our findings support the advantages of adopting a broad methodological approach in studying EF. The highly distinct effects of LPFC, OFC, and MPFC lesions to novelty detection, target processing and error monitoring could not have been detected in a neuropsychological assessment. Likewise, the everyday problems of OFC patients detected by the BRIEF-A are not revealed by ERPs. The study presented here confirms the statement about future development in this research field made by Knight and Stuss in their seminal 2002-book*: " In our view, the most complete picture will emerge from the fusion of classic neuropsychological approaches informed by cognitive theory with powerful new techniques to measure human brain physiology*" (Knight & Stuss, 2002, p. 573). The effort of Stuss (2006) to incorporate the complex dynamic of fractionation and adaptability in one theoretical understanding also bears relevance to how we understand executive impairment in patients. While the behavioral symptoms displayed might be highly complex, the brain injury might well have disturbed very basic and localized cognitive operations. It is thus not necessarily the case, as is often presumed, that complex behavioral problems can only be assessed with real-life complex behavioral tests, as the underlying problem might be both functionally and anatomically distinct and cause cascades of behavioral symptoms. In fact, Stuss summarizes that it is the movement from multidimensional tasks to controlled experimental processes that has resulted in replicable evidence of fractionated frontal lobe functioning (Stuss, 2011).

Clinical use of Event-Related Potentials

The promise of electrophysiological data in research on cognitive control, raises the follow-up question of whether ERPs can provide clinically useful diagnostic information at an individual level. Variations in EEG-equipment, recording procedures, experimental paradigms as well as strategies for data analysis have complicated comparison of findings across studies, and precluded the establishment of normative data across laboratories. Duncan and colleagues (2009) also underscored that as neuropsychiatric diagnoses are based on clinical symptoms, the search for ERP markers will be difficult, and that the diagnostic utility of ERP alterations in clinical disorders is limited. Related to clinical usefulness is the question of reliability of ERP-measures. Studies have typically shown test-retest reliability of amplitudes of common ERP-components (e.g. N1, P2, P3) in the moderate to strong range, but weaker reliability for latency measures (Cassidy, Robertson, & O'Connell, 2012; Walhovd & Fjell, 2002). However, reliability measures might be lower for patients than for healthy subjects (Lew, Gray, & Poole, 2007). Thus, ERPs do not currently hold a position to establish clinical diagnosis. However, the use of theoretically informed experimental paradigms along

with the measurement of robust ERP-components, holds promise as a supplementary method within the context of a broad assessment strategy in patients with e.g. acquired brain injury.

Methodological issues

Lesion etiology

The majority of patients in this study had gone through tumor resections, with a mix of meningiomas and low-grade gliomas (LGG). A minority of the patients had suffered TBI. No cases of CVA were included. Of note, in one patient that was excluded due to the lesion covering extensive parts of both OFC and LPFC, etiology was a ruptured anterior communicating artery. In the review process of paper I, issues related to lesion etiology were raised. Firstly, it was noted that a large number of patients in the study had brain tumor, and ERP recordings were performed after tumor resection, while most previous lesion studies of the Novelty P3 were performed in stroke patients. We were asked whether there was a rationale behind the selection of injury etiology. The majority of the patient sample in the present study was recruited from Oslo University Hospital, Rikshospitalet. This is the major neurosurgical referral site for southern Norway and a large group of tumor patients was accessible to our research group. In Paper I, all LPFC patients had undergone resections of unilateral LGG. The majority (8/13) of patients with OFC lesions had undergone resection of large meningiomas, 4 suffered TBI, and 1 a LGG. The Novelty P3 lesion studies performed by Daffner et al. (Daffner, et al., 2000; Daffner, et al., 2003) included only patients with CVA insults, while in Knight´s initial study of novelty processing (Knight, 1984), 7/14 patients had tumor resections, 5 CVA, 1 trauma and 1 abscess resection. Despite the differing etiologies, the Daffner and Knight studies yielded parallel novelty P3 reductions after lateral PFC damage. In paper I, we report that the Novelty P3 reduction was evident both in patients with tumor resections and in the TBI patients, indicating that the findings were not restricted to one specific etiology. Finally, our patients with lateral PFC glioma resections showed Novelty P3 reductions similar to the Daffner and Knight studies.

Another issue related to etiology raised by a reviewer of paper I, was the meningioma sample in the OFC group, as it was noted that meningiomas can be removed surgically with minimal brain tissue damage because these tumors originate from the dura. We noted that in our sample, large meningiomas had been resected. Thus, the OFC suffered structural damage from long-term compression. The extent of OFC damage was additionally independently confirmed by a neurosurgeon, a neuroradiologist and a neurologist, ensuring that the reported

extent of encephalomalcia was correct. Zald and Andreotti (2010) noted that the most common etiologies for focal OFC lesions are closed head injuries, penetrating wounds, cerebrovascular disease (particularly ACom aneurysms), tumor resections, and neurodegenerative disorders. They further stated that *"when the extent of the lesion is well characterized, and no additional pathology is present, patients with surgical excisions provide some of the best opportunities to examine the effects of orbitomedial prefrontal cortex lesions in isolation"* (p. 3378).

It is well known that frontal lesions and accompanying executive dysfunction is common in the TBI population (Levine, et al., 2002; Ponsford, Draper, & Schonberger, 2008). In a Norwegian study, it was demonstrated that in a representative sample of 71 TBI patients with MRI-confirmed intracranial abnormalities one year post-injury, frontal lobe damage was found in 83 % (Sigurdardottir, Jerstad, Andelic, Røe, & Schanke, 2010). The majority of TBI patients in this study were recruited from Sunnaas Rehabilitation Hospital, the largest specialized rehabilitation unit in Norway. Efforts to recruit patients were made by reviewing medical records from the TBI-unit. In accord with the literature, many patients with marked clinical executive deficit were not eligible for study inclusion due to multifocal injury and/or presence of diffuse axonal injury (DAI). Levine and colleagues (Levine, et al., 2002) noted that the precise relationship between dysfunction in frontal subsystems and clinical consequences have proven difficult to parse out in the TBI population, due to the typical individually unique combination of focal, diffuse and secondary pathology. Thus, although the TBI population might be challenging to include in studies requiring discrete focal lesions, this group is highly relevant in any rehabilitation context where EF is addressed.

The lack of CVA patients in the sample was not intended. Medical journals at Sunnaas Rehabilitation Hospital proved not to be sufficiently detailed on anatomical lesion site to make an informed decision on which patients might be eligible for study inclusion. As the research program evolves, efforts are made to establish collaborative relationships with neurological departments treating stroke patients in the acute phase, as well as an international multi-center study. Although fMRI results are not part of this thesis, the method is an important part of the program at large. It should be noted that including CVA patients in fMRI studies is a particular challenge as cerebrovascular disease will potentially impact on the haemodynamic properties of the brain, thus calling for caution in interpreting differences

in the blood oxygen level dependent (BOLD) signal between healthy subjects and CVA-patients (D'Esposito, Deouell, & Gazzaley, 2003).

Stuss and Alexander (2007) noted that their studies of the neuropsychological effects of focal frontal lesions have demonstrated that lesion location is more important than etiology. Thus, they have included various etiologies in their work, also because restricting inclusion to one particular etiology would imply restrictions on the lesion location. However, they included patients at a minimum of three months post-injury to avoid confounding of acute diffuse symptoms, but discussed that as lesions become more chronic, brain-behavior relationships might be affected by brain plasticity and reorganization.

Desmurget, Bonnetblanc, and Duffau (2007) stated that in order to understand brain plasticity and functional recovery after brain injury, the temporal pattern of injury must be taken into account. They reviewed the human and animal literature on recovery after stroke and LGG, respectively. Two main conclusions were made; 1) functional recovery is better in the context of slow-growing injuries than after acute lesions, and 2) reorganization patterns are dependent on the temporal aspects of the injury, with remote areas both ipsi- and contralateral to lesion being recruited to a larger degree after slow-growing lesions. Voytek and colleagues (2010) performed electrophysiological studies of attention and memory in patients with chronic strokes, and demonstrated evidence of rapid and dynamic compensatory plasticity in that the intact PFC compensated for damage in the lesioned PFC on a trial-by-trial basis dependent on cognitive load. This functional compensation was indexed by transient increases in electrophysiological measures of attention and memory in the intact PFC, detectable within a second after stimulus presentation and only when the lesioned hemisphere was challenged.

In summary, as no single etiology will result in focal lesions to all subdivisions of the PFC, and the fact that discrete PFC injury is relatively rare, it is challenging to obtain large sample sizes (Stuss & Alexander, 2007). Thus, any study of focal frontal damage will contain issues related to sample etiology, included this work. As noted, however, the sample size of this study, particularly the OFC cohort, is comparable to other studies of focal frontal lobe lesions (Baldo, et al., 2002; Stuss, et al., 1998; Stuss, et al., 2001; Yochim, et al., 2007)

Anatomical subgroups

Lesions to the PFC do not typically follow functional anatomical delineations within the brain. As a main goal in this study was to explore functions related to the three primary cognitive subdivisions of PFC, the patients in paper I and II, were a priori assigned to the LPFC or the OFC group depending on injury location. Patient grouping was performed by consensus in the research group, with the author R.T. Knight being a senior consultant. The lesion reconstructions in paper I and II demonstrate that the core lesioned area within each group clearly falls within the central parts of LPFC and OFC, respectively. However, there was some overlap between groups. In the tables reporting affected Brodmann areas in papers I and II, it can bee seen that overlap mainly occurred within BA 9, 10, 46, and 47, thus over polar and ventral PFC. The issue of group overlap is a potential confound in the study. On the other hand, in those cases where differential group effects were demonstrated, either as differences between patient groups or between only one patient group and controls, this took place despite lesion overlap, actually strengthening the result.

Finally, the subgroups established in this study each cover large areas of the PFC, causing potential affection of several cognitive subsystems simultaneously. Also, in a dynamic network perspective, predicting the effect of one "node" being damaged is complicated. Thus, lesion studies provide the most valuable information on the role of specific anatomical areas when performed in concordance with studies of healthy subjects where the dynamics of functional networks are intact (Solbakk, Specht, Korsnes, & Endestad, 2010).

One final issue related to subgroups is that of specificity of findings. A first step would typically be to establish a relationship between a given cognitive measure and prefrontal lesions compared to healthy controls. Establishing regional specificity, however, requires that the PFC patients are compared to patients with lesions in others brain areas (Zald, 2002). Although the main goal of this work was comparison of subdivisions within the frontal lobes, the findings could be strengthened further by including patients with focal posterior cortical lesions. Inclusion of patients with parietal lesions would also provide opportunity to study the role of parietal cortex in attentional control networks, as it has recently been suggested that top-down signals may also arise from this area of the brain (Esterman, Chiu, Tamber-Rosenau, & Yantis, 2009).

Alternative strategies of analysis in lesion studies

Given the aim of validating functional subdivisions of PFC, it was sensible to establish an a priori anatomically based subgrouping of the patients. In the following two other approaches to the exploration of structure-function relationships will be briefly outlined; the performance-based approach of Stuss and coworkers (Stuss, et al., 2002) and voxel-based lesion-symptom mapping (VLSM) (Bates, et al., 2003; Kimberg, Coslett, & Schwartz, 2007; Rorden, Karnath, & Bonilha, 2007).

Performance-based mapping of PFC functions: Stuss and colleagues (2002) hypothesized that if a particular region was necessary to perform a given task, patients with lesions to this area would be impaired on that task, irrespective of whether they had additional lesions to other parts of the PFC. In "the hotspotting approach", the performance of individuals with damage in a particular region was compared to those who did not. Over time, Stuss and his group have increasingly applied a "backwards engineering" approach, where patients are divided into anatomical groups that are maximally different in task performance (Stuss, et al., 2002).

In **voxel-based lesion-symptom mapping (VLSM),** the relationship between tissue damage and behavior is investigated on a voxel-by-voxel basis (Bates, et al., 2003), providing lesion analysis with the advantages of tools originally developed for functional neuroimaging (Kimberg, Coslett, & Schwartz, 2007). This approach does not require dichotomous classification by either lesion location or behavioral cut-off values. Power-issues related to correction for multiple comparisons is a challenge, typically requiring large samples. However, a recent article demonstrated the use of VLSM in 27 patients with PFC lesions in a study of working memory (Tsuchida & Fellows, 2009), using software that corrects for small group size (Rorden, Karnath, & Bonilha, 2007).

The main asset of both approaches is that a priori assumptions about anatomical areas of interest are not made, allowing open-ended exploration of networks involved in a given task. In future studies, it can be explored whether these approaches result in additional knowledge about structure-function relationships.

Choice of neuropsychological assessment tools and questionnaires

The selection of neuropsychological tests and questionnaires in the study was done in order to allow characterization of general cognitive functioning with a particular emphasis on EF. In addition, we wished to include a measure of EF in daily living, and chose the BREIF-A, which has gained tremendous clinical popularity in Norway, despite scarce empirical evidence on the relationship between the inventory and brain pathology.

Although this study had main focus on the effect of lesions to PFC on attentional control mechanisms, interesting issues related to OFC-lesions (paper II) can be explored if measures of basic emotional perception such as "Reading the Mind in the Eyes test" (Baron-Cohen, et al., 1997; Baron-Cohen, et al., 2001), and measures of reward-based decision-making such as the Iowa Gambling task (Bechara, et al., 1994) are included. Likewise, the Brain Injury Rehabilitation Trust (BIRT) Regulation of Emotions Questionnaire (BREQ; Cattran, Oddy, & Wood, 2011) represents one of few and interesting questionnaires attempting to capture emotional dysregulation following brain injury.

The electrophysiology of lesioned brains

The ERP method has contributed greatly to an enhanced understanding of the functioning of the human PFC. Already ten years back, Knight and Stuss (2002) stated that neurophysiological research had strongly supported and extended the neuropsychological literature. They emphasized the impact of electrophysiological studies in the understanding of the role of PFC in the balance between excitatory and inhibitory control, novelty processing and response monitoring, all topics that are focused upon in this thesis. ERPs have also contributed to elucidating the neural underpinnings and cognitive functioning in a wide range of clinical disorders (Duncan, et al., 2009). Benefits of the ERP method are the temporal resolution, the possibility of studying cognition without behavioral requirement, and the potential of studying functional integrity of neural systems. However, there are methodological issues related to the use of ERPs in lesion studies that will be discussed in the following.

Conductance of electrical potentials in lesioned brains

Resistive properties of the skull can be changed by neurosurgical procedures, and volume conduction can be affected by large surgical and/or athropic lesions, as neural tissue is replaced by cerebrospinal fluid. Both factors can result in distortions of a scalp ERP-field

(Rugg, 1995). This issue was raised by a reviewer in relation to paper I, as we were asked whether we could exclude the possibility that the augmented N1 and NSW amplitudes ipsilateral to lesion in the LPFC group were due to craniectomy. An analysis of the signal to noise ratio over lesioned versus non-lesioned electrode groups was performed by computing mean SD of the pre-stimulus baseline period amplitudes. We did not observe a difference in the variation in amplitudes over the lesioned compared to the nonlesioned hemisphere in the LPFC group, indicating that the signal to noise ratio was comparable over hemispheres. As the increased N1 amplitude in the LPFC group was, however, present for all conditions, we found that we could not fully disclaim craniotomy effects in the N1 augmentation. We did however, not think that a mechanical shunting effect alone could explain the results for the P2, Novelty P3 and NSW components. First there was not a general amplitude enhancement across ERP components or stimulus types in the LPFC group. Second, the N1 enhancement was not accompanied by a comparably negative shift nor increased amplitudes in the following P2 component. Third, the NSW-effect was condition-specific, and finally, the N1 amplitude did not predict the NSW amplitude. The dialogue from the review process is included here in order to elucidate that the methodological challenge mentioned by Rugg (1995) needs to be considered when interpreting ERP-findings in lesion studies.

Clinical implications - treatment of executive functions

Despite the huge personal and societal consequences of executive problems, the treatment literature is limited. There has, however, been a shift in research objectives from diagnosis and descriptive analysis to development of evidence-based interventions (Cicerone, et al., 2006; Cicerone, et al., 2000; Cicerone, et al., 2005; Cicerone, et al., 2011; Kennedy, et al., 2008; Wheaton, Mathias, & Vink, 2011).

There are no medications that currently meet a practice standard for treatment of executive deficit (Cicerone, et al., 2006; Fleminger, Greenwood, & Oliver, 2006), although there is some evidence that dopamine-agonists might be helpful in treating behavioral and attentional problems after TBI (Wheaton, et al., 2011; Whyte, et al., 2004), and in facilitating post-acute recovery (Giacino et al., 2012; Giacino & Whyte, 2003; Meythaler, Brunner, Johnson, & Novack, 2002).

An increasing volume of cognitive rehabilitation studies addressing attention and executive deficit is available (Cicerone, et al., 2000; Cicerone, et al., 2005; Cicerone, et al., 2011).

Attention training is considered practice standard during post-acute rehabilitation after TBI, and treatment should include direct attention training combined with metacognitive training to promote development of compensatory strategies and foster generalization to real-world tasks (Cicerone, et al., 2011; Tiersky, et al., 2005; Westerberg, et al., 2007). In relation to EF, training in formal problem-solving strategies, including emotional regulation, and their application to everyday activities and functional situations is recommended as practice standard. Since executive deficit will have potential adverse effect on treatment outcome of other cognitive domains such as attention, memory, language and social functioning, it is recommended that metacognitive strategy training is included in rehabilitation efforts aimed at these functions as well (Cheng & Man, 2006; Cicerone et al., 2011; Goverover, Johnston, Toglia, & Deluca, 2007; Hewitt, Evans, & Dritschel, 2006)).

One of the few theoretically based and manualized treatment interventions of EF is **Goal Management Training (GMT)** (Levine, et al., 2000). GMT has proven promising in elderly (Levine, et al., 2007; Stuss, et al., 2007; van Hooren, et al., 2007) as well as in patients with acquired brain injury (ABI) (Chen, et al., 2011; Levine, et al., 2000; Novakovic-Agopian, et al., 2011). In cooperation with Sunnaas Rehabilitation Hospital, the research project that this thesis forms part of will conduct a group-based intervention study exploring the efficacy of GMT following ABI. Thus, promising results from intervention studies give increased hope in the quest to help patients with executive deficit. Future promise lies in the development of highly specified treatment programs that are theoretically informed from advances made in neuroscience. For example, we suggest that physiological analysis will be crucial in providing data to inform the future of neurorehabilitation.

Conclusions and future directions

The frontal lobes, which were spoken of as silent and dispensable half a century ago, attract huge scientific interest today, as it has been realized that the PFC plays a pivotal role in top-down regulation of human cognition, emotion and motivation. This study forms part of the effort to increase our understanding of the PFC and its functional and anatomical subdivisions. Two overarching aims of the study were to investigate the functional validity of the lateral, orbital and medial anatomical subdivisions of PFC. A key research objective was to investigate whether indices of controlled attention were differently influenced by lesion site. A secondary aim was to explore the additional value of studying EF with a wide array of

methodological approaches tapping into different levels of analysis. Thus, the study combined the strengths of several research approaches; experimental cognitive psychology, clinical neuropsychology, cognitive electrophysiology, and lesion studies.

The findings in paper II confirmed that while injury to the LPFC is likely to result in deficit in cognitive aspects of EF, OFC damage affects self-regulatory behaviors of everyday living. The ERP findings in papers I and III, demonstrated that PFC lesions result in disturbances of basic aspects of attentional processing that are not detected with neuropsychological behavioral methods. As the Novelty P3 was abolished after LPFC, OFC as well as MPFC lesions, the findings suggest that all three major subdivisions of PFC contribute and are necessary for normal detection and evaluation of salient changes in the sensory environment. This finding extends the current knowledge base, as the extant literature has indicated that lesions to LPFC diminishes the ERP Novelty response, but less has been known about the role of OFC and MPFC. LPFC lesions additionally seem to result in prolonged processing of task irrelevant novel stimuli, confirming the role of this area for on-task attentional control (Petersen & Posner, 2012). This finding might index a neurophysiological correlate of the observed behavioral distractibility of patients with LPFC damage. Papers I and III furthermore confirm that normal target detection can take place despite PFC lesions, irrespective of lesion location. In the two cases reported in paper III it was demonstrated that the ERN component is not necessarily abolished by unilateral ACC lesions, although knowledge derived from imaging studies of healthy controls have implied that the ERN is generated in the ACC. It was also demonstrated that MPFC lesions were associated with altered learning and memory functions, but not with impaired performance on the Stroop task. Taken together, the findings in paper I-III lend support both to theories that highlight functional and anatomical specificity within the PFC, and to theories that emphasize adaptive, supramodal properties of the PFC.

Devinsky (2005) stated that the prior connotation that some parts of the brain are without functional value, was grounded in an insensitivity of our scientific tools rather than the realities of the brain. In line with this, Stuss and Knight (2002) said that the controversy about EF and the PFC is the result of inconsistency of operational definitions. The combination of lesion studies, neuropsychological data, measures of everyday function and experimental and neurophysiological data have contributed to elucidate cognitive control functions at different levels of analysis.

This thesis represents a small part of a larger research program. As more results are generated, a broader picture will emerge regarding functional specificity and network dynamics within PFC. In future developments of the program, inclusion of patients with focal posterior lesions in addition to frontal will further enhance the potential to study large-scale functional brain networks. Advanced methodological strategies both for lesion and EEG-analysis should be adopted in order to explore the dynamic properties of highly specific anatomical areas and the networks they are part of. New experimental and clinical measures should be applied with particular emphasis on those that are sensitive to OFC dysfunction. Finally, it is promising that an intervention study has been initiated. Future cognitive rehabilitation efforts should benefit from theoretical contributions derived from cognitive neuroscience. Ultimately, a clinical neuropsychologist should not be content with solely diagnosing deficit, but should strive to help patients improve their lives.

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I

Contribution of Subregions of Human Frontal Cortex to Novelty Processing

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Abstract

■ Novelty processing was studied in patients with lesions centered in either OFC or lateral pFC (LPFC). An auditory novelty oddball ERP paradigm was applied with environmental sounds serving as task irrelevant novel stimuli. Lesions to the LPFC as well as the OFC resulted in a reduction of the frontal Novelty P3 response, supporting a key role of both frontal subdivisions in novelty processing. The posterior P3b to target sounds was unaffected in patients with frontal lobe lesions in either location, indicating intact posterior cortical target detection mechanisms. LPFC patients displayed an enhanced sustained negative slow wave (NSW) to novel sounds not observed in OFC patients, indicating prolonged resource allocation to task-irrelevant stimuli after LPFC damage. Both patient groups displayed an enhanced NSW to targets relative to controls. However, there was no difference in behavior between patients and controls suggesting that the enhanced NSW to targets may index an increased resource allocation to response requirements enabling comparable performance in the frontal lesioned patients. The current findings indicate that the LPFC and OFC have partly shared and partly differential contributions to the cognitive subcomponents of novelty processing. ■

INTRODUCTION

The pFC constitutes about one third of the human cortex (Stuss & Benson, 1986) and has extensive bidirectional connections to other cortical and subcortical regions (Petrides & Pandya, 2002). This neuroanatomical organization places pFC in a unique position to monitor and control diverse human behaviors with lesions to the frontal lobes resulting in problems with higher-order control of cognition, emotion, and behavior. There is emerging consensus that there is no unitary executive function. Rather, subregions within the frontal lobes are associated with distinct cognitive functions supporting the general concept of cognitive control (Stuss & Alexander, 2000). One major functional anatomical distinction is between lateral pFC (LPFC) and OFC with each region having multiple subareas. Although the LPFC is primarily associated with cognitive executive functions such as controlled attention, working memory, goal selection, planning, sequencing, and set shifting (Royall, 2002), injury to the OFC is associated with altered self-regulatory behavior such as poorly modulated emotional reactions and social interactions and defective decision-making. OFC damage tends to affect the ability to utilize cues in the environment to predict future rewarding or aversive events and the ability to regulate behavioral responses, particularly in the context of changing reinforcement contingencies. Lack of insight into the consequences of the brain injury is typical after OFC damage (Koenigs & Tranel, 2006; Stuss & Levine, 2002).

Although the cognitive executive problems following LPFC lesions are more likely to be detected in neuropsychological evaluations, patients with OFC injury will often display normal results on formal cognitive evaluations despite marked problems with "real-life" decision-making, such as maladaptive personal, social, and occupational functioning (Zald & Andreotti, 2010).

A prominent clinical symptom in patients with frontal lobe injury is a reduced ability to adapt efficiently to changed requirements from their environment (Stuss & Levine, 2002). Coping with change is a prerequisite for survival because failure to detect and respond to salient changes in our surroundings could be fatal. This process of novelty detection is related to the orienting response (Sokolov, 1963), enabling the redirection of attention toward a new stimulus. When a stimulus is perceptually salient, this reorienting of attention is largely reflexive (Corbetta, Patel, & Shulman, 2008), although there is evidence that the automatic bottom–up driven reorienting is also modulated by the top–down attentional set of the subject (Chong et al., 2008; Folk, Leber, & Egeth, 2002) or by the degree of task relevance of the stimulus

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(Yantis & Egeth, 1999). Subsequent to detecting the occurrence of a novel event, there is a need to rapidly evaluate the significance of this change and to decide whether action is called for.

The ERP method provides a physiological probe well suited to address psychological theories of frontal lobe function (Stuss, Shallice, Alexander, & Picton, 1995). Two frontally distributed ERP components have been proposed to represent a neurophysiological marker of the orienting response; the Novelty P3 and a later negative slow wave (NSW) with a frontal scalp distribution (Rohrbaugh, Syndulko, & Lindsley, 1979; Kok, 1978).

The P3 complex is one of the most widely studied ERP components (for comprehensive reviews, see Polich, 2007; Polich & Criado, 2006; Friedman, Cycowicz, & Gaeta, 2001; Kok, 2001; Soltani & Knight, 2000). The P3b component with a positive polarity and parietal maximum is associated with voluntary target detection (Soltani & Knight, 2000), whereas the earlier and more frontocentrally distributed Novelty P3 is elicited by infrequent, task-irrelevant, but perceptually salient, stimuli (Courchesne, Hillyard, & Galambos, 1975; Squires, Squires, & Hillyard, 1975). The Novelty P3 has been considered to be a neurophysiological marker of the orienting response (Debener, Makeig, Delorme, & Engel, 2005; Debener, Kranczioch, Herrmann, & Engel, 2002; Soltani & Knight, 2000). Although frontal brain structures contribute to generation of the Novelty P3, parietal cortices and the TPJ are associated with the target P3b (Mecklinger & Ullsperger, 1995).

Deviant stimuli can also generate a frontally distributed NSW in the same time window as the posterior P3b (Spencer, Dien, & Donchin, 2001; Näätänen, 1992). The NSW has been discussed in relation to the orienting response and is typically observed in contingent negative variation paradigms where an initial stimulus (S1) signals that the second and imperative stimulus (S2) will follow (Walter, 1964). Rohrbaugh and colleagues (1979) propose that the NSW represents a nonspecific cortical activation reflecting the transient appearance of alerting, orienting, arousal, or activation. The frontal NSW is sensitive to task load, aspects of encoding and retrieval from long-term memory and working memory (Ruchkin, Canoune, Johnson, & Ritter, 1995). Although some debate persists as to what specific cognitive operations are indexed by late slow waves, all current theories of the NSW link this ERP to the level of mental processing (Ruchkin et al., 1995; Ritter & Ruchkin, 1992).

Earlier latency ERP components preceding the P3, such as the N1 and P2 components, are modulated by top–down processes. Knight, Hillyard, Woods, and Neville (1980) showed that, although LPFC damage resulted in an enhanced N1 component, the following P2 was normal, a finding that was interpreted as a demonstration of altered inhibitory control over sensory processing because of prefrontal deficit. Thus, the process of detecting salient novel events is performed using interrelated cognitive operations, where the Novelty P3 represents an important but not exclusive part of the novelty-processing cascade.

Studies of patients with heterogeneous lesion distributions provide mixed results, reporting both attenuation (Solbakk, Reinvang, & Andersson, 2002) and enhancement (Kaipio et al., 1999) of the Novelty P3. Studies of patients with focal brain lesions have, however, provided a strong case for anatomical network specificity. Knight and Scabini (1998) summarized several studies showing that focal lesions to the LPFC result in reduced Novelty P3 amplitudes in visual, auditory, and somatosensory tasks. Superior parietal lesions affect neither the P3b to targets nor the Novelty P3, but lesions to the TPJ attenuate both components. The reduction of the Novelty P3 amplitude following frontal lobe lesions has been confirmed by Daffner and colleagues (2000, 2003). Importantly, these studies demonstrated shorter viewing time to visual novel events in patients with frontal lobe damage, providing key behavioral evidence that patients with frontal lobe injuries exhibit reduced orienting behavior to novel events. Similarly, LPFC lesions eliminate the classic von Restorff memory boost seen in normal subjects for novel events (Kishiyama, Yonelinas, & Knight, 2009).

Whereas the role of the LPFC has been documented, the role of OFC in novelty processing is not well defined. In one study, four OFC patients were reported to have enhanced Novelty P3s, but the stimuli were embedded in an emotionally laden context (Rule, Shimamura, & Knight, 2002). Another study with traumatic brain injury (TBI) patients (Kaipio et al., 1999) also reported enhanced P3s, but the lesions were of mixed etiology compromising strong conclusions on the role of OFC in novelty processing.

In the present study, we examined a large cohort of OFC patients in a cognitive task with no emotional component. An auditory novelty oddball paradigm was administered to one patient group with OFC damage (OFC group) and one with LPFC damage (LPFC group). On the basis of previous studies, we hypothesized that LPFC lesions would result in altered novelty detection reflected in a reduction of the Novelty P3 amplitude (Daffner et al., 2000, 2003; Knight, 1984). Rule et al. (2002) reported an enhanced novelty response in patients with OFC damage. However, as noted, these findings were derived from a design involving affectively laden stimuli and would not necessarily apply to a paradigm where the environmental novels are presented in an emotionally neutral task context. The extant literature did thus not allow for strong predictions about the effects of OFC lesions.

A second objective was to examine the contributions of OFC or LPFC lesions to other aspects of the Novelty processing cascade, indexed by alterations in ERP components both preceding and following the P3 complex. The extant literature suggests an increase in N1 amplitudes after LPFC lesions. As for the P3 complex, previous studies did not give rise to strong predictions about the N1 after OFC lesions. It was expected that later parts of

the orienting response would be indexed by slow negative waveforms. Although it is well known that oddball paradigms tend to elicit NSWs following the P3 complex, the literature did not provide a specific hypothesis regarding the effect on this aspect of novelty processing after focal frontal brain injury, and this part of the analysis was exploratory.

METHODS

Participants

Nineteen patients with prefrontal lesions and 15 healthy controls were included in the study. All subjects were right handed. The OFC group consisted of 13 patients, and the LPFC group consisted of 6 patients (see Table 1 and Figures 1 and 2 for patient characteristics). The OFC group consisted of four patients with traumatic brain injury (TBI), one with low-grade glioma (LGG), and the remaining eight who had undergone resection of large meningiomas. The majority (10 of 13) of OFC patients had bilateral damage. All patients in the LPFC group had unilateral lesions because of LGG. All patients with tumors had gone through surgical tumor resection. None of the patients had received radiation therapy, whereas one patient in the LPFC group had received chemotherapy.

Patient inclusion was based on preexisting frontal brain lesions indicated on structural CT and/or MRI scans. Lesion

Table 1. Lesion Characteristics: Etiology, Time since Injury, Lesion Volume, and Affected Brodmann's Areas

Subject	*Etiology*	*Time since Injury (months)*	*Lesion Volume (ccm)*	*BA Right Hemisphere*	*BA Left Hemisphere*
OFC group mean		**33**	**Total: 50.3**		
			RH: 28.9		
			LH: 21.3		
1	TBI	45	140	6, 8, 9, 10, 11, 32, 45, 46, 47	8, 9, 10, 11, 32, 46, 47
2	Meningioma	13	69.1	10, 11, 32, 46, 47	10, 11, 47
3	Meningioma	48	79.8	10, 11, 47	10, 11, 46, 47
4	Meningioma	13	39.7	10, 11	10, 11, 47
5	Meningioma	19	5.1		11
6	Meningioma	43	134.8	9, 10, 11, 32, 46, 47	9, 10, 11, 32, 46, 47
7	Meningioma	27	7.2	11, 47	11
8	Meningioma	44	2.9		10, 11
9	LGG	7	28.6	10, 11, 25	11, 25
10	TBI	44	23.6	10, 11	11
11	TBI	59	33.3	10, 11, 47	10, 11, 46
12	TBI	15	41.1	11	10, 11, 38, 45, 46, 47
13	Meningioma	52	48.7	9, 10, 11, 32, 46, 47	
LPFC group mean		**46**	**Total: 33.8**		
			RH: 55.8		
			LH: 11.9		
1	LGG	30	34.4	8, 9, 32, 44, 45, 46	
2	LGG	27	24.8		4, 6, 9, 44
3	LGG	68	60.1	4, 6, 8, 9, 32, 44, 45, 46	
4	LGG	112	72.8	6, 9, 32, 44, 45, 46, 47	
5	LGG	31	0.8		45
6	LGG	9	10.1		6

Lesions that comprise <0.5 ccm in any given Brodmann's area are not reported. BA = Brodmann's area, RH = right hemisphere, LH = left hemisphere; TBI = traumatic brain injury; LGG = low-grade glioma.

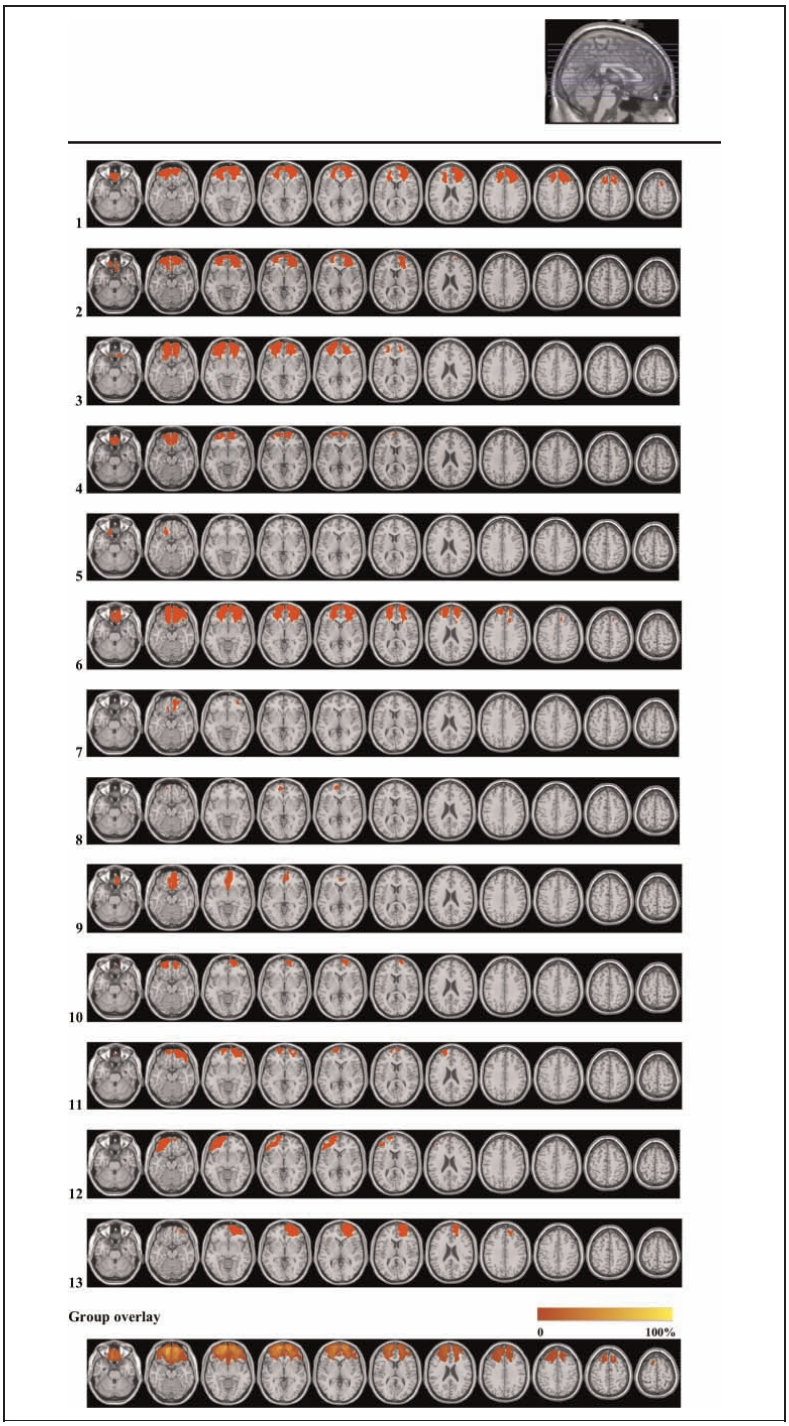

Figure 1. Lesion reconstructions for the OFC group. Individual patients (1–13) and group overlay (bottom row). Eighty-two percent of the cortical lesion volume was within Brodmann's areas 10, 11, and 47.

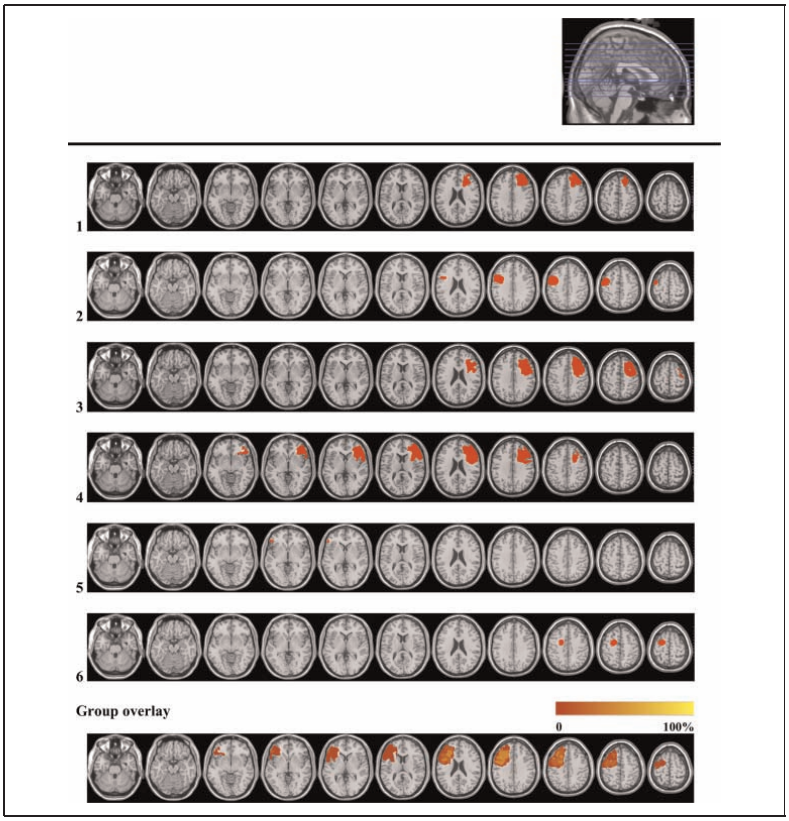

Figure 2. Lesion reconstructions of the LPFC group. Individual patients (1–6) and group overlay (bottom row). Eighty percent of the cortical lesion volume was within Brodmann's areas 6, 8, 9, 44, 45, and 46.

reconstructions were based on structural MRIs obtained after inclusion and have been verified by the neuroradiologist, neurologist, and neurosurgeon in the research group (P. Due-Tønnessen, R. T. Knight, & T. Meling). Testing took place at least 6 months after injury or surgery. Patients were matched with healthy controls by age, sex, and years of education (Table 2). Participants with a history of serious psychiatric disease, drug or alcohol abuse requiring treatment, premorbid head injury, pre-/comorbid neurological disease, IQ below 85, substantial aphasia, visual neglect, or marked sensory impairment were excluded from participation.

The functional outcome of the patients was classified with the Glasgow Outcome Scale Extended (GOS-E; Wilson, Pettigrew, & Teasdale, 1998). GOS-E is a hierarchical scale in which overall rating is based on the lowest outcome indicated. Total, verbal, and performance IQ were estimated on the basis of all four subtests of the Wechsler

Table 2. Subject Characteristics

	Control	*OFC*	*LPFC*	*ANOVA*
N (% women)	15 (53)	13 (54)	6 (33)	
Age in years	41.6 (12.2)	45.92 (10.10)	46.17 (7.25)	*ns*
Education in years	13.2 (2.1)	13.0 (2.38)	14.17 (2.56)	*ns*
Total IQ	111.93 (9.9)	107.85 (11.87)	103.83 (16.92)	*ns*
Performance IQ	111.6 (9.9)	109.77 (13.2)	105 (14.97)	*ns*
Verbal IQ	109.07 (9.6)	103.92 (11.71)	102.33 (17.51)	*ns*

Values given are mean (±*SD*).

Abbreviated Scale of Intelligence (Wechsler, 1999). Two subtests were selected from the WAIS-III and Digit Span and Letter–Number Sequencing (Wechsler, 1997). The following four subtests from the Delis–Kaplan Executive Function System were included: Trail Making Test, Design Fluency, Verbal Fluency, and Color–Word Interference Test (Delis, Kaplan, & Kramer, 2001). Screening of emotional distress was performed using the Symptom Checklist 90 Revised (SCL-90-R; Derogatis, 1994). The presence of obsessive–compulsive symptoms was explored using the Obsessive–Compulsive Inventory Revised (OCI-R; Foa et al., 2002).

Patients and controls gave their informed consent to participation. Controls were paid NOK 500 (approximately USD 80) for participation in the entire research program that included neuropsychological assessment, EEG, as well as structural and functional MRI examination. The study was approved by the Regional Committee for Medical Research Ethics, Region South, and was conducted in agreement with the Helsinki declaration.

Task

Subjects were seated 1 m from a 24-in. computer screen. They were instructed to fixate on a star in the center of the screen during data acquisition. Auditory stimuli were presented binaurally through stereo headphones. The novelty oddball paradigm consisted of 280 (70%) 1000-Hz tones designated standard and 60 (15%) designated target tones of 1500 Hz presented in a pseudorandomized order where a target tone was never followed by another target. The duration of standard and target tones was 50 msec. Sixty (15%) unique environmental sounds (e.g., dog barks, door slams, and laughter) with matched intensity and a presentation time of 400 msec were interspersed in a pseudorandomized order. A novel stimulus never preceded a target tone or another novel. Subjects were instructed to press a button to target stimuli with the index finger of their dominant hand and to ignore all other sounds. They were asked to respond as fast and as accurately as possible. The experiment was presented in two blocks containing 140 standard, 30 target, and 30 novel stimuli each. A training session containing 15 standard tones and five targets, but no novel stimuli, was presented before EEG recording started. Subjects were not informed that novel stimuli would appear during the experimental run. Stimulus presentations and response recordings were controlled using E-prime software, version 2.0 (Psychology Software Tools, Pittsburgh, PA).

EEG Recording

EEG data were acquired using a 128-channel HydroCel Geodesic Sensor Net and Net Amps 300 amplifier (Electrical Geodesics, Eugene, OR). Impedance was kept below 100 kΩ (Ferree, Luu, Russell, & Tucker, 2001). Recordings were initially referenced to Cz and subsequently re-referenced to an average reference before data analysis. EEG signals were sampled at 250 Hz with a 24-bit analog-to-digital converter and a DC to 125-Hz band pass.

ERP Analysis

ERP analyses and identification of peaks/computation of mean amplitudes from averaged ERP waveforms was carried out using Net Station, Version 4.3.1 software (Electrical Geodesics, Eugene, OR). Continuous EEG data were filtered off-line with 0.3-Hz high pass and 20-Hz low pass filters. Data were epoched, time-locked to stimulus onset in segments from −100 to 900 msec. Artifact detection, artifact correction, and bad channel interpolation were performed using Net Station custom procedures. Channels were marked as bad throughout the entire recording if bad in more than 20% of the segments, and segments were defined as bad if they contained more than 10 bad channels as defined by the computer algorithm or visual inspection. Averaged ERPs were based on correct trials for the three stimulus types (standard, target, and novel).

ROI electrode groups were established as shown in Figure 3 with the following anatomical sites: one right, midline, and left frontal group; one right and left frontocentral group with Cz as midline electrode; and one right, left, and midline parietal ROI. Statistical analyses and illustrations were performed on extracted mean values over electrodes in each ROI. All patients in the LPFC group had unilateral lesions, with three patients having right hemisphere lesions. In statistical analyses and illustrations, the electrodes of the group with right hemisphere

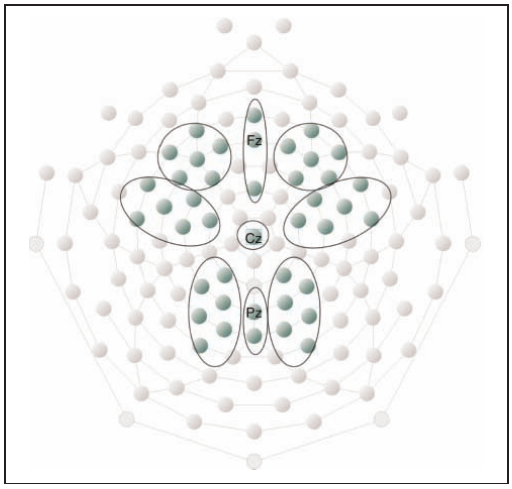

Figure 3. ROI electrode groups. Three electrode groups were established along the anterior–posterior axis (frontal, frontocentral, and parietal) and three groups along the right–left axis (right, center, and left).

lesions are exchanged so that left hemisphere electrodes are synonymous with lesioned hemisphere for the whole LPFC group.

The ERP amplitudes and latencies were extracted as follows:

N1: N1 peak was defined as the most negative point 60–120 msec poststimulus. Latency of this point was derived for all three stimulus types and analyzed over frontal and frontocentral electrode groups.

P2: Because of the temporal overlap between the P2 and the P3a component for deviant tones, P2 mean amplitude 100–250 msec poststimulus was analyzed over frontal and frontocentral electrode groups for standard tones only.

N2: The deviance related negativity (N2) is best observed in difference waveforms where the ERP to standard tones is subtracted from ERPs to novel and target sounds. The N2 appeared at a shorter latency to novel stimuli compared with targets. Peak amplitude and latency for novel N2 was derived as the most negative point 125–300 msec after stimulus onset and target N2 as the most negative point 150–300 msec. The N2 was analyzed statistically over the frontocentral midline electrodes Cz and Fcz.

P3b to target: P3b peak amplitude and latency was derived at the most positive amplitude 300–500 msec poststimulus over parietal electrode groups. Mean amplitude in the 300–500 msec time window was also computed.

Novelty P3: Peak amplitude and latency was analyzed at the most positive point 270–400 msec poststimulus with all ROI electrode groups included in the initial overall analysis. Mean amplitude for the same time interval was also calculated. Habituation of the Novelty response was studied by comparing the mean amplitude of the first three novel stimuli over the frontal midline electrodes with the mean amplitudes of novel stimuli numbers 4–6 and 7–9, respectively.

Sustained late negativity: A sustained late NSW following P3 was seen over frontal and frontocentral electrode groups. Visual inspection of group averaged ERPs revealed that the NSW had shorter duration for the target stimuli compared with the novels. Accordingly, the NSW was independently analyzed as the mean amplitude 400–600 msec (early NSW) and 600–800 msec (late NSW) poststimulus over frontal and frontocentral electrode groups for target and novel deviant stimuli.

Statistical Methods

SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL) was used for statistical analyses. ERP data were analyzed using repeated measures ANOVA. There were three levels of stimulus type (standard, target, and novel), three levels of electrode groups along the anterior–posterior axis (frontal, frontocentral, and parietal), and three levels along the left/right (hemisphere) topographical axis (right, midline, and left). There were also three levels of the between-subject factor group (control, OFC, and LPFC group). Greenhouse–Geisser epsilon corrected p values along with uncorrected degrees of freedom are reported for computations involving more than two levels of a repeated measures factor. Analyses that yielded significant interactions between Group, Stimulus Type, Anterior–Posterior, or Hemisphere resulted in planned contrasts between the levels of the variable. In those cases where the patient groups differed from each other, lesion volume was entered as covariate in the ANOVA. Demographic, psychometric, and performance data were analyzed using one-way ANOVA with Group as between-subject factor. Bonferroni corrected p values are reported in post hoc analyses. Effects involving differences between patient groups and controls were of primary interest. The relationship between behavioral responses and ERP measures was explored with Pearson two-tailed correlation coefficients and comparisons of amplitudes over the hemispheres within groups were conducted with paired samples t test. Results are reported with a significance level of $\leq .05$.

RESULTS

Functional Outcome

Both patient groups had GOS-E scores categorizing them as "Moderately impaired–Upper Level" (OFC: 6.3, SD = 1.1; LPFC: 6.2, SD = 1.0), an outcome level that characterizes patients who are capable of living an independent life despite having disabilities because of the brain injury (Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998). The patient groups did not differ significantly from each other or the healthy controls in total, verbal, or performance IQ (see Table 2). Performance was within normal range, and there were no significant group effects on any of the Wechsler Abbreviated Scale of Intelligence, WAIS-III, or Delis–Kaplan Executive Function System subtests. However, there was a group effect on the Obsessive–Compulsive subscale of the SCL-90-R ($F(2, 31) = 4.62$, $p < .02$) because of the OFC group having higher scores than the controls (OFC: 10, SD = 5.8; controls: 3.5, SD = 4.6, $p < .03$). There was also a group effect on the Hostility subscale of the SCL-90-R ($F(2, 31) = 5.71$, $p < .01$) because of the LPFC group reporting more symptoms of irritability than the controls (LPFC: 3, SD = 2.9; controls: 0.38, SD = 0.7, $p < .01$). The OFC group reported more obsessive–compulsive symptoms on the OCI-R as well, as there was a significant group effect on the Ordering ($F(2, 33) = 5.83$, $p < .01$) and Hoarding ($F(2, 32) = 3.58$, $p < .04$) subscales. This effect was due to the OFC group reporting significantly more symptoms than controls on the Ordering subscale (OFC: 3.9, SD = 2.7; controls: 1.1, $SD = 1.5$, $p < .01$) and near significantly more on the Hoarding subscale (OFC: 4.1, SD = 2.6; controls: 1.9, SD = 2.1, $p < .06$).

Performance Data

Table 3 displays mean hit rate and RT to targets, as well as false alarms to novels and standards. There were no statistically significant differences between groups. Both patient groups and healthy controls had a high hit rate to targets (>99%) and showed few commission errors to nontargets (<2%). RTs to targets did not differ significantly between groups.

ERP Data

Overview

Grand average ERPs for each of the three groups to standard, target, and novel stimuli are presented in Figures 4–6. Scalp topographies for the Novelty P3 response along with ERP difference waves for novel minus standard tones over frontal electrode sites are depicted in Figure 7, and scalp topographies for the NSW to deviant sounds are illustrated in Figure 8. Visual inspection suggested that the task elicited the expected frontally distributed Novelty P3 to novel sounds (Figures 6A and 7) and that both patient groups displayed an amplitude reduction of the novelty response. The parietally maximal P3b to target stimuli was present in all groups (Figure 5C). Both types of deviant sounds elicited a frontal/frontocentral sustained NSW that was more pronounced with a longer duration for novel stimuli compared with targets. The NSW was particularly pronounced for the LPFC group (Figures 5A, 6A, and 8).

Early Latency ERP Components—N1, P2 and N2

N1. Regardless of stimulus type, the LPFC group had enhanced N1 amplitudes over the lesioned hemisphere compared with both the OFC group ($p < .01$) and controls ($p < .01$). This effect was evident in a significant interaction between Hemisphere and Group ($F(4, 62) = 9.61$, $p < .001$). The OFC group and controls did not differ significantly from each other. Both patient groups displayed a shorter left/lesioned frontal N1 latency to targets than the control group (controls: 99.3 msec, $SD = 7.9$ msec; OFC: 88.5 msec, $SD = 17$ msec; LPFC: 90.78 msec, $SD = 5.5$ msec). This was seen in a significant effect of Group over this electrode location for target stimuli ($F(2, 31) = 5.48$, $p < .01$). The difference between OFC patients and controls was significant ($p < .05$) and approached significance for the LPFC group compared with the controls ($p < .06$). The two patient groups did not differ significantly from each other.

The LPFC patients had all undergone craniotomy, which could potentially influence amplitude levels over the lesioned hemisphere through current shunting caused by skull defects or to changes of current flow patterns due to the surgical resection cavities filled with cerebrospinal fluid. To partly address this issue, an analysis of signal-to-noise ratio over lesioned versus nonlesioned electrode sites was performed by computing mean standard deviations of the amplitudes in the baseline period. There was not a significantly larger variation in amplitudes over the lesioned compared with the nonlesioned hemisphere in the LPFC group ($p < .3$), indicating that the signal-to-noise ratio was comparable across hemispheres.

P2. Over the frontal electrodes, there was a main effect of Group ($F(2, 31) = 5.07$, $p < .01$) as the OFC group had significantly smaller mean P2 amplitude to standards than the control group ($p < .001$). The LPFC group did not differ significantly from either of the two other groups. See Figure 4.

N2. There were no significant main effects or interactions involving Group on amplitude (Fs = 0.21–2.0, ps = .08–.94) or latency (Fs = 0.27–1.67, ps = .21–.76) of the N2 difference waves (target minus standard and novel minus standard computations).

ERPs to Target and Novel Deviants

Parietal P3b to targets. There was no significant main effect involving Group for the parietal P3b latency ($F(2, 31) = .17$, $p < .85$; controls: 386.1 msec, $SD = 57.3$; OFC: 394.9 msec, $SD = 54.1$; LPFC: 398.9 msec, $SD = 28$). The analysis revealed no significant main effect of Group on the parietal P3b peak ($F(2, 31) = 1.17$, $p < .32$) or mean ($F(2, 31) = 1.34$, $p < .28$) amplitude, as well as no significant interactions between Group and Hemisphere neither for the peak ($F(4, 62) = 1.46$, $p < .23$) nor the mean ($F(4, 62) = 1.42$, $p < .24$) amplitude analysis.

Novelty P3. There was no significant main Group latency effect for the frontal Novelty P3 ($F(2, 31) = .36$, $p < .7$; controls: 314.7 msec, $SD = 17.6$; OFC: 328.1 msec, $SD = 34.5$; LPFC: 309.5 msec, $SD = 28.2$). Amplitude analysis was performed on mean values. Both patient groups displayed attenuated Novelty P3 amplitudes compared with healthy controls. The overall analysis showed both significant Anterior–Posterior × Group ($F(4, 62) = 3.53$, $p < .05$) and Hemisphere × Group ($F(4, 62) = 3.65$, $p < .05$) interactions. Follow-up analyses were, thus, performed on the right, midline, and left/lesioned

Table 3. Behavioral Results from the Novelty Oddball Task

	Control	*OFC*	*LPFC*	*ANOVA*
Hit rate target (%)	99.7 (0.9)	99.6 (1.0)	99.2 (2.0)	*ns*
False alarms (%)				*ns*
Standard	0.6 (0.3)	0.6 (0.3)	0.7 (0.4)	*ns*
Novel	1.2 (2.3)	1.1 (1.4)	1.1 (1.3)	*ns*
RT target (msec)	381.9 (66.2)	422.5 (73.5)	421.9 (46.7)	*ns*

Results are reported as mean values (±*SD*).

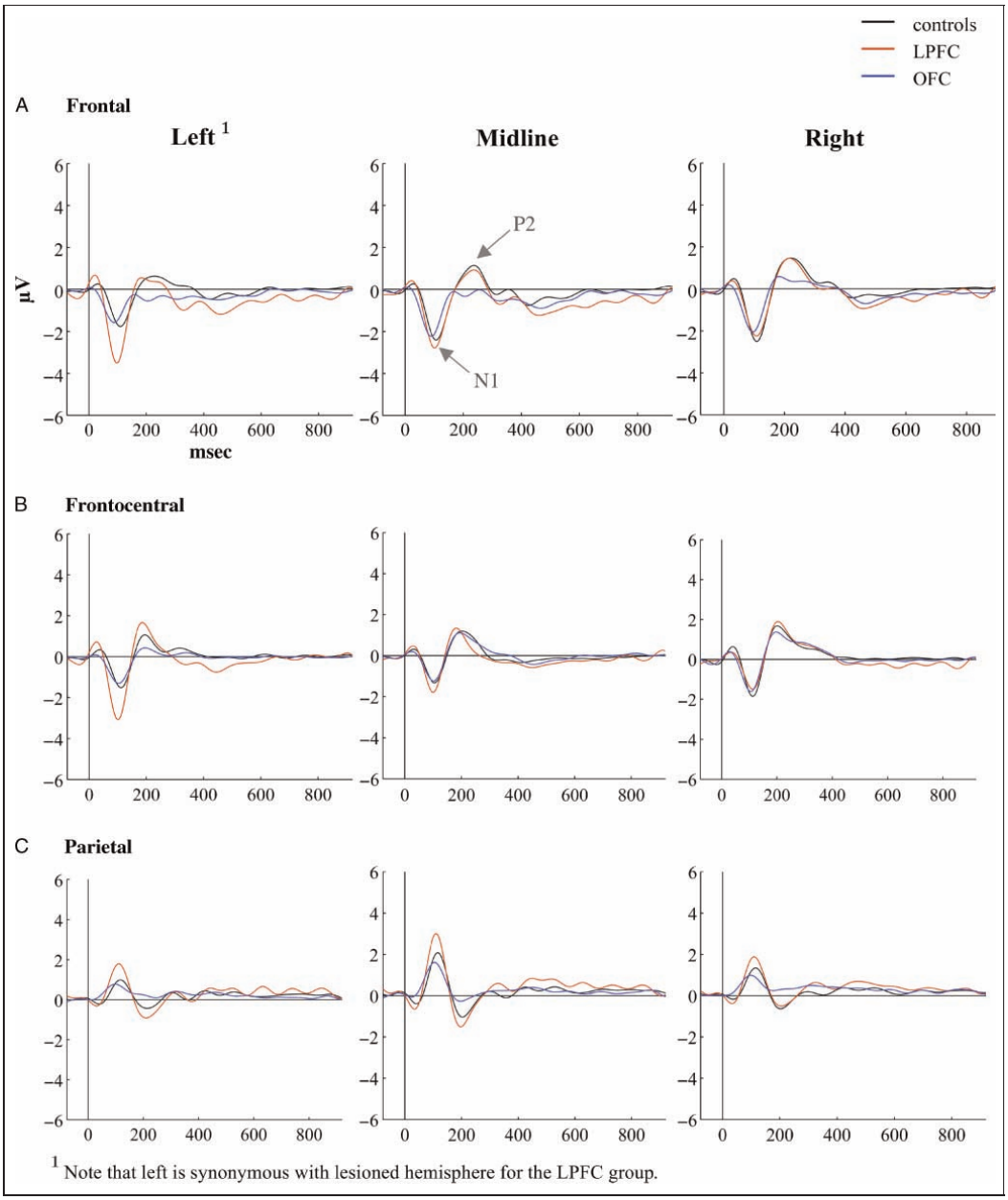

Figure 4. ERPs to standard tones over (A) frontal, (B) frontocentral, and (C) parietal electrode groups.

electrode groups separately. Compared with controls, the OFC group had attenuated mean amplitudes over frontal left ($p < .001$) and frontal midline ($p < .05$) electrode groups. The LPFC group differed from the control group by displaying smaller Novelty P3 amplitudes over the lesioned hemisphere only, a difference that was significant both over frontal ($p < .01$) and frontocentral ($p < .01$), but not midline, electrode sites. The patient groups did not differ significantly from each other (see Figures 6 and 7).

Novelty P3 was compared between controls and the patients with OFC lesions due to tumor (n = 9) and TBI (n = 4), respectively, and both etiologies resulted in Novelty P3 reductions. The patients with tumor resections had significantly reduced Novelty P3 amplitudes over both left ($F(1, 23) = 16.82$, $p < .001$) and midline ($F(1, 23) = 10.32$, $p < .005$) frontal electrode groups, whereas the smaller TBI group had reduced

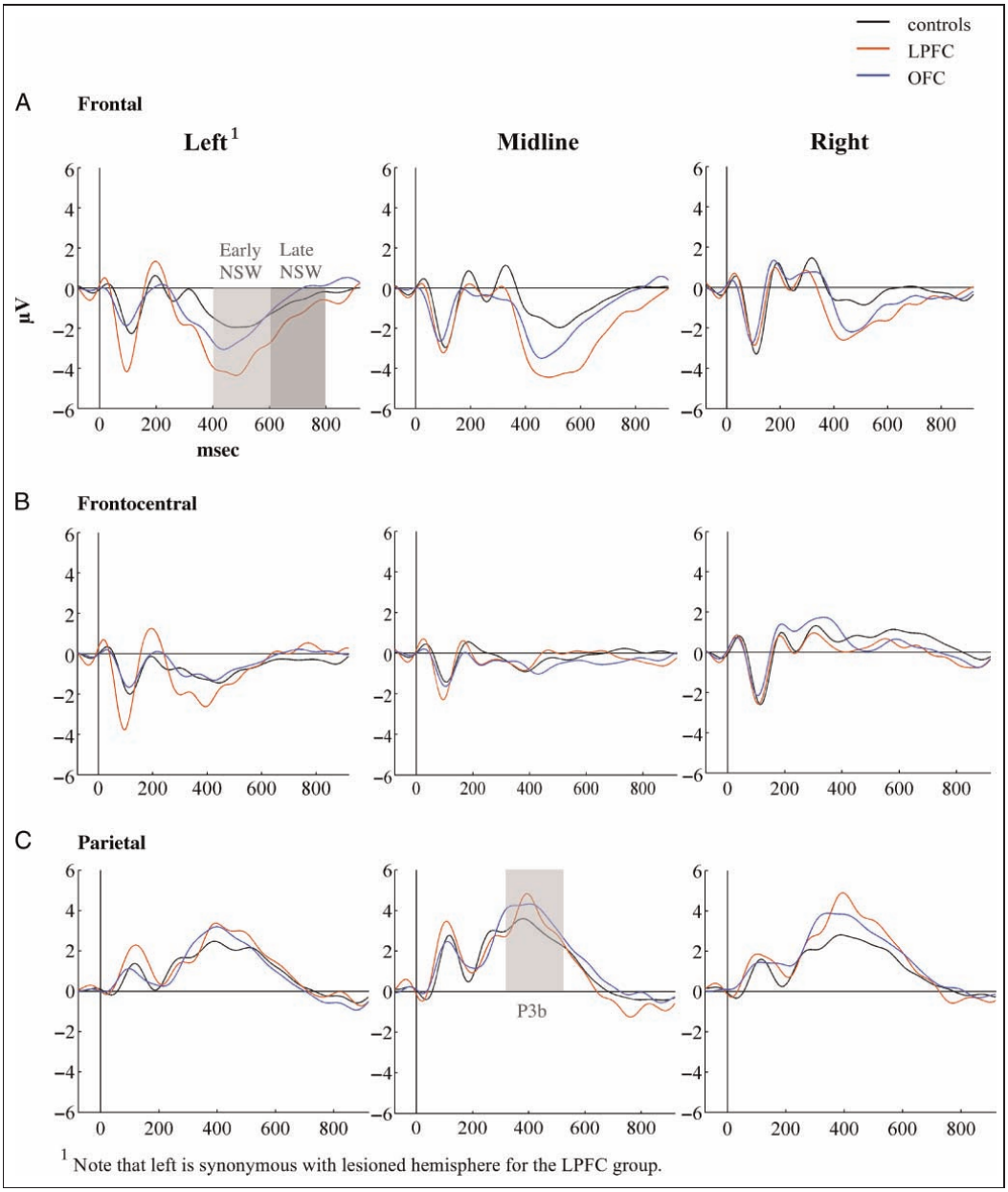

Figure 5. ERPs to target tones over (A) frontal, (B) frontocentral, and (C) parietal electrode groups.

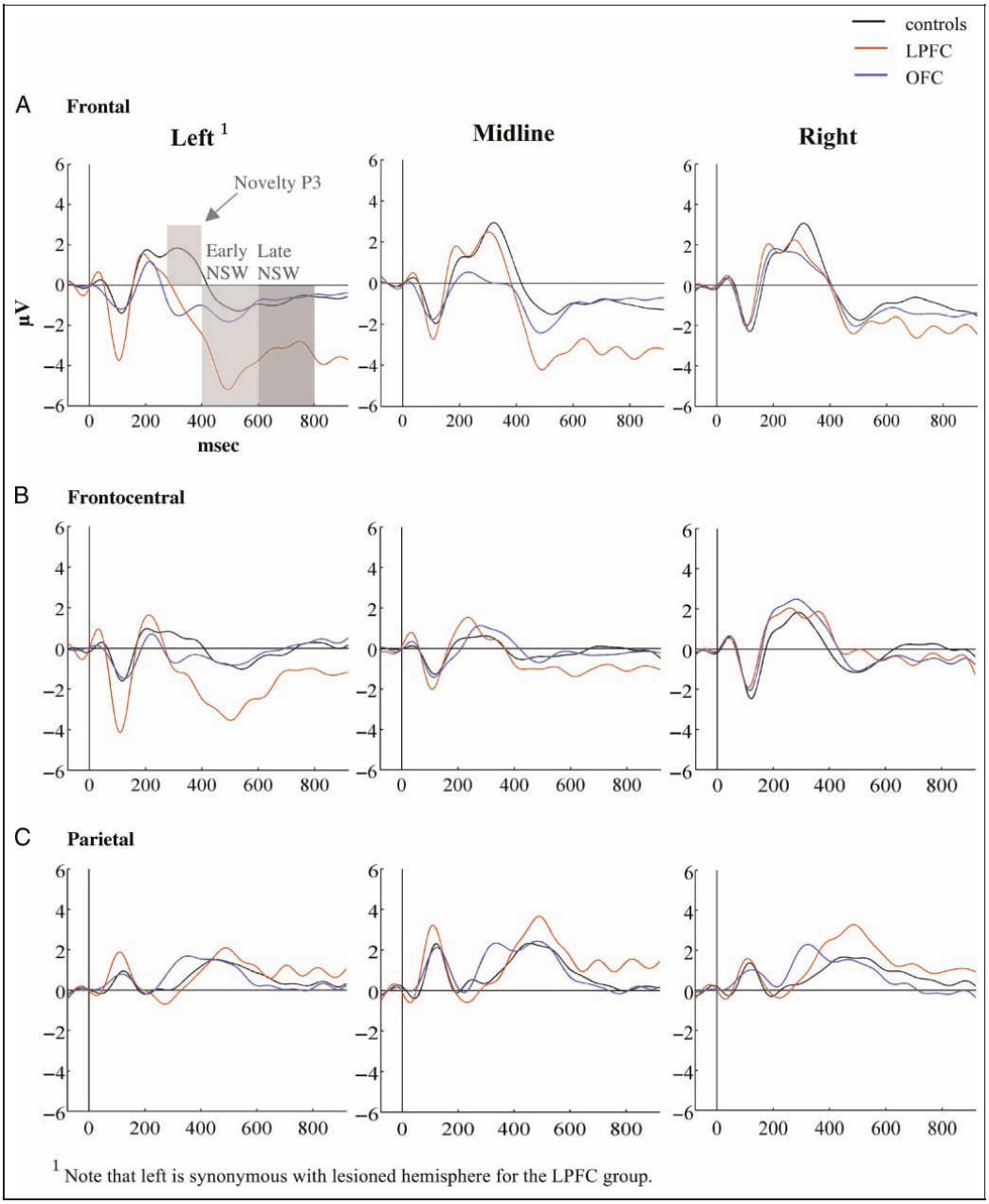

Figure 6. ERPs to novel sounds over (A) frontal, (B) frontocentral, and (C) parietal electrode groups.

Novelty P3s only over the left hemisphere ($F(1, 18) = 5.35$, $p < .05$).

Amplitudes to the first nine novel stimuli were examined over the frontal midline electrodes by comparing the first three novel stimuli to the next three (Novel Stimuli 4–6) and again to Novel Stimuli 7–9. The raw data of the control group showed the expected decline in amplitudes over the three stimulus groups (Novel Stimuli 1–3: 3.7 μV,

SD = 3.6 μV; Novel Stimuli 4–6: 3.0 μV, *SD* = 2.7 μV; Novel Stimuli 7–9: 1.1 μV, *SD* = 5.3 μV), whereas the OFC group had negative polarity ERP amplitudes to novel stimuli from all three groups with no evidence of habituation (Novel Stimuli 1–3: −0.5 μV, *SD* = 4.1 μV; Novel Stimuli 4–6: −2.1 μV, *SD* = 4.5 μV; Novel Stimuli 7–9: −0.6 μV, *SD* = 4.6 μV). The LPFC group had a small Novelty P3 of positive polarity over the mean of the first three stimuli only (Novel Stimuli 1–3: 1.9 μV, *SD* = 4 μV; Novel Stimuli 4–6: −0.9 μV, *SD* = 2.6 μV; Novel Stimuli 7–9: −0.4 μV, *SD* = 2.6 μV). The change in amplitudes over stimulus groups did not turn out as significant for any of the subject groups. There was, however, a main effect of Group ($F(2, 29) = 5.12$, $p < .01$), indicating that the Novelty P3 diminishment was evident already from the first novel stimuli presented (mean amplitudes of Novel Stimuli 1–9 controls: 2.6 μV, *SD* = 2.6 μV; OFC: −0.9 μV, *SD* = 3.3; LPFC: .23 μV, *SD* = 2.1). Post hoc analysis showed that the OFC group differed significantly from controls ($p < .01$).

Early (400–600 msec) NSW. There was a main effect of Group ($F(2, 31) = 9.16$, $p < .001$) because of larger amplitudes in the LPFC group than in controls ($p < .01$). There was an additional Stimulus Type × Hemisphere × Group interaction ($F(8, 124) = 3.08$, $p < .01$; see Figures 6 and 8). For the target sounds, there was a magnitude difference between the LPFC group and controls ($p < .05$) over left/lesioned electrode sites, and both OFC and LPFC groups had larger amplitudes than controls over frontal midline electrodes ($p < .05$ and $p < .01$, respectively). For the novel sounds, there was an interaction between Group and Hemisphere for both frontal ($F(4, 62) = 7.30$, $p < .001$) and frontocentral electrodes ($F(4, 62) = 6.53$, $p < .001$). Over the lesioned hemisphere, the LPFC group had larger frontal and frontocentral NSW to novel sounds than both OFC patients and controls ($p < .001$). The effect was still present when lesion volume was entered as covariate in the model ($F(2/30) = 6.66$, $p < .005$). The LPFC group also differed from the other groups over frontal midline sites ($p < .001$). There were no significant differences between the OFC group and the controls. Irrespective of group, the early NSW was most pronounced over the left (lesioned for the LPFC group) hemisphere for both targets ($F(2, 62) = 15.75$, $p < .0005$) and novels ($F(2, 62) = 8.32$, $p < .001$). There were no significant effects involving standard tones.

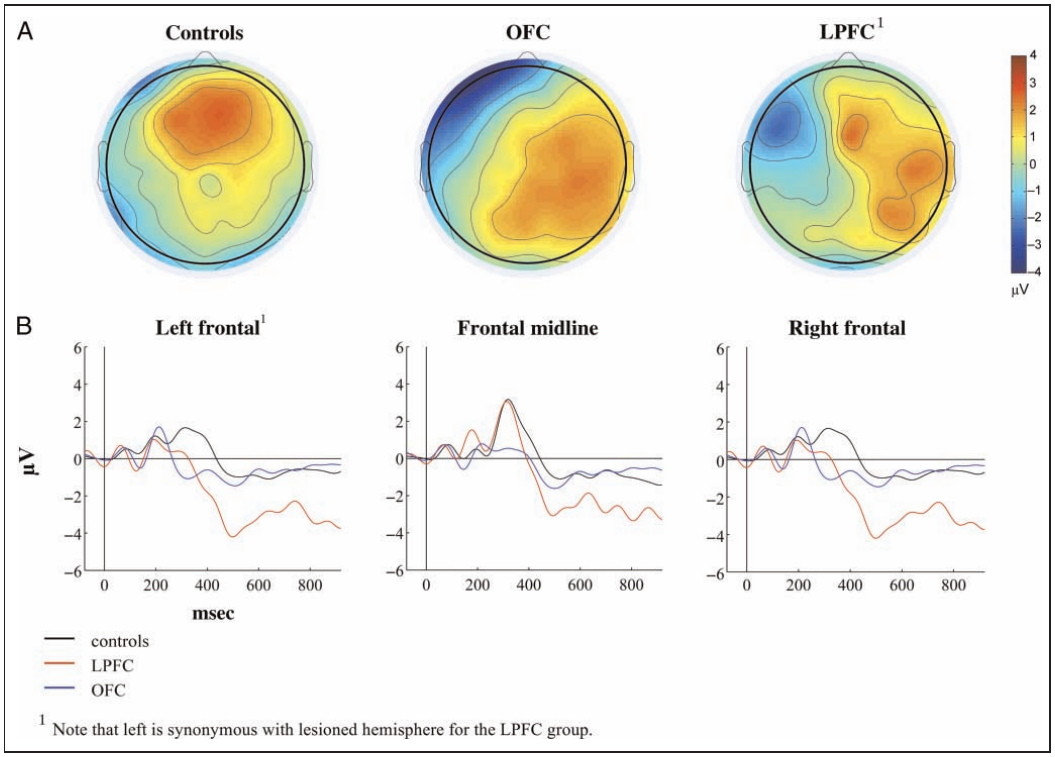

Figure 7. Novelty P3. (A) Scalp topography of the Novelty response (270–400 msec) for each group. (B) ERP difference waves (Novels minus standards) over frontal electrode groups.

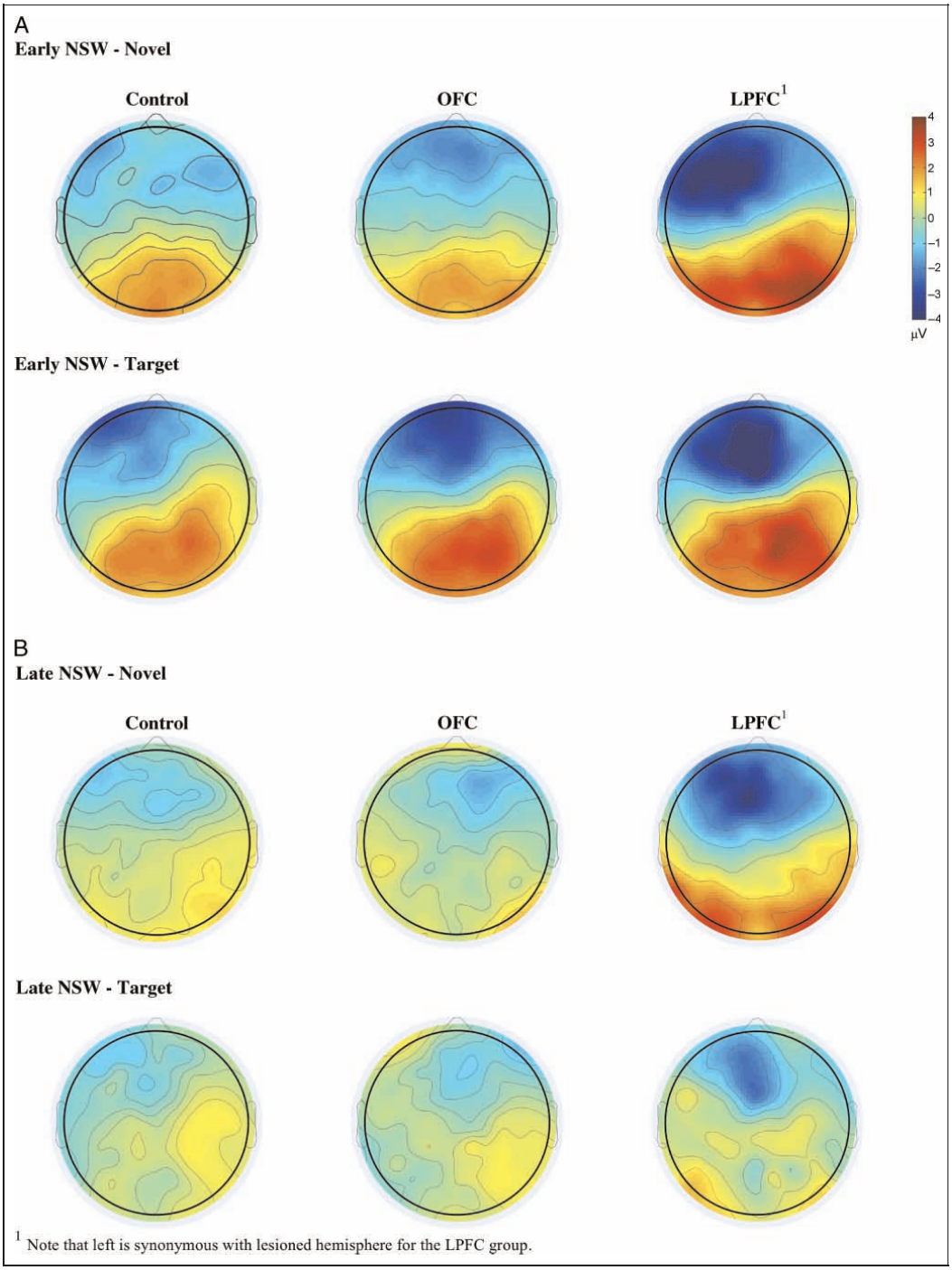

Figure 8. Scalp topographies for (A) early (400–600 msec) and (B) late (600–800 msec) NSW for each group.

Late (600–800 msec) NSW. A main effect of Group ($F(2, 31) = 5.15$, $p < .01$) reflected that the LPFC group had a larger mean amplitude than the other groups (see Figure 6). There were additional Stimulus Type × Group ($F(4, 62) = 2.62$, $p < .05$) and Anterior–Posterior × Hemisphere × Group ($F(4, 62) = 2.59$, $p < .05$) interactions. Follow-up analyses revealed no significant Group differences for the target stimuli. For the novel sounds, however, there was a main effect of Group ($F(2, 31) = 8.37$, $p < .001$) but also an interaction between Hemisphere and Group ($F(4, 62) = 2.52$, $p < .05$). Over the lesioned hemisphere, the LPFC group had a significantly larger NSW than both controls ($p < .01$) and the OFC group ($p < .01$). This effect was still present when lesion volume was entered as covariate ($F(2, 30) = 5.73$, $p < .001$). This was also the case for the midline electrodes ($p < .01$). Over the nonlesioned hemisphere, the LPFC group differed significantly from controls only ($p < .05$). There were no significant differences between controls and the OFC group. As for the early NSW, there were no significant effects involving standard tones.

Relationship between RT and ERP Measures

In the healthy controls, but not the patient groups, there was a significant negative correlation between the amplitude of the early NSW to target stimuli and RT to successful target trials over the left hemisphere ($r = -.53$, $p < .04$). There were no other significant correlations between RT to target stimuli and ERP measures.

DISCUSSION

Neurophysiological markers of novelty processing were studied in patients with lesions to the LPFC or the OFC in an auditory oddball task containing unexpected and task-irrelevant novel environmental sounds. The patient groups were classified as moderately impaired by the GOS-E. Despite this, their IQ and neuropsychological test results were normal, indicating that the patients experience functional deficits that were not readily detected by traditional neuropsychological measures. Of note, the OFC group reported more obsessive–compulsive symptoms and the LPFC group reported more irritability than controls. Obsessive–compulsive symptoms have been described in patients with OFC damage (Coetzer, 2004; Woessner & Caplan, 1995). Both patient groups displayed few commission errors to task-irrelevant stimuli, and their RTs and hit rates to target sounds were comparable to healthy controls, in accord with earlier studies showing typical behavioral performance in patients with focal frontal lesions on simple oddball tasks (Knight & Scabini, 1998; Knight, 1984, 1997; Yamaguchi & Knight, 1991). Despite normal scores on neuropsychological tests and normal performance on the experimental task, there were robust effects of frontal lesions on ERP measures of novelty processing.

Dissociation of Target and Novelty Processing after Frontal Lobe Damage

All three groups displayed a parietal maximum P3b to target stimuli supporting normal target detection in this simple task, a finding previously demonstrated in patients with LPFC lesions (Knight & Scabini, 1998). The present study indicates that the same conclusion can be extended to the role of OFC lesions on parietal-dependent target processing.

LPFC damage resulted in reduced amplitudes of the Novelty P3 response as has also been reported. Novelty P3 attenuation was evident for patients with OFC lesions as well, indicating that both OFC and LPFC participate in novelty processing. The reduction of the Novelty P3 was predominantly found at frontal and frontocentral electrode sites over the lesioned hemisphere in the LPFC group. The relative sparing of midline novelty P3 activity in the LPFC group might be because of reorganization of frontal function in the spared cortex of these patients (Voytek, Davis, et al., 2010).

In the OFC group, the Novelty P3 reduction was seen over frontal electrodes only, but the effect was present both over midline and left hemisphere electrodes. A habituation analysis of the Novelty response to the first nine Novel stimuli showed that the OFC patients failed to generate a Novelty P3 over frontal midline electrodes for any of the novel stimuli, providing additional support for the role of OFC in novelty processing. Of interest, the LPFC group showed habituation of the Novelty P3 response.

The lateralized reduction of the Novelty response in OFC patients was unexpected. The majority of OFC patients had bilateral lesions. In fact, the OFC group had a larger mean lesion volume over the right hemisphere (28.9 ccm) compared with the left (21.3 ccm), indicating that the laterality effect was not merely a product of the amount of damaged cortex. One possibility is that the Novel sounds used were meaningful environmental sounds and could have given rise to semantic processing (Mecklinger, Opitz, & Friederici, 1997). It has been demonstrated that novel environmental sounds activate left frontal brain regions in a verbal encoding task (Opitz, Mecklinger, & Friederici, 2000). Although speculative, it is possible that the effect of OFC lesions on novelty processing was larger over the left hemisphere because of altered processing of acoustic meaning.

Differential Frontal Lesion Effects on the NSW

The NSW to targets was enhanced for both patient groups with a maximum around the time of manual response delivery (mean RT = 422 msec in both patient groups). A left and midline frontal maximum was observed, corresponding to the lesioned hemisphere for the LPFC patients. Novel stimuli elicited a larger frontal negativity with a longer duration than the NSW to target stimuli for

the LPFC group compared with both the OFC group and healthy controls. The enhanced NSW to novels in the LPFC group was predominantly present over the lesioned hemisphere.

Studies of healthy subjects (Schroger & Wolff, 1998), neurological populations (Potter, Bassett, Jory, & Barrett, 2001), and children (Maatta et al., 2005) suggest a link between auditory novelty-related NSW and controlled allocation of attentional resources. It has been proposed that the orienting response consists of two stages; first, the reaction that something novel has appeared, and second, an evaluation of stimulus characteristics and response requirements (Germana, 1968). Kok (1978) proposes that the Novelty P3 and the NSW reflect these two decision stages of the orienting response. A seeming paradox has been noted in Knight's (1984) conclusion that lateral frontal lesions result in a deficit, both in inhibitory control and in novelty detection, implying that patients with frontal lobe lesions are both more distractible and less susceptible to deviant events (Kok, 1999). Kok (1999) resolves this paradox by assuming that these two phenomena reflect deficits in separable attentional mechanisms. Reduced novelty detection could reflect a deficit in automatic or involuntary aspects of attention, whereas increased distractibility could result from a deficit in active focusing of selective attention. This implies that it should be possible to observe differential effects on ERP indicators of novelty processing. The OFC group in the present study presented with reduced Novelty P3 only, whereas the LPFC group displayed both a reduced Novelty P3 and an enhanced novelty-related NSW indicating that the Novelty P3 and the NSW can be differentially affected by brain injuries.

A second possibility is that the Novelty P3 is not as automatic or reflexive as traditionally believed. The Novelty P3 amplitude is modulated by familiarity and semantic context (Friedman, Cycowicz, & Dziobek, 2003), implying that the Novelty P3 also is affected by the process of bringing the event to consciousness for evaluation of salience and appropriate action. If a Novelty P3 reduction indexes changes in the cognitive evaluation of novel events in addition to an involuntary orienting response, one might expect to observe signs of subsequent prolonged processing. This notion would be in line with the proposal that late NSW is associated with working memory and level of mental processing (Ruchkin et al., 1995). The prolonged enhancement of the NSW to meaningful novel sounds could, thus, index a tendency for sustained stimulus processing in the LPFC group even after a decision has been made to not respond.

A related question is the functional association between the NSW to target and novel stimuli. These stimuli are both deviant events of low frequency and both elicit slow waves in an oddball paradigm (Ritter & Ruchkin, 1992). The novel stimuli, unlike the target sounds, are acoustically complex and meaningful. They are also unique on every presentation, whereas the targets are identical but task relevant. The amplitude of the frontal NSW can be affected by a range of factors, such as degree of novelty, stimulus probability, response probability, and task relevance (Kok, 1978). The NSW elicited by target stimuli could be because of factors related both to physical deviance, task relevance, and motor response requirements. The novel sounds might elicit a slow negativity largely because of perceptual novelty and inherent meaningfulness. The NSW to target and novel deviants could thus be reflecting both distinct and overlapping cognitive processes that we could not disentangle in the current study.

Increased NSW amplitudes were associated with longer RTs. This has been demonstrated in earlier studies, as well, and has been interpreted as indicating that slow waves are related to task demand (Roth, Ford, & Kopell, 1978). Thus, an enhanced NSW in patients with frontal lobe injury might be associated with an abnormal allocation of "mental effort" to the deviant stimuli to cope efficiently with the task (Voytek, Davis, et al., 2010).

Distinct Lesion Effects on Early ERP Potentials: N1 and P2

Enhancement of the N1 in patients with frontal lobe injury (Knight et al., 1980) and in older subjects (Kok, 2000) has previously been interpreted as indexing altered inhibitory control because of prefrontal deficit. However, in this study, there was a possibility that the ERP effects in the LPFC group could be influenced by surgical skull defects over the lesioned hemisphere because of current shunting caused by craniotomy defects in the skull or to changes of current flow patterns due to the resection cavities being filled with cerebrospinal fluid (Voytek, Secundo, et al., 2010). The spontaneous EEG of the prestimulus baseline period did not show significantly larger amplitude variation over the lesioned compared with the nonlesioned hemisphere in the LPFC group. Thus, the amplitude enhancements are not likely because of increased noise or activity not related to task requirements. It is not possible to entirely rule out a contribution of craniotomy effects because the increased N1 amplitude in the LPFC group generalized across stimulus types. Although factors not related to the task such as current shunting may have contributed to the N1, the effect might also reflect changed inhibitory top–down control over early perceptual processes.

There are several reasons why current shunting cannot explain the results observed for the P2, Novelty P3, and NSW components. First, there is not a general amplitude enhancement across all ERP components or stimulus types for the P2, Novelty P3, and NSW. Second, the N1 enhancement was not accompanied by a comparably negative shift or enhancement in the following P2 component to standard tones. Third, the NSW was condition specific. Finally, a regression analysis showed that the N1 amplitude did not predict NSW amplitude.

Although N1 was unaffected in the OFC group, these patients had a reduced P2 to standard tones. The functional significance of the P2 is poorly understood, but it has been shown to be related to aspects of auditory discrimination and stimulus classification as well as attentional processing (Tong, Melara, & Rao, 2009; Crowley & Colrain, 2004; Näätänen, 1992). The N1 and P2 have been shown to be differentially affected by frontal brain injury as patients with lateral frontal damage displayed enhanced N1 and normal P2 when stimuli were presented to the ear contralateral to lesion site compared with ipsilateral stimulation (Knight et al., 1980). The results of the current study are in line with these findings, as the LPFC group displayed an increased N1 amplitude and a normal P2 over the lesioned hemisphere. The OFC group had a normal N1 but reduction of the P2 to standard stimuli. One hypothesis is that the OFC patients might be presenting signs of dampened perceptual classification, although not to the degree where it caused a breakdown in target discrimination in this fairly simple auditory oddball task.

Novelty P3 and OFC Lesions

Two earlier studies have described enhancement of P3 amplitudes after frontal lobe injury. The Rule et al. (2002) study is the only work that has explored the effects of OFC lesions. A parietal (Pz) Novelty P3 distribution seen in controls was enhanced in OFC patients. The parietal distribution of the Novelty P3 stands in contrast to many studies showing a more frontal–central novelty distribution. A passive novelty task was used by Rule et al. The patients watched a silent movie during stimulus presentation, and auditory and somatosensory stimuli were interspersed among each other in an unpredictable fashion at long ISI, causing the somatosensory and the auditory stimuli to be emotionally laden because they automatically pulled attention away from the movie. Of note, the study included only four OFC patients, of which one had additional lesion to the temporal lobe. The extent of OFC damage was comparable between our study and the study by Rule and colleagues.

The second study reporting enhancement of the P3 is Kaipio et al. (1999), wherein 11 patients with closed head injuries were included and exposed to a passive design as they were instructed to ignore standard and deviant (600 and 660 Hz, respectively) tones as well as complex Novel sounds presented during a visuomotor tracking task. Enhancement of a later portion of the Novelty P3 (350–450 msec) was shown over Cz. No lesion effects were seen over frontal electrode sites. The findings were taken to indicate enhanced processing of novel sounds. Six patients were described to have predominantly frontal damage, one no parenchymal lesion, one retained fluid in the sphenoid sinus, one subcortical diffuse axonal injury, and two temporal lobe lesions. Information on exact lesion site or size was not provided. Although this study might elucidate general effects of acquired brain injury, it is not well suited to provide information about the distinct relationship between subregions of the frontal lobes and novelty processing.

Taken together, differences in lesion location, study design, Novelty P3 scalp distribution, and sample size across studies render direct comparisons with earlier studies difficult. However, the differing results might indicate that an enhancement of the posterior P3 is associated with passive paradigms and emotionally laden stimuli. Contrasting the effect of predominantly cognitive and emotionally charged tasks on the P3 complex in patients with OFC lesions is needed to address this issue. A strength of the current study is the size of the OFC group and the active nature of the task. The findings in this study are in line with an animal study where neurons that responded to novel but not to familiar visual stimuli and habituated rapidly were demonstrated in the anterior OFC of the rhesus macaque monkey (Rolls, Browning, Inoue, & Hernandi, 2005).

Variation in lesion etiology between the two patient groups and within the OFC group might contribute to the findings in this study. All LPFC patients had undergone resections of unilateral LGG. The majority (8 of 13) of patients with OFC lesions had undergone resection of large meningiomas, four suffered TBI, and one had an LGG. The studies performed by Daffner et al. (2000, 2003) included only patients with cerebrovascular insults, whereas in Knight's initial ERP study of frontal novelty processing (Knight, 1984), 7 of 14 patients had tumor resections, 5 had cerebrovascular, 1 had trauma, and 1 had abscess resection. Stuss and Alexander (2007) note that their studies of the neuropsychological effects of focal frontal lesions have demonstrated that lesion location is more important than etiology. Of note, despite the differing etiologies, the Daffner et al. and Knight studies yielded parallel results on Novelty P3 reductions after LPFC damage. The subgroup analysis of the OFC group in this study demonstrated that the Novelty P3 reduction was evident both in patients with tumor resections and in the TBI patients, indicating that the findings were not restricted to a specific etiology.

Although studies of the effect of LPFC lesions to the ERP complex are almost exclusively performed on patients with unilateral lesions, both Rule et al.'s work (Rule et al., 2002) and our study included OFC patients with predominantly bilateral damage. Whether the Novelty P3 reduction observed in the patients with OFC damage would have been seen in a sample with unilateral OFC damage awaits further study.

Conclusion

This study showed that despite normal task execution and neuropsychological profiles, patients with LPFC and OFC lesions present distinct neurophysiological evidence of alterations in novelty processing. Patients with LPFC and OFC lesions exhibited a normal parietal P3b response to

target stimuli, indicating unaffected target detection. Conversely, both patient groups displayed attenuation of the Novelty P3 component, indicating an altered orienting response to unexpected and task irrelevant novel events. Previous work has demonstrated this for patients with LPFC lesions, and here, we extend this finding to OFC damage patients. Both patient groups displayed enhanced NSW to target deviants, possibly related to increased processing to successfully performing the task. Only the LPFC group showed an additional enhanced NSW to novel sounds, an effect that might index prolonged processing of task-irrelevant sounds in this group. Taken together, the results suggest that OFC and LPFC lesions have a partly shared and partly differential effect on the cascade of cognitive subcomponents involved in novelty processing. Normal novelty processing is the result of a cascade of sensory/perceptual and cognitive processes, with subregions of the frontal lobes providing critical input throughout the process of deviance detection and evaluation of stimulus significance.

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II

III

Appendix A. EEG-recordings, Experimental paradigms, and ERP-analysis.

A.1. EEG recordings

All EEG-data was acquired using a 128-channel HydroCel Geodesic Sensor Net and Net Amps 300 amplifier (Electrical Geodesics, Eugene, OR). Impedance was kept below 100 kΩ (Ferree et al., 2001). Recordings were initially referenced to Cz and subsequently re-referenced to an average reference. EEG-signals were sampled at 250 Hz with a 24 bit analog-to-digital converter and a DC to 125 Hz bandpass. All stimulus presentations and response recordings were controlled using E-prime software, version 2.0 (Psychology Software Tools, Pittsburgh, PA). Subjects were seated 1 meter from a 24-in. computer screen. As noted, the current study forms part of a larger research program exploring the effects of focal frontal lesions on cognitive control. As these data have been analyzed at different time-points in the research program, methodological choices have been adjusted somewhat, resulting in some variation in the software tools utilized. The control group consisted of 15 persons in the novelty oddball paradigm, and 14 in the Stop-signal task. Deletion of control subjects was due to either extensive ocular and/or muscular artifacts that we were not able to correct to an acceptable level with the correction procedures used in the two studies, or due to technical problems with the EEG-recordings.

A.2. Experimental paradigms and ERP-analysis

A.2.1 Target and Novelty detection; Auditory novelty oddball task:

Experimental paradigm. Subjects were instructed to fixate on a star in the centre of the screen during data acquisition. Auditory stimuli were presented binaurally through stereo headphones. The task consisted of 280 (70 %) 1000 Hz tones designated standard and 60 (15 %) designated target tones of 1500 Hz presented in a pseudo-randomized order where a target

tone was never followed by another target. The duration of standard and target tones was 50 milliseconds (ms). Sixty (15 %) unique environmental sounds (e.g. dog barks, door slams, laughter) with matched intensity and a presentation time of 400 ms were interspersed in a pseudo-randomized order. A novel stimulus never preceded a target tone or another novel. Subjects were instructed to press a button to target stimuli with the index finger of their dominant hand and to ignore all other sounds. They were asked to respond as fast and as accurately as possible. The experiment was presented in two blocks containing 140 standard, 30 target and 30 novel stimuli each. A training session containing 15 standard tones, 5 targets, but no novel stimuli, was presented before EEG recording started. Subjects were not informed that novel stimuli would appear during the experimental run.

ERP-analysis. Continuous EEG data was filtered offline with 0.3 Hz high pass and 20 Hz low-pass filters. Data was epoched time-locked to stimulus onset in segments from -100 to 900 ms. Artefact detection, artefact correction and bad channel interpolation was performed using Netstation custom procedures. Channels were marked as bad throughout the entire recording if bad in more than 20 % of the segments, and segments were defined as bad if they contained more than 10 bad channels as defined by the computer algorithm or visual inspection. Averaged ERPs were based on correct trials for the three stimulus types (standard, target, novel).

Region of Interest (ROI) electrode groups were established as shown in fig. 1 with the following anatomical sites: one right, midline and left frontal group, one right and left frontocentral group with Cz as midline electrode, and one right, left and midline parietal ROI. Amplitude values were calculated as the mean amplitudes from the electrodes in each ROI.

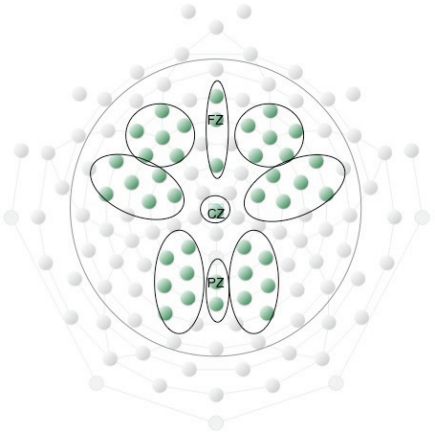

Figure 1. Region of interest electrode groups in the Novelty Oddball paradigm.

Three electrode groups were established along the anterior-posterior axis (frontal, frontocentral and parietal) and three groups along the right-left axis (right, midline and left).

Amplitude of the parietal P3b to target was analyzed as mean amplitudes in the 300-500 ms time window, while the frontally distributed Novelty P3 was calculated as mean amplitude in the 270-400 ms time window. Amplitude of the frontal negative slow wave was calculated as mean amplitude 400-600 ms post-stimulus. For a detailed description of results of this paradigm in healthy controls as well as patients with lateral prefrontal and orbitofrontal lesions, see Løvstad et al. (2012).

A.2.2. Behavioral inhibition and performance monitoring; the Stop-signal task

Experimental paradigm. The Stop-signal task consisted of blocks of lateralized presentation of 70 Go stimuli where arrows pointing to the right required a right button press and left-pointing arrows required a left button press. Each block contained 30 (43%) Stop trials where an upwards-pointing arrow following the Go stimuli indicated that the button press should be withheld. The time interval between offset of the Go- and onset of the Stop signal (stop-signal delay) varied randomly within 5 stop signal intervals that were initially: 50-150, 150-250,

250-350, 350-450 and 450-550 ms. Approximately equal distribution between successful and failed inhibitions was ensured through individually tailoring inhibitory difficulty by correcting the stop signal delay according to reaction time (RT) to correct GO-trials in the preceeding block (see Pliszka et al., 2000 for detailed description of procedure). New blocks were run until a minimum of 30 successful and 30 failed inhibitions was ensured for each individual. An estimation of the stop-signal reaction time in successful inhibitions was calculated by subtracting the subjects average stop-signal delay from the n-th percentile of the reaction time distribution of correct go-responses, with n being the probability of failed inhibitions (Band et al., 2003).

ERP-analysis. Continuous EEG data was filtered offline with 0.5 Hz high pass and 30 Hz low pass filters. Data was epoched time-locked to stimulus onset in segments from -300 to 1000 ms with the baseline from -100 to 0 ms. Analyses were performed with custom-written scripts in MATLAB (Natick, MA) and the EEGLAB toolbox (Delorme & Makeig, 2004). Vertical and horizontal eye movements were corrected based on an independent components analysis as implemented in EEGLAB and trials with muscle artifacts were rejected from the analysis. Averaged ERPs were based on correct trials for the GO-stimulus time locked to the Go-signal as well as response-locked ERP´s to failed inhibitions (error-related negativity) and correct Go-trials. Response-locked ERPs were computed with a 300 ms baseline preceding the button-press. Parietal P3 responses to successful GO-trials were calculated as mean amplitudes 300-500 ms post stimulus. Central error-related negativity to failed inhibitions as well as comparable ERPs to successful Go-trials were calculated as mean response-locked amplitudes in the 50-100 ms time window. The error-positivity following the error-related negativity was calculated as mean amplitudes 250-400 ms post response delivery. For

presentation purpose only, ERPs were low-pass filtered with 15Hz. Statistics were performed on unfiltered data.

Region of Interest (ROI) electrode groups were established as shown in fig. 2 with right, midline and frontal electrode groups over frontal, central, parietal and occipital electrode sites. A detailed description of results of this paradigm in healthy controls as well as patients with orbitofrontal lesions, will be presented elsewhere (Solbakk et al., in prep).

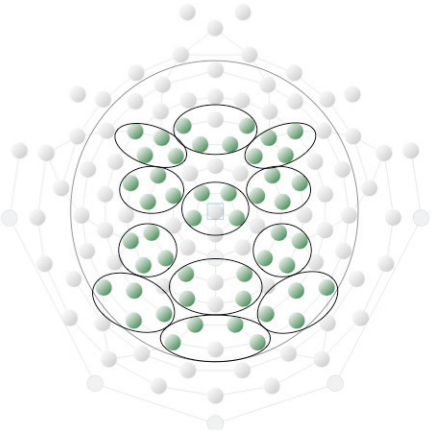

Figure 2. Region of interest electrode groups in the Stop-signal task.

Four electrode groups were established along the anterior-posterior axis (frontal, central, parietal and occipital), and three groups along the right-left axis (right, midline and left).

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