Mental Fatigue: Costs and Benefits

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Mental Fatigue: Costs and Benefits

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Maarten Alex Sander Boksem

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Promotor:	Prof. Dr. T.F. Meijman
Copromotor:	Dr. M.M. Lorist
Beoordelingscommissie:	Prof. Dr. A. Johnson Prof. Dr. M. Falkenstein Prof. Dr. J.L. Kenemans

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Chapter 1
Introduction

Introduction

Mental Fatigue

Mental fatigue refers to the feeling that people experience after or during prolonged periods of cognitive activity. These feelings generally involve an aversion to continue with the present activity and appear to concern a decrease in the level of commitment to the task at hand. This thesis presents four studies examining changes in task performance resulting from a prolonged time in which subjects are actively performing a task. It is important to realize that this kind of mental fatigue probably differs from lack of sleep, or muscle fatigue which may, or may not involve different effects on cognition and behaviour. These differences however, are beyond the scope of the present thesis.

Box 1 | Fatigue

1. Physical or mental weariness resulting from exertion.
2. Something, such as tiring effort or activity, that causes weariness
3. The decreased capacity or complete inability of an organism, an organ, or a part to function normally because of excessive stimulation or prolonged exertion.
4. A sensation of boredom and lassitude due to absence of stimulation, to monotony, or to lack of interest in one's surroundings.

Source: *The American Heritage® Dictionary of the English Language, Fourth Edition.*

Mental fatigue is a very common phenomenon in everyday modern life. Over the past decades, work has changed to a large extent from being predominantly physical in nature, to being more mentally oriented. This has resulted in a substantial increase in fatigue related complaints: in the Netherlands, half of the women in the working population complain about being fatigued, while a third of the men report such complaints. Fifteen years ago, only 38% of the women and 24% of the men reported such complaints.

Moreover, mental fatigue is a common symptom in a large number of chronic medical conditions such as cancer, Human Immunodeficiency Virus (HIV), Multiple Sclerosis (MS), Chronic Fatigue Syndrome (CFS), Alzheimer's disease, Huntington's disease and Parkinson's disease.

Tragically, fatigue has been implicated as one of the causes of catastrophes like the nuclear accidents at Chernobyl and Three Mile Island, and the Exxon Valdez oil spill. On a somewhat smaller scale, more and more studies are finding that driver fatigue is a major factor, perhaps the most important after alcohol, in causing traffic accidents. Fatigue-related traffic accidents usually involve no more than one or two vehicles. Yet, they are the most destructive of all to life and property.

Although fatigue cannot be easily 'measured', making it difficult to quantify their effect on accident rates, studies report the effects of fatigue as:

- reduced decision making ability,

- reduced ability to do complex planning,
- reduced productivity / performance,
- reduced attention and vigilance,
- reduced reaction time - both in speed and thought (a few studies have shown this effect as similar to being legally drunk),
- loss of memory or the ability to recall details,
- failure to respond to changes in surroundings or information provided,
- increased tendency for risk-taking,
- increased forgetfulness,
- increased errors in judgment,
- increased accident rates.

Still, very little is known about the physiological mechanisms underlying mental fatigue. In this thesis, we will try to gain some insight in the mechanisms that are central to mental fatigue and in the cognitive functions that are most affected by mental fatigue.
When we examine the list above, on the effects of fatigue, we may notice a pattern. All the points listed, refer to problems with, what cognitive psychologists call, 'cognitive control', the overseeing and regulation of more lower level cognitive processes that are involved in goal directed behaviour. This implies that under fatigue, there will be a reduced probability that the selection of actions will be controlled by high-level regulatory control processes (Lorist et al., 2000; Meijman, 2000). As a consequence, actions are more likely to 'escape' control, which would lead to an increased proneness for errors and inattentiveness that are typical of fatigued people (Van der Linden et al., 2003; see also Box 2).

Cognitive Control

Every day, we engage in complex and prolonged behaviours to reach goals that are often far removed in time. To be able to do so, humans have evolved mechanisms that can override or enhance habitual or automatic behaviours. This allows us to guide our behaviour in such a way that it corresponds to our goals. These mechanisms are commonly termed control mechanisms in that they control lower level sensory, memory and motor operations to reach a predetermined goal (Miller, 2000).

Cognitive control refers to those emergent 'higher order' mental functions that oversee and regulate more basic cognitive functions in accordance with internal intentions (Hommel et al., 2002; Miller, 2000). It is invoked in situations when the task is novel or complex, or when information from the environment is likely to trigger inappropriate actions. Theories of cognitive control suggest that these control mechanisms are implemented in the brain in a distributed network, involving closely interacting components that are engaged in monitoring and evaluating behaviour and the implementation of executive control when adjustments in control are needed (MacDonald et al., 2000). We will discuss these components of cognitive control below, but first we turn to the question how cognitive control might be implemented in the brain.

Neural Correlates of Cognitive Control. Because of its connectivity with neocortical sensory and motor systems and various subcortical structures (Pandya and Barnes, 1987; Goldman-Rakic, 1987; Fuster, 1989), the prefrontal cortex (PFC) seems to provide an ideal infrastructure for integrating the diverse range of information that is needed for complex behaviour. In addition, the PFC projects back to these systems which provides it with a means to exert top-down influence over a large array of brain processes (Pandya and Barnes, 1987; Goldman-Rakic, 1987; Fuster, 1989) .

Box 2 | The Cambridge Cockpit Studies (1943)

In these classic studies, subjects sat in a simulated cockpit for long periods of time, responding on aircraft controls to changes in a variety of instruments. The deterioration of skill over time, described by Bartlett (1943), was shown by a number of measures. As fatigue increased, progressively larger deviations of the instrument readings came to be tolerated before any corrective action was taken. Lapses of attention became increasingly frequent, as operators became more easily distracted. Attention came to be reserved for items of central importance, like the course heading of the plane and speed, while items like fuel level were neglected.
In addition, the operators' responses became more variable, independent from a drop in accuracy. This was particularly evident in their timing: many correct actions were executed at the wrong time. In general, the skills seemed to have lost cohesion; the overall pattern of action disintegrated into separate components. The instruments were apparently perceived one by one and the appropriate control responses were no longer smoothly sequenced.
There were also some interesting subjective observations: the operators reports became less reliable, 'violent language' gradually replaced mild sighs, and errors were blamed on 'recalcitrant equipment'.

Adapted from Holding (1983).

Goal directed behaviour requires not only information about the current environment and actions that are predicted to achieve a goal, but also about the internal state of the organism such as energetical resources, hunger, thirst or other motivational factors. Integration of more immediate needs like food or rest with more long term goals is of course essential for successful attainment of goals that are farther removed in time. This internal information is conveyed to the PFC by connections (through the ventromedial PFC) with limbic structures (Sugrue, 2005).

These limbic structures also provide the PFC with information on the identity and size of expected rewards of specific actions. Goal directed behaviour depends heavily on reward prediction and this reward information has a profound influence on PFC activity (Watanabe, 1990; 1992; 1996; Tremblay and Schulz, 1999). These reward related signals are most likely mediated by dopamine (DA) projections from the ventral tegmental area (VTA) of the midbrain (Schulz, 2002, see also box 3). DA influx in the PFC may strengthen the connections between neuron ensembles in the PFC that represent goals and the means to achieve them (Miller, 2000). When a certain behaviour is successful, dopaminergic reinforcement signals from the VTA augment the corresponding pattern of PFC activity by strengthening the connections between neurons that are activated by that behaviour. This will increase the probability that in the future, the same context will elicit

reactivation of the PFC activity that led to the rewarded behaviour (Miller and Cohen, 2001).

By the same process, DA may be involved in sustaining PFC activity over longer periods of time, enabling us to persist toward goals, protecting our goal relevant task representations from disruption by irrelevant, distracting information (Durstewitz et al., 1999; 2000). Indeed, one of the classic signs of PFC damage is increased distractibility: 'frontal' patients seem unable to focus on a task or ignore irrelevant distracting stimuli (Duncan et al., 1996). Moreover, they are unable to organize their lives, making it difficult for them to hold a job for a longer period of time or stay married. They appear severely impaired in persisting toward future goals.

This is remarkably similar to what has been found with mentally fatigued subjects. Van der Linden and colleagues (2003;2004) showed that fatigued subjects had difficulties in focussing their attention, planning, and adaptively changing strategies in the face of negative outcomes. This strongly suggests a reduction in cognitive control with mental fatigue, implicating a possible failure of the involved DA projections to the PFC. In chapters 3,4, and 5, experiments are presented that were aimed at gaining support for this hypothesis.

Box 3 | Dopamine ($C_6H_3(OH)_2$-CH_2-CH_2-NH_2).

As a member of the catecholamine family, dopamine is a precursor to epinephrine (adrenaline) and norepinephrine (noradrenaline) in the biosynthetic pathways for these neurotransmitters. Arvid Carlsson won a share of the 2000 Nobel Prize in Physiology or Medicine for showing that dopamine is not just a precursor to these, but is a neurotransmitter as well.

Role in Movement. Dopamine is critical to the way the brain controls our movements and is a crucial part of the basal ganglia motor loop. Shortage of dopamine, particularly the death of dopamine neurons in the nigrostriatal pathway, causes Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements.

Role in Cognition and Frontal Cortex Function. In the frontal lobes, dopamine controls the flow of information from other areas of the brain. Dopamine disorders in this region of the brain can cause a decline in neurocognitive function, particularly those linked to memory, attention and problem solving. This function is particularly related to the mesocortical dopamine pathway.

Role in Pleasure and Motivation. Dopamine is commonly associated with the 'pleasure system' of the brain, providing feelings of enjoyment and reinforcement to motivate us to do, or continue doing, certain activities. It is released (particularly in areas such as the nucleus accumbens and striatum) by naturally rewarding experiences such as food, sex, use of certain drugs and neutral stimuli that become associated with them. This theory is often discussed in terms of drugs (such as cocaine and amphetamine) which seem to directly or indirectly related to increase dopamine in these areas, and in relation to neurobiological theories of addiction, which argue that these dopamine pathways are pathologically altered in addicted persons.

However, the idea that dopamine is the 'reward chemical' of the brain now seems too simple as more evidence has been gathered. Dopamine is known to be released when unpleasant or aversive stimuli are encountered, suggesting that it is not only associated with 'rewards' or pleasure. Also, the firing of dopamine neurons occurs when a pleasurable activity is expected, regardless of whether it actually happens or not. This suggests that dopamine may be involved in desire rather than pleasure. Drugs that are known to reduce dopamine activity (e.g. antipsychotics) have been shown to reduce people's desire for pleasurable stimuli, despite the fact that they will rate them as just as pleasurable when they actually encounter or consume them. It seems that these drugs reduce the 'wanting' but not the 'liking', providing more evidence for the desire theory.

Other theories suggest that the crucial role of dopamine may be in predicting pleasurable activity. Related theories argue that dopamine function may be involved in the salience ('noticeableness') of perceived objects and events, with potentially important stimuli (including rewarding things, but also things which may be dangerous or a threat) appearing more noticeable or more important. This theory argues that dopamine's role is to assist decision making by influencing the priority of such stimuli to the person concerned.
Dopamine and Psychosis. Disruption to the dopamine system has also been strongly linked to psychosis and schizophrenia. Dopamine neurons in the mesolimbic pathway are particularly associated with these conditions. This is partly due to the discovery of a class of drugs called the phenothiazines (which block D_2 dopamine receptors) that can reduce psychotic symptoms, and partly due to the finding that drugs such as amphetamine and cocaine (which are known to greatly increase dopamine levels) can cause psychosis. Because of this, all modern antipsychotic medication is designed to block dopamine function to varying degrees.

Cognitive Control: Monitoring and Evaluation of Behaviour. The engagement of cognitive control is rarely perfect. Fortunately, we are able to actively monitor our performance and use this information to adjust cognitive control allocated to the task when necessary. The detection of errors has a role of central importance in the regulation of cognitive processes. The discovery of the neural correlates of performance monitoring has inspired an abundance of research in recent years. In particular, event-related potential (ERP) studies have revealed a neural response to errors that has been termed the error-related negativity (ERN) or error negativity (Ne). The ERN/Ne consists of a large negative shift in the response locked ERP occurring after subjects have made an erroneous response (Falkenstein et al.,1990; Gehring et al., 1990). Localization with dipole localization algorithms has led most authors to conclude that the ERN/Ne is generated in the Anterior Cingulate Cortex (ACC; Dehaene et al., 1994; Wijers and Boksem, 2005), a neural structure in the medial wall of the PFC. These findings are corroborated with results from fMRI studies (Ullsperger et al., 2003; Ridderinkhof et al., 2004) that show increased activation of the ACC during error trials, relative to correct trials.

Holroyd and Coles (2002) proposed a monitoring system located in the basal ganglia (BG) that predicts the outcome (good or bad) of an action, on the basis of information received from the external environment and an ‘efference copy’ of the action. When the BG find that events are ‘better’ than expected, they produce a ‘good’ error signal, and when they find that events are ‘worse’ than expected they produce a ‘bad’ error signal. These error signals are coded as phasic increases and decreases, respectively, of the tonic activity of the mesencephalic DA system (Schulz, 2002). These authors propose that a phasic decrease in activity of mesencephalic dopaminergic neurons following the commission of an error, disinhibits the apical dendrites of motor neurons in the ACC, producing the ERN/Ne (Holroyd and Yeung, 2003).

The involvement of the DA neurotransmitter in the generation of the ERN/Ne and the finding that the ERN/Ne reflects the evaluation of current behaviour, implies that if mental fatigue indeed involves impaired DA transmission resulting in reduced cognitive control, ERN/Ne amplitude should be reduced in fatigued subjects. In chapters 3, 4 and 5 we report on studies

that aimed to investigate these effects of mental fatigue on this performance monitoring system in the ACC, reflected by the ERN/Ne.

Cognitive Control: Implementation. Cognitive control is a dynamic process implemented in the brain by a distributed network that involves closely interacting, but nevertheless anatomically dissociable, components. Within this system, the ACC appears to be involved in evaluative processing indicating when control needs to be more strongly engaged, while other parts of the PFC (most likely the dorsolateral PFC, DLPFC), actually provides the top-down support of task appropriate behaviours (MacDonald et al., 2000). The DLPFC may be responsible for representing context information, including the attentional demands of the task (Cohen and Servan-Schreiber, 1992).

As already mentioned, 'frontal' patients have severe difficulties in the focussing of attention; they are highly distractible. The capacity to focus on relevant information and ignore irrelevant information is commonly termed selective attention and reflects the engagement of cognitive control. Desimone and Duncan (1995) have proposed a model of visual attention that builds on the principle that processing in the brain is competitive: different pathways, carrying different sources of information, compete for expression in behaviour. These authors assume that visual cortical neurons processing different aspects of a scene compete with each other via mutually inhibitory interactions. The neurons that 'win' the competition reach higher levels of activity than those with which they share inhibitory connections. Focussing of attention results from the influence of excitatory top-down signals from the PFC to visual cortical neurons that represent the to-be-attended features of the scene and, by virtue of mutual inhibition, suppressing activity of neurons processing other features (Kanwisher and Wojciulik, 2000).

If cognitive control is indeed compromised in mentally fatigued subjects, we would expect that the top-down influence of the PFC on visual cortical neurons would be reduced, resulting in increased distractibility and difficulties in sustaining attention for a prolonged period of time. In chapter 2, we report on a study that investigated these effects of mental fatigue on visual attention.

Costs and Benefits

Mental fatigue appears to involve a reduced motivation to invest effort (Holding, 1983; Hockey, 1997; Meijman, 2000). This implies that cognitive processes that rely heavily on effort, which is the case for all higher order cognitive processes, are particularly vulnerable to the effects of mental fatigue. In addition, this implies some kind of motivational evaluation of current performance that is associated with mental fatigue.

Tops (2004) proposed that mental fatigue involves an effort/reward analyses of current behaviour: as long as one feels that the invested effort in the end will result in sufficient rewards, one will continue working. However, when the perceived effort becomes to great and the reward no longer compares to this, the motivation to continue will dissipate and one will want to disengage from the task, feeling fatigued. In this view, the feeling of fatigue

may result from a subconscious analyses of cost and benefits to expend energy, or to conserve energy. People will only expend energy on a certain task when costs are low and benefits are high. This will be the case when behaviour can be expected to bring long term or short term rewards, when not performing the task would have negative consequences, or when current behaviour is intrinsically motivating (i.e. the behaviour is 'fun'). Conversely, people may choose not to expend energy when costs are high and benefits are low. This will also be the case when the internal energetical state of the subjects is sub optimal, for example because of disease or fatigue. Being fatigued adds to the cost of reaching a goal: performance under fatigue involves more effort compared to a similar level of performance in an optimal state (Hockey, 1993; 1997). Moreover with increasing levels of fatigue a task goal has to compete stronger with goals that are directed towards maintaining general wellbeing (Hockey, 1993; 1997).

The DA neurotransmitter has a central role in the regulation of the propensity for expending energy (Neil & Justice, 1981; Salamone et al., 1999; Szechtman et al., 1994), which makes it a likely candidate for involvement in mental fatigue. Recently, mental fatigue has been causally linked of hampered dopaminergic functioning in striato-thalamo-cortical fibres. (Chaudhuri & Behan, 2000; Gold & Chrousos, 1998).

Interestingly, the ACC, in addition to its role in performance monitoring mentioned above, also has a broad role in encoding the relationship between an action and the reinforcement value of its outcome even when the outcome is a positive reward and not an error. For example, macaque ACC sulcal neurons respond when actions lead to errors or when reinforcement is not delivered but similar or higher proportions of ACC sulcal neurons also respond to the delivery of positive reinforcers (Ito et al, 2003; Rushworth et al., 2004). The ACC might not just encode *which* outcome is expected from an action and whether the action is expected to lead to an error. It might also be a crucial part of a system for encoding whether or not an action is *worth* performing given the value of the expected outcome and the cost of performing the action. (Gehring and Willoughby, 2002). In a study by Walton et al. (2002), normal rats chose effortful but high reward actions while rats with ACC lesions rarely did. This deficit reflects an impaired ability to integrate both the expected costs and benefits of an action rather than a simple insensitivity to reward differentials.

Salamone and colleagues (1994) obtained results similar to Walton and colleagues, however, these authors lesioned animals in the Nucleus Accumbens (Nac; part of the BG), instead of the ACC. The Nac is part of a complex system of interconnected frontostriatal regions and receives projections from the medial frontal cortex (Berendse et al., 1992; Haber et al., 1995). Holroyd and Coles (2002) proposed that the dopaminergic projections from the BG to the ACC are responsible for the generation of the ERN/Ne.

Salamone suggested that release of dopamine in the NAc might be an important part of the neural process that enables organisms to overcome work-related response costs. The nucleus accumbens may indirectly perform cost/benefit analyses, setting constraints on energy expenditure that profoundly influences the relative allocation of instrumental responses toward various alternatives, such that accumbens DA depletion biases behaviour in the direction of lower effort alternatives (Salamone et al, 1999). Additional

evidence is provided by pharmacological studies, reporting that dopaminergic agents are able to increase energetic arousal (Corr & Kumari, 2000; Dalley et al., 2002; see box 4 for an extreme example of the effects of this neural circuit going awry).

The remarkable similarity between the behavioural effects of ACC and Nac lesions suggest that these interconnected structures are both involved in the evaluation of current behaviour in the light of costs and benefits. Moreover, the proposed involvement of both the ACC and BG in the generation of the ERN/Ne indicate that this ERP component would provide us with an excellent tool for investigating changes in this effort/reward balance that is proposed to occur with mental fatigue. In chapter 4, we will explore this possibility of involvement of an implicit effort/reward analysis in mental fatigue. In addition, in chapters 4 and 5, we will relate possible deficits of mental fatigue to a hampered DA transmission in the frontostriatal regions implicated in the evaluation of behaviour that is proposed to be indexed by the ERN/Ne.

Outline of the thesis

The aim of the present thesis can be considered to be twofold. First, we will investigate whether mental fatigue selectively impairs cognitive control processes, as opposed to affecting cognitive processes requiring little conscious control. Second, we will investigate the apparent relationship between fatigue, motivation and reward. These two aims may not be as divergent as they appear at first glance.

The DA neurotransmitter takes a prominent position in our theory formation on mental fatigue. In addition to the fact that hampered DA transmission has been observed in many neurological diseases with

Box 4 | Drowning Mr. M

One warm summer, Mr M, seated beside his pool, decides to take a refreshing dip in the cold water. He dives in and takes a couple of strokes. Then, suddenly, he stops. He exhales, sinks to the bottom and simply stares straight ahead. “I’m drowning”, he realizes, strangely unperturbed. He knows that only a few strong kicks would bring him back to the surface. But he can’t quite bring himself to do so.
As luck would have it, his daughter witnessed the event from inside the house, and saves him. Later he tells his family, “I don’t know what was wrong with me. I just didn’t want to swim anymore.”
Neurologist Dominicque Laplane first described such bizarre behaviour in 1981. He called the phenomenon “PAP syndrome”, from the French *perte d’auto-activation psychique* (loss of mental self activation). Apparently, in PAP patients such as Mr. M, motivational mechanisms seem completely inactive. They are unable to see themselves in any kind of future scenario and cannot comprehend the consequences of their inactions.
So far, in every case of PAP syndrome, an acute illness has been found that affects some area of the basal ganglia. This probably disrupts the dopamine projections to the frontal lobes, depriving cognitive functioning of any motivational incentive.

Adapted from Verstichel and Larrouy (2005)

symptoms of fatigue (Chaudhuri and Behan, 2000), release of DA in the Nac might be an important part of the neural process that enables organisms to overcome work-related response costs (Salamone et al., 1999). Moreover, DA projections to the PFC are of central importance in the reward prediction that is essential for cognitive control processes (Miller and Cohen, 2001), which are probably adversely affected by mental fatigue (Lorist et al., 2000).

The ERN/Ne provides us with an ideal tool for investigating these processes. This ERP component reflects an evaluative signal thought to be essential for the engagement of cognitive control, it is strongly dependant on motivation and effort, and it originates from the ACC, a structure involved in assessing the costs and benefits of actions. Importantly, the ERN/Ne is thought to be elicited by phasic dopamine decreases in midbrain structures that project to the ACC. Therefore, the ERN/Ne is of primary importance in all the following chapters, except for chapter 2.

In chapter 2, we investigated the effects of mental fatigue on attention, a key feature of cognitive control and of dynamic human behaviour: attention allows us to (i) bias the processing of incoming information (Dosher and Lu, 2000; Murray and Wojciulik, 2004; Posner et al., 1980) so that we can focus on the information that is relevant for achieving the current goals, and (ii) to actively ignore irrelevant information that might potentially interfere with those goals (Kanwisher and Wojciulik, 2000). In this chapter, we examined how mental fatigue affects these attentional processes. Therefore, we had our subjects perform a visual attention task (Okita et. al., 1985) continuously for three hours, without rest. This way we were able to detect changes in performance on a task that places high demands on the attentional system, while subjects become more and more fatigued. In addition, by using electroencephalogram (EEG) and event-related-potential (ERP) measures, we were able to examine the neurophysiological changes related to fatigue and attention.

In chapter 3, the effects of mental fatigue on another important aspect of cognitive control, performance monitoring, were examined. This investigation was designed to assess whether performance monitoring involving the ACC, as indexed in the ERN/Ne, and related post-error adjustments in behaviour, were modulated by mental fatigue, induced by two hours of task performance. To this end, we examined ERPs in a study designed to track the effects of fatigue on error monitoring, as well as remedial behavioural adjustments subsequent to errors. We predicted a decrease in ERN/Ne amplitude as subjects became more fatigued, reflecting impaired action monitoring in fatigued subjects.

In chapter 4, we sought to replicate the effects of mental fatigue on action monitoring presented in chapter 3. A second important issue we addressed however, was the relationship between fatigue and (lack of) motivation to continue task performance. To test this, we manipulated motivation by offering our subjects a certain amount of money if they performed well in the remainder of the task, after they had already performed the task for two consecutive hours. If fatigue can indeed be viewed as an effort/reward imbalance, the increased reward should lead to a better balance between effort and reward, thus counteracting the effects of fatigue.

Interestingly, many studies have shown the ERN/Ne to be related to motivational processing: when by task instructions the motivation to perform well is reduced, a reduction in ERN/Ne amplitude can be observed (Gehring et al., 1993). Motivation appears to be essential for observing a robust ERN/Ne (Gehring et al., 1993; Gehring and Knight, 2000; Dikman and Allen 2000; Luu et al., 2000). Bush et al. (2000) argued that ERN/Ne and related ACC activity represent a general evaluative system that processes the motivational significance of events including, but not limited to errors and conflict. In chapter 4, we will investigate whether the effects of fatigue on behaviour are due to reduced performance monitoring as indexed by different ERP components and also whether these changes are related to motivational processes.

In chapter 5, we present a study that was aimed at gaining more support for our DA hypothesis on fatigue. In the previous chapters, we demonstrated that the amplitude of the ERN/Ne is reduced in mentally fatigued subjects (Boksem et al., in press; Lorist et al., 2005). In addition we found that increasing the rewards could (partly) undo the effects of fatigue on ERN/Ne amplitude (Boksem et al., in press). We proposed that mental fatigue involves an effort/reward imbalance, resulting from a reduction in activity of DA projection systems, comprising the striatum (BG) and medial frontal structures such as the ACC, comparable to the monitoring system proposed by Holroyd and Coles (2002).

In chapter 5, we investigated whether a response locked theta component and DA mediated delta component of the ERN/Ne are differentially affected by mental fatigue and reward, providing us with additional evidence for our DA hypothesis on mental fatigue. Response locked ERPs were filtered to obtain the delta and theta frequency components of the error related ERP components (ERN/Ne en Pe).

Finally, in chapter 6 we evaluate the findings reported the previous chapters and present these findings in the broader context of underlying psychological and physiological mechanisms involved in human reward based behaviour and cognitive control.

Chapter 2
Effects of Mental Fatigue on Attention

Adapted from:
Boksem, M.A.S., Lorist, M.M., & Meijman, T.F. (2005). Effects of mental fatigue on attention: an ERP study. *Cognitive Brain Research, 25,* 106-117.

Effects of Mental Fatigue on Attention: An ERP Study

The effects of mental fatigue on attention were assessed. Subjects performed a visual attention task for three hours without rest. Subjective levels of fatigue, performance measures and EEG were recorded. Subjective fatigue ratings, as well as theta and lower-alpha EEG band power increased, suggesting that the three hours of task performance resulted in an increase in fatigue. Reaction times, misses and false alarms increased with time on task, indicating decreased performance efficiency in fatigued subjects. Subjects were unable to inhibit automatic shifting of attention to irrelevant stimuli, reflected by a larger negativity in the N1 latency range for irrelevant, compared to relevant stimuli. This difference in negativity was unaffected by time on task. However, N1 and N2b amplitude did change with time on task: N1 amplitude decreased and the difference in N2b amplitude between relevant and irrelevant stimuli (larger N2b amplitude evoked by relevant stimuli) decreased with time on task. The results indicate a dissociation in the effects of mental fatigue on goal–directed (top-down) and stimulus-driven (bottom-up) attention: mental fatigue results in a reduction in goal-directed attention, leaving subjects performing in a more stimulus-driven fashion.

Introduction

Mental fatigue refers to the effects that people may experience after or during prolonged periods of cognitive activity. In this sense, it is a very common phenomenon in everyday modern life. Still, very little is known about the psychophysiological mechanisms underlying mental fatigue. Here, we will try to gain some insight in the mechanisms that are central to mental fatigue and in the cognitive functions that are most affected by mental fatigue.

When people become fatigued, they usually report difficulties in concentrating and focusing their attention on the tasks they are required to perform. For example, Bartlett (1943) in his studies in which pilots were required to fly a simulator for extended periods of time, reported that lapses in attention happened with increasing frequency and that operators became more easily distracted. Similarly, Brown (1994) noted that the main time on task effect in driving is a progressive withdrawal of attention from road and traffic demands, which, as expected, had adverse consequences on task performance. These results suggest that attention is specifically affected by mental fatigue.

Attention is a key feature of dynamic human behaviour: it allows us to (i) bias the processing of incoming information (Dosher and Lu, 2000; Murray and Wojciulik, 2004; Posner et al., 1980) so that we can focus on the information that is relevant for achieving the current goals, and (ii) to actively ignore irrelevant information that might potentially interfere with those goals.

In the present study we will examine how mental fatigue affects these attentional processes. Therefore, we had our subjects perform a visual attention task (Okita et al., 1985) continuously for three hours, without rest. Subjects were presented with stimulus displays that consisted of two letters at

four possible locations (Fig. 2.1). They were to respond when a target letter appeared at one of the locations that was cued as being relevant. Subjects had to focus their attention on the cued relevant positions and had to ignore stimuli presented on the irrelevant positions. This way we were able to detect changes in performance on a task that places high demands on the attentional system, while subjects become more and more fatigued. In addition, by using electroencephalogram (EEG) and event-related-potential (ERP) measures, we were able to examine the physiological changes related to fatigue and attention.

Studies on the topic of attention have shown that ERP components reliably reflect the differential processing of attended and unattended information (Wijers et al., 1996). By recording ERPs to attended and unattended stimuli, direct evidence can be obtained about the level of processing attained by these stimuli. The most consistent finding is a modulation of the posterior P1 (peaking between 100 and 160 ms after stimulus presentation) and N1 (160-210 ms) components by attention (e.g. Eason, 1981; Rugg et al., 1987; Wijers et al., 1989). When a particular location is attended, the exogenous P1 and N1 waves elicited by stimuli at that location are enlarged (Hillyard and Münte, 1984; Mangun and Hillyard, 1988; 1990), an effect that has been interpreted as a sign of attentional modulation of sensory processing in the visual pathways (Mangun et al., 1993). This has been viewed as a representation of a 'sensory gain' mechanism (Hillyard et al., 1990): as a result of biasing the information processing system, the responsivity to stimuli presented at attended locations is amplified and further processing of these stimuli will therefore be enhanced.

A later component, starting at approximately 200-250 ms post stimulus, consisting of negativity at central electrodes, with a maximum at Cz has been labelled the N2b component. This ERP component has been found to reflect the further processing of relevant information (i.e. stimuli that require a response) (Lange et al., 1998; Okita et al., 1985; Wijers et al., 1989). Selective modulation of these attention related ERP components by the induction of mental fatigue would provide strong evidence that attentional processes are indeed affected by mental fatigue.

One of the most common findings of EEG studies is a shift from fast, low amplitude waves to slow, high amplitude waves when the level of alertness drops. More specific, under decreased arousal levels, there is a progressive increase in low-frequency theta and alpha activity (Klimesh, 1999; La France and Dumont, 2000; Oken and Salinsky, 1992), probably reflecting a decrease in cortical activation (Cook et al., 1998; Laufs et al., 2003). Therefore, the amount of alpha and theta power provides an adequate index of the level of fatigue that subjects experience. When subjects become fatigued, we would expect the level of arousal to drop and this would be reflected by an increase in alpha and theta power.

In addition to this objective measure of fatigue, we obtained an indication of the subjective level of fatigue that the subjects were experiencing at that moment. According to Holding (1983) and Hockey (1997), aversion to further investment of effort in task performance is central to mental fatigue. Therefore we presented subjects with a visual analogue scale on which they could indicate the level of aversion they felt regarding task performance (after Borg (1978)), on multiple occasions during the experiment.

In summary, we predict that mental fatigue results in an increase in subjective ratings of the level of fatigue and a shift to slow, high amplitude waves in the EEG. In addition, we predict a selective modulation of ERP components known to be related to selective attention. A deterioration of selective attention would lead to a decreased ability of subjects to focus their attention on task relevant items and an increased distractibility by irrelevant information. This would result in an increase in the number of missed targets and an increase in false alarms with time on task.

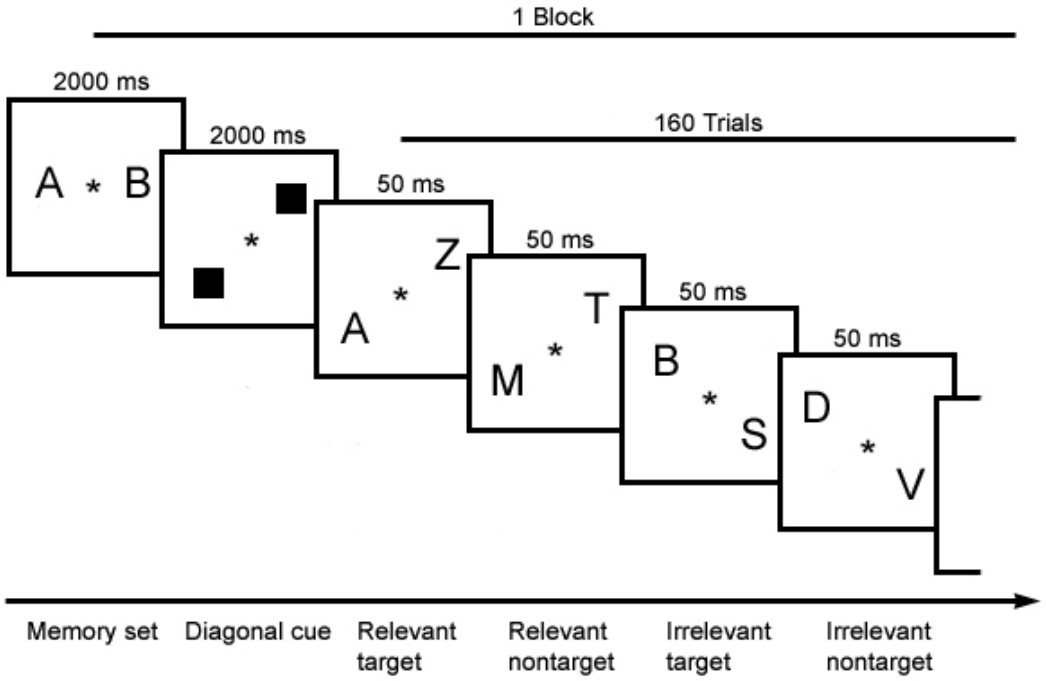

Figure 2.1. *Stimulus presentation. The numbers above the frames indicate the duration of the presentation in msec. Memory-set presentation is followed by a cue indicating the relevant diagonal. Thereafter, 160 stimulus frames are presented, each during 50 msec with an inter stimulus interval between 1000 and 1500 msec. After 160 stimuli (1 block) subjects are presented with either a new memory set or with a new diagonal cue. Four stimulus types are depicted here: relevant target, relevant nontarget, irrelevant target and irrelevant nontarget.*

Methods

Subjects. Seventeen healthy participants (8 males), between 18 and 26 (M=22) years of age, were recruited from the university population. They were paid for their participation and had normal or corrected-to-normal vision. Two participants described themselves as being left handed. None of the subjects worked night shifts or used prescription medication.

Stimuli. Each experimental block began with the presentation of a fixation cross, which remained on screen throughout a block of trials, and was followed by the presentation of a memory set of two letters (2000 ms). Next, a cue frame, also presented for 2000 ms, was presented to indicate which display positions (left-up or right-up diagonal) were relevant. Thereafter,

participants were randomly presented a series of 160 stimulus displays (constituting 1 block), each 50 ms in duration, as illustrated in Figure 2.1. Interstimulus intervals varied randomly between 1000 and 1500 ms. Subjects received a new memory set after every odd block and a new diagonal cue after every even block. The following restrictions applied: memory set letters for one block could not be memory set letters for the next seven blocks and the cued diagonal could not be the same for more than four subsequent blocks.

The stimulus display contained two letters which were randomly presented on either the left-up (50%) or the right-up (50%) diagonal positions. In 25% of the trials a memory set item appeared at a relevant diagonal position (relevant target), in 25% of the trials, a memory set item appeared at an irrelevant diagonal position (irrelevant target) and in the remaining trials the display contained no memory set items (nontargets). Stimulus letters were randomly chosen from the alphabet, excluding the letters g,i,o,q,u,x and y. The visual angle from the centre of fixation to each of the elements was 1.5°. The letters were 0.5° in height.

Procedure. Subjects were instructed to abstain from alcohol 24 hours before the experiment and from caffeine containing substances 12 hours before the experiment. The experimental session started between 12.30 and 14.00 hours. After arrival at the laboratory, the subjects handed in their watches. They had no knowledge of the length of the session other than that it would not last beyond 18.00 hours.

Subjects were seated in a dimly lit, sound-attenuated, electrically shielded room at 0.90 m from a 17” PC monitor. The index finger of their preferred hand rested on a touch-sensitive response box. Before the start of the experiment, subjects were given written task instructions, where after they were trained for 4 blocks of 160 trials (approximately 14 min).

Following the application of the electrodes, they were presented with 50 blocks of 160 trials, lasting for 3 hours in total. Every block was immediately followed by the next, so no rest pauses were given. Subjects were instructed to attend to the relevant display positions as indicated by the cue frame and, in case of the occurrence of a target on one of these positions, to lift their finger from the response button as quickly as possible, maintaining a high level of accuracy.

Before the task and after every 10^{th} block, subjects received a question about the level of resistance they felt at that moment against performing the task (the *aversion scale*). Subjects could respond to this question with a number between zero and ten, zero meaning no aversion, ten meaning maximum aversion.

Recording. The electroencephalogram (EEG) was recorded using 30 Sn Electrodes attached to an electro cap (Electro-Cap International), from positions Fp1, Fp2, Af3, Af4, F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8, Cp5, Cp1, Cp2, Cp6, P7, P3, Pz, P4, P8, O1, Oz and O2. All electrodes were referenced to linked earlobes. The electro-oculogram (EOG) was recorded bipolarily from the outer canthi of both eyes and above and below the left eye, using Sn electrodes. Electrode impedance was kept below 5kΩ. EEG and EOG were amplified with a 10s time constant and a 200 Hz

low pass filter, sampled at 1000 Hz, digitally low pass filtered with a cut-off frequency of 30 Hz, and online reduced to a sample frequency of 100 Hz.

Data Analysis. To investigate the effects of time on task, the data (except for the aversion scale) were divided into four time intervals of 45 minutes each, so that each interval consisted of 12.5 blocks. Data were subjected to SPSS ANOVA for repeated measurements, using the ε-adjustment procedure recommended by Quintana and Maxwell (1994).

Performance. For the different stimulus conditions in each time on task interval, mean reaction times (RTs), misses and false alarms were calculated. Reactions occurring within a 200-1000 ms interval after the presentation of an attended target were considered as hits. Incidentally, subjects reported they sometimes forgot the letterset or the relevant diagonal positions. Therefore, blocks in which performance accuracy was less than 45% were excluded from analysis. On average, this occurred in about 3 blocks per subject. For the performance measures, we tested the factor Time on task.

ERPs. All ERP analyses were performed using the Brain Vision Analyser software (Brain Products). ERPs were averaged off-line. Out of range artefacts were rejected and eye movement artefacts were corrected, using the Gratton & Coles method (1983). Trials in which subjects made performance errors were also excluded. A baseline voltage over the 100 ms interval preceding stimulus onset was subtracted from the waveforms. The ERPs were averaged over replications and calculated separately for each subject, time on task interval and stimulus category. Using the grand average waveforms, we determined the electrodes showing the largest amplitudes for each of the ERP deflections of interest (P1, N1 and N2B). The P1 was maximal on O1 and O2 and was quantified as the average amplitude in the 100-160 ms latency interval. N1 amplitude was maximal on P7 and P8 and was quantified as the average amplitude in the 160-220 ms latency interval. N2b amplitude was maximal on Cz and was quantified as the average amplitude in the 320-410 ms time interval. The grand averages suggested that overall ERP amplitude on Cz appeared to change with time on task; however, as we were interested specifically in changes in the N2b latency range, we used the difference in amplitude between P2 (quantified as the average amplitude in the 200-260 ms latency interval) and N2b for analysis. Statistical analyses was performed on the average amplitude of the different ERP components in their respective specified time windows, testing the factors Time on task, Relevance (relevant diagonal vs. irrelevant diagonal), and Target (the presence or absence of a memory set item).

EEG Spectral Power Analysis[1]*.* In addition to the ERP analysis, we performed a spectral analysis on the data. Every time on task interval was segmented into 50% overlapping, 5.12 s segments. After artefact detection and ocular correction as described above, the data was submitted to a fast Fourier transform, using a 100% Hanning window. After averaging, power was determined in five separate frequency bands for each subject, electrode and time on task interval. Average power in these frequency bands was log transformed (ln) for normalization (Gasser et al, 1982). We tested for effects in the delta frequency band (0.5-3.5 Hz), theta frequency band (3.5-7.5 Hz), the lower-alpha band (7.5-10 Hz), the upper alpha band (10-12.5 Hz) and the beta band (12.5-30 Hz) on frontal electrodes (F3, Fz, F4), central electrodes

(C3, Cz, C4), parietal electrodes (P3, Pz, P4) and occipital electrodes (O1, Oz, O2). Average EEG band power was analysed for effects of Laterality (left, midline, and right), Region (frontal, central, parietal, and occipital) and of course Time on task.

Results

Aversion Scale. With time on task, subjects developed more aversion against continuation of task performance. Scores increased from 1.0 (SD=0.9) at the beginning of the experiment to 8.6 (SD=2.3) at the end, that is from hardly any, to very strong aversion to continue task performance ($F(5,80)=40.97$, $p<.001$).

Performance. The average RTs, percentage of misses and false alarms are shown in Table 2.1. Subjects on average slowed down and missed more targets with increasing time on task ($F(3,48)=6.97$, $p<.001$ and $F(3,48)=7.65$, $p<.005$, respectively). In addition, the number of false alarms increased with time on task ($F(3,48)=2.97$, $p<.05$). Most false alarms were made when nontargets are presented on the relevant diagonal; almost no false alarms were made when nontargets are presented on the irrelevant diagonal. When targets were presented on the irrelevant diagonal, the number of false alarms lies somewhere in between the other two conditions ($F(2,32)=34.39$, $p<.001$). This difference in false alarms between conditions was not modulated by time on task ($F(6,96)=.41$, ns.).

	INTERVAL 1	INTERVAL 2	INTERAL 3	INTERVAL 4
RT (ms)	539 (12.0)	550 (11.2)	557 (11.5)	567 (10.3)
Misses (%)	11.5 (1.6)	13.8 (1.4)	16.1 (2.1)	19.7 (2.8)
False Alarms (%)	1.5 (0.1)	1.7 (0.2)	2.0 (0.2)	2.1 (0.3)

Table 2.1. *Effect of time on task on performance. Shown are reaction times (RT), misses, false alarms and their standard errors for the four time on task intervals.*

EEG Analysis[1].

Delta power. Delta power was greatest on midline electrode positions on Cz and Pz (Region-by-Laterality, $F(6,96)=19.80$, $p<0.001$). No change in delta power was found with time on task ($F(3,48)=2.39$, n.s.).

[1]As suggested by a reviewer, the ongoing band power is potentially confounded with evoked band power: changes in ongoing band power with time on task might also result from changes in evoked band power. Therefore we performed an additional analysis in which the average evoked activity was subtracted from the EEG before performing the FFT (Smulders et al., 1997). This analyses revealed that results were minimally affected by this subtraction, indicating that the contribution of evoked activity band power to ongoing band power is negligible. For reasons of clarity, the results without evoked activity subtraction are presented here.

Theta power. Theta power was greatest on frontal midline electrodes (Fz and Cz; Region-by-Laterality, $F(6,96)=36.23$, $p<0.001$). Theta power increased with time on task ($F(3,48)=9.81$, $p<0.001$; Fig. 2.2). This increase in theta power, however, was the same for all electrode positions.
Lower-Alpha power. Lower-alpha power was greatest on Pz (Region-by-Laterality, $F(6,96)=13.61$, $p<0.001$). Lower-alpha power increased with time on task ($F(3,48)=35.66$, $p<0.001$; Fig. 2.2), especially on electrodes on parietal sites (Time on task-by-Region, $F(9,144)=6.43$, $p<0.005$). Interestingly, the increase in power in this frequency band was positively correlated with the increase in scores on the aversion scale ($r=.44$, $p<.05$).
Upper-Alpha power. Upper-alpha power was largest over occipital sites (Region, $F(3,48)=27.34$, $p<0.001$). No effects of laterality could be observed. Power in this frequency band also appeared to increase with time on task, but this failed to reach significance ($F(3,48)=3.28$, $p=0.07$).
Beta power. Beta power was greatest on lateral frontal sites (F3 and F4; Region-by-Laterality, $F(6,96)=8.73$, $p<0.001$). Beta power also increased with time on task ($F(3,48)=6.65$, $p<0.005$), although the difference was rather small (17% increase). This increase was not different on different electrode positions.

ERPs.
P1. There was no statistical difference in P1 amplitude between electrodes O1 and O2, so amplitude effects in the P1 latency range (100-160 ms) will be reported collapsed over these electrodes. In accordance with findings reported in the literature, averaged ERP waveforms showed a larger positive deflection for stimuli presented on the relevant positions, compared to stimuli presented on irrelevant display locations ($F(1,16)=29.65$, $p<.001$; Fig. 2.3). P1 amplitude was similar for targets and nontargets. No change in P1 amplitude with time on task could be observed.
N1. Again, there was no statistical difference in amplitudes measured on P7 and P8, so effects will be reported collapsed over electrodes. Contrary to previous findings (Hillyard and Münte, 1984; Mangun et al., 1988; 1990), stimuli displayed on the irrelevant diagonal showed a larger amplitude in the N1 latency range (160-220 ms) compared to stimuli presented on relevant diagonal positions ($F(1,16)=23.88$, $p<0.001$; Fig. 2.3). This difference was not affected by time on task. In general however, N1 amplitude decreased with time on task ($F(3,48)=21.69$, $p<0.001$; Fig. 2.3) independent of stimulus type.
N2b. The N2b amplitude (350-410 ms) increased with time on task ($F(3,48)=8.21$, $p<0.005$). This change was found to be dependent on whether a relevant or an irrelevant diagonal was presented (Time on task-by-Relevance, $F(3,48)=7.15$, $p<0.01$). As shown in Figure 2.4, in interval 1, the N2b amplitude for stimuli presented on the relevant diagonal is much more pronounced than the amplitude for stimuli presented on irrelevant display locations. This difference, however, disappeared with time on task as the N2b amplitude for stimuli presented on the irrelevant diagonal increases to the level of the N2b amplitude for stimuli presented on the relevant diagonal. The effects of diagonal were independent of whether a target or a nontarget was presented on these positions.

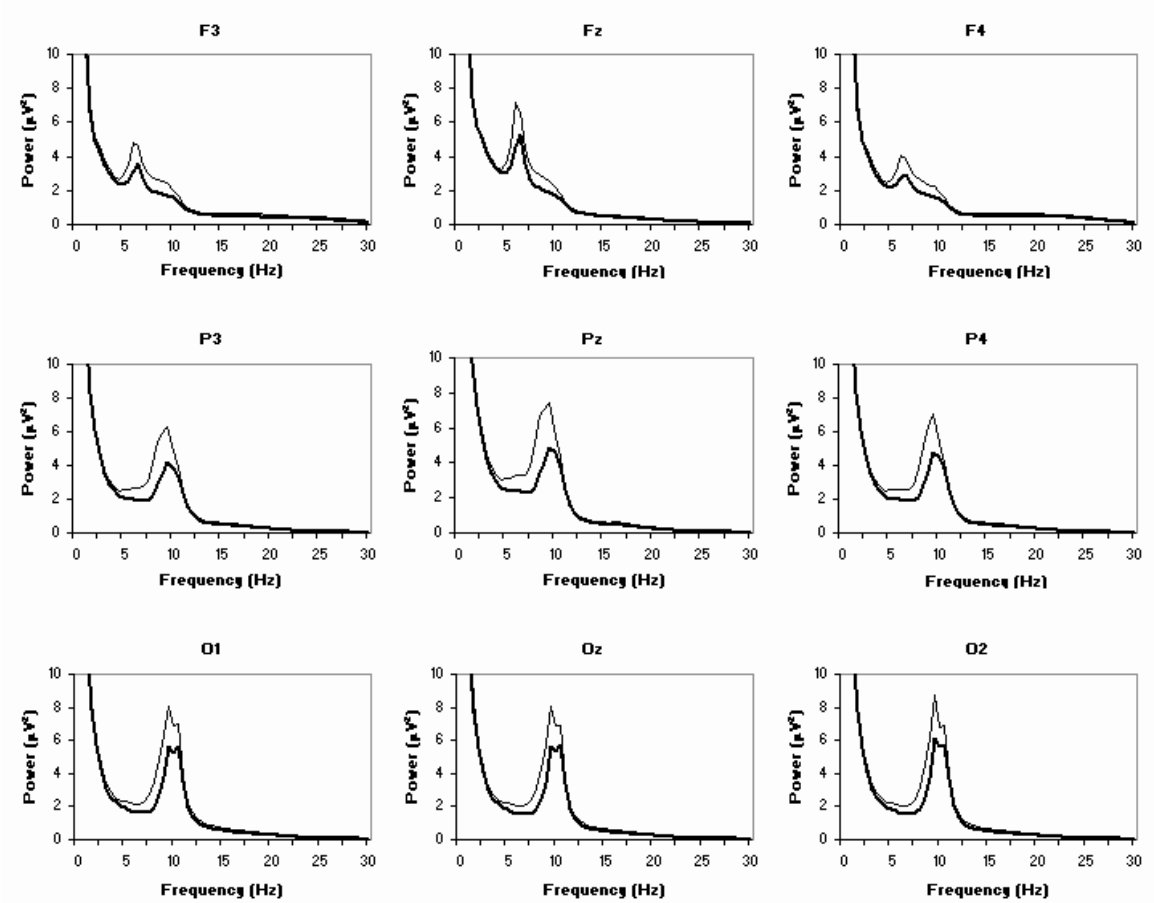

Figure 2.2. *Effect of time on task on EEG power on frontal (F3, Fz, F4), parietal (P3, Pz, P4) and occipital (O1, Oz, O2) sites in the first (strong line) and last (thin line) time on task interval.*

Discussion

Mental fatigue is a very common phenomenon that can have major consequences for everyday task performance. Fatigued people often experience difficulties in concentration and appear more easily distractible. This seems to indicate a problem in the focussing of attention. In the present experiment we examined the effects of mental fatigue on attention, using a visual attention task. To induce fatigue, subjects performed this task continuously, for three hours without rest.

Subjects reported increased aversion to continue task performance with time on task. According to Holding (1983) and Hockey (1997), aversion to invest further effort into task performance is the most reliable characterization of mental fatigue. In this view, the observed increase in subjective levels of aversion against continued performance indeed indicate that subjects became more fatigued during task performance. Additional support for this was gained form the observed increase in alpha, theta and beta power during three hours of task performance. An increase in alpha and theta band power has been found to be related to a decrease in arousal (Klimesh, 1999; Laufs et al., 2003; Oken and Salinsky, 1992; Tanaka et al., 1997). In addition, Klimesch (1999) argued that an increase in lower alpha power is related to increased efforts (and probably difficulties) of subjects to maintain an alert state. Also, it

has been proposed that an increase in beta power results from increased efforts to stay alert (La France and Dumont, 2000); possibly reflecting a mounting tension in cranio-facial muscles. Only the observed increase in lower alpha power in the present experiment was shown to be significantly correlated with the increase in subjectively reported levels of fatigue. Together, this suggests that in the present experiment, subjects developed increasing difficulties in staying alert and sustain attention so that they could continue to perform the task at an acceptable level. Moreover, the observed increase in scores on the aversion scale and the increase in lower-alpha, theta and beta power suggest that we were able to induce mental fatigue by using time on task.

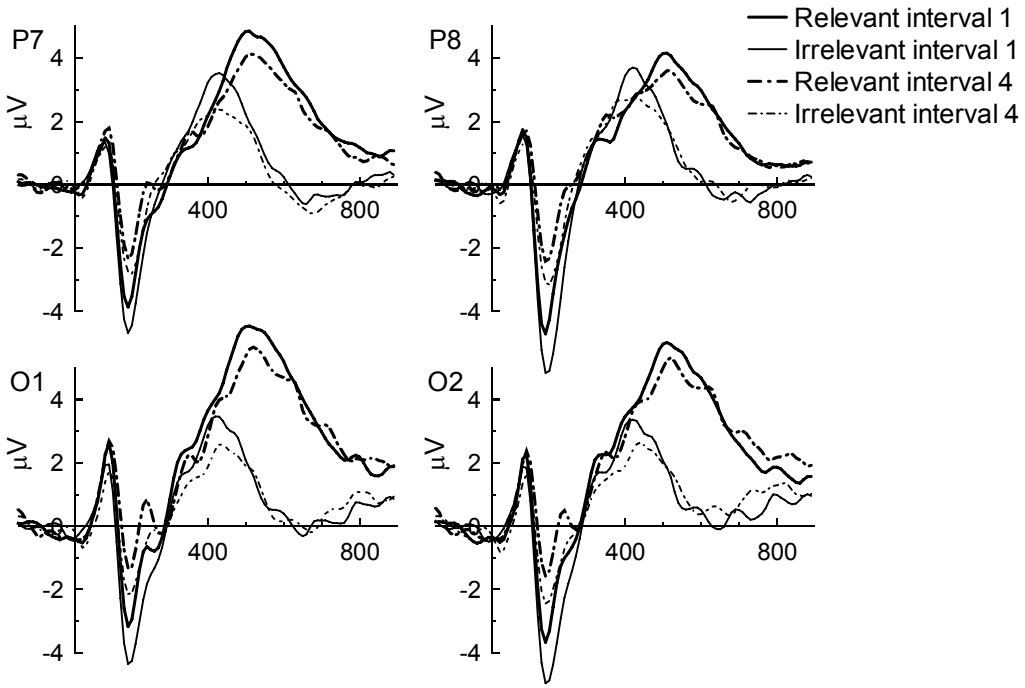

Figure 2.3. *ERP waveforms on parietal (P7, P8) and occipital (O1, O2) sites for stimuli presented at relevant (strong lines) and irrelevant locations (thin lines) in time on task interval 1 (solid lines) and interval 4 (dashed lines).*

This increase in fatigue was associated with a clear decrement in performance. Reaction times and the number of false alarms and missed targets increased significantly during three hours of task performance. The fact that the number of false alarms increased, suggests that the rather dramatic increase in missed targets was not due to a simple reduction in the number of responses: the number of responses to nontargets even increased. This suggests that the observed deterioration of performance is not caused by task disengagement, but may result from increasing difficulties for subjects to correctly identify targets. To examine whether the changes in performance resulted from changes in efficiency of attentional mechanisms, we now turn to the ERP data.

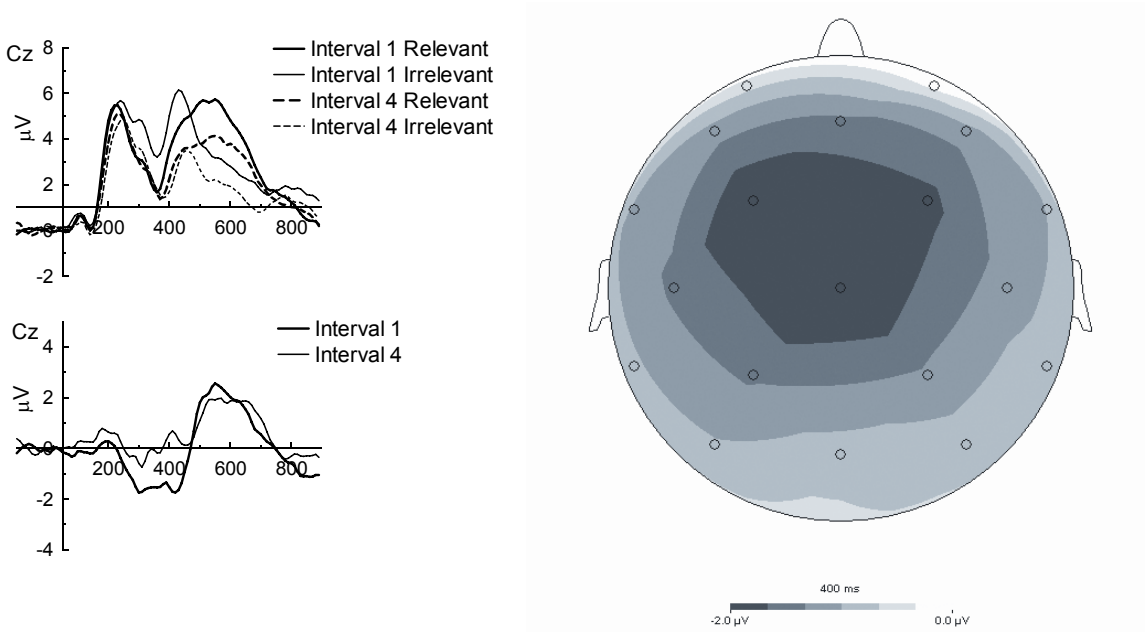

Figure 2.4. *(a) Top: Effect of time on task on N2b amplitude. Shown are ERPs for stimuli presented at relevant and irrelevant locations in interval 1 and interval 4 on Cz. Bottom: Difference waves (relevant – irrelevant) for interval 1 and interval 4 on Cz. (b) Topography of the effect of time on task on the difference in N2b amplitude between relevant and irrelevant stimuli.*

Selective attention mechanisms regulate which information has most impact on behaviour by enhancing sensory processing of relevant information and suppressing irrelevant information (Kastner et al., 1999; Murray and Wojciulik, 2004). Selectivity prevents us from reacting reflexively to stimuli in the environment and enables flexibility of behaviour (Wijers et al., 1996).

In the present study, we found selective attention effects on the early visual ERP components (P1 and N1). These effects, however, were quite different for both components: P1 amplitude was larger for stimuli presented at relevant locations compared to irrelevant locations, while the exact opposite was true for N1 amplitude. Moreover, N1 amplitude decreased with time on task, while P1 amplitude did not. These differential effects on P1 and N1 indicate that these early attention related components cannot reflect a single concept like sensory gain. The dissociation between P1 and N1 effects observed in the present study is not a novel finding: several experiments have shown that the P1 attention effect may be observed in absence of the N1 attention effect and vice versa (Heinze et al., 1990; Luck et al., 1990; Mangun and Hillyard, 1991). While the P1 may reflect the rather exogenous facilitation of early sensory processing within the focus of attention, the N1 may reflect additional top-down modulation of this early sensory processing.

Here, stimuli presented on the relevant diagonal elicited a larger P1 amplitude, compared to stimuli presented on the irrelevant diagonal. This seems consistent with the gain control function that is thought to be reflected by this component (Eason, 1981; Eason et al., 1983; Hillyard et al., 1985); the P1 may represent a facilitation of early sensory processing of items presented at locations where attention is focussed (Luck et al., 1990). Subjects were attending to the relevant diagonal and processing of stimuli displayed on the

other diagonal did not receive as much amplification as did the processing of relevant stimuli. This attentional process was not affected by time on task.

Compared to the P1, the attentional mechanism that is reflected by the N1 component is less clear. As already mentioned, several authors have proposed that these components reflect distinctly different kinds of attentional processes (Eimer, 1993; Heinze et al., 1990; Luck et al., 1990; Luck, 1995; Mangun, 1995). In addition, it has been argued that more than one attentional process is active in the N1 latency range (Heinze and Mangun, 1995; Luck and Hillyard, 1995; Mangun, 1995; Vogel and Luck, 2000). First, the N1 attention effect (i.e. larger N1 amplitude for attended stimuli) appears to reflect an enhanced processing of attended stimuli, probably involving a discriminative process that is applied to a restricted area of visual space (Vogel and Luck, 2000). We will refer to this as the 'N1 discrimination effect'. Second, an enhanced negativity occurs in the N1 latency range when subjects switch their attention from one location to another [Heinze et al., 1990; Heinze and Mangun, 1995; Luck et al., 1990; Yamaguchi et al., 1995). We will refer to this as the 'N1 reorienting effect'.

The amplitude in the N1 latency range changed with time on task, independent of stimulus category (i.e. relevant or irrelevant). This reduction in N1 amplitude might reflect a reduced amplification of the responsivity to both relevant and irrelevant stimuli, resulting in a reduction in the operation of the discriminative process that is reflected by the N1 component (i.e. N1 discrimination effect). Thus, fatigued subjects appear to be less able to discriminate targets from nontargets, accounting for the observed increase in the number of missed targets and false alarms.

Comparable to the results reported by Heinze et al. (1990) and Luck et al. (1990), we observed a larger N1 amplitude for stimuli presented at irrelevant locations, compared to stimuli presented at relevant locations. According to these authors, the obtained N1 enhancement resulted from a reorienting of attention: when a stimulus occurred at unattended locations, an automatic orientation to that location was invoked and this orientation was accompanied by a negative shift in the N1 latency range (see also Yamaguchi, 1995; but see Heinze and Mangun, 1995). It appears that our subjects, even though they were instructed to attend to the relevant diagonal, were unable to suppress the tendency to orient their attention to the irrelevant diagonal, resulting in a more negative deflection in the N1 latency range, the N1 reorienting effect Importantly, this N1 reorienting effect did not change with time on task, suggesting that the automatic reorienting of attention was not altered when our subjects became fatigued.

While the early effects of attention (i.e. P1 and N1) reflect that the formation of stimulus representations is modified, the N2b reflects the further processing within the focus of attention of the stimulus after an earlier identification process has determined that the stimulus is relevant (Lange et al, 1998; Okita et al., 1985; Rugg et al., 1987; Wijers et al., 1989). The N2b ERP component showed an increase in negativity with time on task. This increase was shown to be restricted to stimuli presented on the irrelevant diagonal. In the first interval of the present experiment, subjects selected only stimuli that were presented on the relevant diagonal for further processing, reflected by the much more pronounced negativity in the N2b latency range for stimuli on relevant locations; subjects processed stimuli that were cued as

being relevant to a higher level, compared to irrelevant stimuli. This selectivity, however, disappeared with time on task: the N2b amplitude elicited by stimuli presented on the irrelevant diagonal increased with time on task, until it was of comparable magnitude as the amplitude for stimuli presented on the relevant diagonal. It appears that subjects no longer distinguished between relevant and irrelevant display positions, instead selecting stimuli presented at all locations for further processing.

It is noteworthy that already in the first interval subjects oriented their attention to the irrelevant diagonal, as indicated by the N1 reorientation effect which was present in all intervals. However, in the first interval subjects were able to prevent the further processing of these irrelevant stimuli, as indicated by the smaller N2b amplitude for these stimuli in the first interval, compared to relevant stimuli. In the remaining intervals they were unable to inhibit this further processing: the N2b difference between relevant and irrelevant stimuli disappeared.

These results provide us with an interesting dissociation in the way the different attention related ERP components are affected by mental fatigue. Many authors (e.g., Jonides, 1980) have argued that attention can be under active voluntary control of subjects, but can also be driven externally and automatically. Corbetta and Shulman (2002) proposed that two separate subsystems of attention can be distinguished. One is involved in applying goal-directed selection of relevant stimuli. The other system is specialized in the (stimulus driven) detection of salient stimuli.

The present results indicate that these subsystems of attention are differentially affected by mental fatigue. The finding that the N2b amplitude for stimuli presented on the irrelevant diagonal positions increases with time on task to the level of stimuli presented on relevant positions, suggest that subjects no longer apply the goal-directed selection of relevant stimuli when they become fatigued. Instead of selecting only relevant stimuli, they also selected irrelevant stimuli for further processing when they became more fatigued; they seem to become more easily distractible. Moreover, the N1 discrimination effect decreased with time on task. This implies that subjects had increasing difficulties in applying the top down modulation of early sensory processing that is required for extracting relevant information from the focus of attention. Together, these data strongly suggest that goal directed attention is negatively affected by mental fatigue. In contrast, the automatic shifting of attention when stimuli were presented on irrelevant locations, reflected by the N1 reorienting effect was unaffected by time on task. This indicates that the more automatic, or stimulus-driven processes are relatively unaffected by mental fatigue. This is corroborated further by the observation that the more exogenous P1 component remained unaffected by time on task.

Interestingly, previous studies in which caffeine (a mild stimulant acting on the central nervous system) was administered, show results exactly opposite to the present data. Lorist and colleagues (1994) reported enlargement of the N2b component in response to relevant stimuli and a smaller N2b component elicited by irrelevant stimuli, illustrating a more effective selection mechanism due to caffeine, which is indeed exactly opposite to what we found in fatigued subjects. Moreover, a robust finding observed in a number of studies concerns the reduction of power in the theta and lower alpha band after caffeine treatment (Bruce et al,. 1986; Kenemans

and Lorist, 1995; Newman et al., 1992). As several studies have shown that caffeine counteracts the effects of fatigue (Lorist and Tops, 2003), these results argue in favour of interpretation of the present data in terms of mental fatigue, instead of more general stressors.

In summary, the effects of mental fatigue on behaviour seem to a large extent to be caused by an inability of fatigued subjects to allocate their attention efficiently. However, a distinction must be made between the effects of mental fatigue on goal-directed and stimulus-driven attention. Goal-directed attention is shown to be negatively affected by mental fatigue, while stimulus driven attention was largely unaffected. These results account for both the increased distractibility as well as the decrease in flexibility that is characteristic of fatigued people. When behaviour becomes increasingly stimulus driven, salient stimuli in the environment will have a greater influence on behaviour. At the same time, goal directed control over behaviour will decrease, causing behaviour to be guided more by automatic stimulus response couplings, resulting in a reduced behavioural flexibility.

This has some clear implications for everyday task performance. For example, driving a car for most people is a highly automatized behaviour. When people are fatigued when driving, this results in a decrease in attention for the road and the other traffic. This would not result in major performance decrements if one can rely on automated behavioural patterns. However, when an unexpected and potentially dangerous situation arises, fatigued people lack the flexibility that is needed to handle the new and unexpected situation in an adequate way, which may result in the high number of traffic accidents that are due to driver fatigue.

Chapter 3
Impaired Cognitive Control and Reduced Cingulate Activity During Mental Fatigue

Adapted from:
Lorist, M.M., Boksem, M.A.S., & Ridderinkhof, K.R. (2005). Impaired control and reduced cingulate activity during mental fatigue. *Cognitive Brain Research, 24*, 199 – 205.

Impaired Cognitive Control and Reduced Cingulate Activity During Mental Fatigue

Neurocognitive mechanisms underlying the effects of mental fatigue are poorly understood. Here we examined whether error-related brain activity, indexing performance monitoring by the anterior cingulate cortex (ACC), and strategic behavioural adjustments were modulated by mental fatigue, as induced by two hours of continuous demanding cognitive task performance. Findings that (1) mental fatigue is associated with compromised performance monitoring and inadequate performance adjustments after errors, (2) monitoring functions of ACC and striatum rely on dopaminergic inputs from the midbrain, and (3) patients with striatal dopamine deficiencies show symptomatic mental fatigue, suggest that mental fatigue results from a failure to maintain adequate levels of dopaminergic transmission to the striatum and the ACC, resulting in impaired cognitive control.

Introduction

Mental fatigue refers to the effects that people experience following and during the course of prolonged periods of demanding cognitive activity, requiring sustained mental efficiency. It is, at least to some extent, a common part of many daily-life activities, such as taking part in traffic, or operating complex computer programs or machinery. Mental fatigue may lead to sub-optimal functioning or even human error. In extreme cases, these failures give rise to catastrophic events such as traffic accidents or surgical imprecision. Despite these obvious perils, little is known about the cognitive processes affected by mental fatigue, or the neurocognitive mechanisms underlying these effects (Craig and Cooper, 1992; Van der Linden et al., 2003; Lorist et al., 2000).

Here we examined the hypothesis that the effects of mental fatigue on neurocognitive function involve mechanisms of cognitive control. Cognitive control refers to those emergent 'higher-order' mental functions that oversee and regulate more basic cognitive functions in accordance with internal intentions (Hommel et al., 2002; Miller, 2000). Theories of cognitive control suggest that these control mechanisms are implemented in the brain in a distributed network, involving closely interacting components that are engaged in monitoring and evaluating behaviour (overseeing) and in the implementation of executive control (regulation) when adjustments in control are needed (Cohen et al., 2000; MacDonald et al., 2000; Milham et al., 2003). The engagement of cognitive control is crucial especially under novel and complex task demands, conditions under which fatigued individuals most prominently experience performance difficulties.

Neuroimaging studies and event-related brain potential research have established that the ACC is central to performance monitoring (Carter et al., 1998; Gehring and Knight, 2000; Luu et al., 2000; Ullsperger and Von Cramon, 2003). ACC is thought to detect the activation of erroneous or conflicting responses and to signal the need to activate adaptive control processes, serving to instigate remedial performance adjustments that

minimise the risk of subsequent error (Botvinick et al., 2001; Cohen et al, 2000; Kerns et al., 2004). Such interventions may involve immediate corrective actions (e.g., post-error slowing) or long-term strategic adjustments (e.g., tonic changes in speed/accuracy balance) (Gehring and Knight, 2000; Rabbit, 1966). Neural activity in the ACC has been found to change with time-on-task (Cohen et al., 1988; Paus et al., 1997), suggesting that alterations in ACC functioning is a possible mechanism of mental fatigue. The monitoring function of ACC relies on the mesencephalic dopamine system (De Bruin et al., 2004; Hollroyd and Coles, 2002), which projects diffusely to the cortex and the striatum (Hollroyd and Coles, 2002). Disturbances in the striatal system have also been related to mental fatigue (Chaudhuri and Behan, 2000), supporting the dopaminergic involvement in mental fatigue. If prolonged periods of demanding cognitive activity result in reduced mesencephalic dopaminergic projections to ACC, the consequence may be impaired performance monitoring and inadequate performance adjustment.

An electrophysiological index of performance monitoring in ACC is the error-related negativity (ERN or Ne) (Falkenstein et al., 1990; Gehring et al., 1993), which occurs immediately following the response. This event-related brain potential (ERP) is observed when subjects generate an error or when task conditions elicit high levels of response conflict (Botvinick et al., 2001; Carter et al., 1998; Hollroyd and Coles, 2002; Luu et al., 2000; Ullsperger and Von Cramon, 2004). Based on the association between ERN/Ne amplitude and the role of ACC in error monitoring, observed consistently in the literature (Carter et al., 1998; Gehring and Knight, 2000; Holroyd and Coles, 2002; Luu et al., 2000; Ullsperger and Von Cramon, 2003), the ERN/Ne can be used to examine the effects of psychoactive substances, such as alcohol (Ridderinkhof et al., 2002), or state variables, such as fatigue (Falkenstein et al., 1999; Scheffers et al., 1999) on cognitive control mechanisms. The ERN/Ne amplitude was observed to be reduced after sleep deprivation (Scheffers et al., 1999). Consistent with observations that cognitive failures associated with sleep-deprivation can be counteracted by caffeine (Wesensten et al., 2002), ERN/Ne amplitude is increased after moderate doses of caffeine consumption (Tieges et al., 2004).

The current investigation was designed to assess whether performance monitoring involving the ACC, as indexed in the ERN/Ne, and related post-error adjustments in behaviour, were modulated by mental fatigue, induced by two hours of prolonged task performance. To this end, we examined ERPs in a study designed to track the effects of fatigue on error monitoring, as well as remedial behavioural adjustments subsequent to errors. Participants performed a variant of the Eriksen flanker task, in which they searched for a centrally presented target letter that was flanked by distracter stimuli, associated either with the same response as the target (compatible condition) or with the opposite response (incompatible condition). The subjects' task was to respond to the target letter and ignore distracting information. This task was selected because of its demonstrated success at eliciting ERNs/Ne's (Botvinick et al., 2001; Holroyd and Coles, 2002).

Materials and methods

Participants. Fifteen healthy young women, ranging in age from 19 to 25 years (M = 21.1, SD = 1.8), participated in the study. All reported to be non-smokers, to have normal sleep patterns, not to work night shifts, and not to use prescription medication. They all had normal or corrected-to-normal visual acuity, and were right-handed according to self-report. Subjects received a monetary bonus in return for their participation. Informed consent was obtained from all subjects prior to the study.

Stimuli and Apparatus. Stimuli were presented in the centre of a computer screen positioned at a viewing distance of 80 cm. On each trial, the participants were presented with a horizontal array of three uppercase letters, the central one of which was the target letter and the remaining letters were the flankers. The participants were instructed to make a speeded left-hand response if the central letter was an H, and a right-hand response if the central letter was a S. The letter array remained on the screen until a response was given, or in case no response was issued the letters disappeared after 1200 ms. If the first response was considered incorrect, the subject was allowed to correct it by a second response within 500 ms following the initial response.

The target letter was presented in red in 50% of the trials or in green, on the other half of the trials, against a black background. On half of the trials the flankers had the same identity and colour as the target letter (e.g., HHH or SSS: compatible). In the other half of the trials flankers had a different identity and colour than the target letter (e.g., SHS or HSH: incompatible). The different stimulus categories were presented in random order but with equal probability. A pre-cue, appearing 1000 ms before the three letters, was presented for 150 ms, designating either the colour of the target letter (the Dutch word for 'red' or 'green') or the response hand (the Dutch word for 'left' or 'right')[1]. Hand- and colour cues were presented in random order with equal probability. The cues were valid on 80% of the trials. During the trial a fixation mark remained visible on the screen (an asterisk of 0.5 x 0.5 cm). Stimuli were presented 0.5 cm above this fixation mark and the visual angle per stimulus letter was 0.18° by 0.18°. The interval between the (initial) response to one trial and the onset of pre-cue presentation on the next trial varied randomly between 900 and 1100 ms.

Procedure. The experimental sessions started around 1.00 p.m. and lasted three hours. After the subject arrived at the laboratory, the EEG montage (see below) was applied and the experimental procedure was explained, without giving specific information about the duration of the experimental task. Subsequently the subject was seated in a dimly illuminated, sound attenuated electrically shielded room. The subject was instructed to respond as quickly as possible, maintaining a high level of accuracy, and to minimise eye movements and blinking during task performance. A 2-hour experimental

[1] In addition to the relation between mental fatigue and performance monitoring, we were interested in the effect of type of information provided before a stimulus was presented. Results concerning this research question will be discussed elsewhere.

block without breaks followed a practice block of 80 trials. Written informed consent was obtained from all subjects prior to the experiment, after the nature and possible consequences (but not the duration) of the study were explained to them. The experiment was performed in compliance with relevant laws and institutional guidelines, and was approved by the ethical committee of the Department of Psychology of the University of Groningen.

EEG recordings. EEG was recorded from 22 scalp sites, using *Sn* electrodes attached to an electrode cap (ElectroCap International). Standard 10-20 sites were F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz, and O2. Additional intermediate sites were FC5, FC1, FC2, and FC6. The electrodes were referenced to electronically linked earlobes. Electro-oculograms were recorded bipolarily with *Sn* electrodes from the outer canthi of both eyes and from above and below the left eye. An *Ag/AgCl* ground electrode was placed on the sternum. Electrode impedance was reduced to less than 5 kΩ. The signals were amplified with a band pass set at 30 Hz and a time constant of 10 s and digitised at a rate of 100 Hz.

EEG Data Reduction. Averaged stimulus-locked and response-locked ERPs were computed separately for each combination of conditions, the conditions being time-on-task interval (first/second/third/fourth half hour), cue type (colour/hand), and performance accuracy (correct/incorrect hand). For stimulus-locked ERPs, the averaging epoch started 100 ms prior to stimulus onset and lasted until 1000 ms post-stimulus. For response-locked ERPs, the averaging epoch started 200 ms prior to the response and lasted until 500 ms thereafter. Standard psychophysiological procedures were applied to correct for eye movement artefact (Gratton et al., 1983), exclude trials containing other types of movement artefacts or amplifier saturation. All stimulus-locked averages were aligned to a 100 ms pre-stimulus baseline; response-locked averages were synchronised to a 100 ms pre-response baseline.

Results

Dependent variables were entered into univariate repeated-measures analysis of variance in SPSS, using the ε˜*-adjustment procedure recommended by Quintana and Maxwell (1994). For clarity, uncorrected *df*s are presented.

Overall Performance[2]. The number of trials performed during the experimental session decreased as a function of time-on-task ($F(3,42) = 6.27$, $p = .010$), from 732 (SD = 24) during the first 30-min interval to 716 (SD = 30) in the fourth 30-min interval. In 2% of the trials subjects failed to give a response. This number was not affected by time on task. Error rate was quantified as the proportion of hand errors within each condition. Response times (RT) were determined for trials in which the first response was correct. Trials containing motor responses considered being too fast (<50 ms) were excluded from RT analysis.

[2] RT data of three subjects contained either one or two missing data points and were rejected from part of the statistical analyses.

		0-30 min	31-60 min	61-90 min	91-120 min
Mean RT (ms)	compatible	447	446	446	469
	incompatible	476	483	478	500
Proportion of errors	compatible	0.10	0.10	0.10	0.10
	incompatible	0.17	0.16	0.18	0.17
Proportion of misses	compatible	0.01	0.02	0.02	0.04
	incompatible	0.01	0.01	0.02	0.04

Table 1. *Mean reaction time (RT) and proportion of errors and misses during different time-on-task intervals for compatible and incompatible stimuli.*

In line with previous studies, we found incompatible trials to be associated with longer RTs and higher error rates than compatible trials ($F(1,11) = 36.16$, $p < .001$ and $F(1,14) = 79.59$, $p < .001$, for reaction times and proportion of errors, respectively; see Table 1). Importantly, RT was modulated by time-on-task. While subjects performed relatively stable during the first 90 min of prolonged task performance, after 90 min RTs increased with on average 22 ms (contrast between third and fourth interval: $F(1,12) = 6.99$, $p = .021$). This decrease in speed of performance was independent of the identity of the distracters. Notably, performance accuracy was not affected by prolonged task performance, indicating that the observed time-on-task effects on RT were not likely confounded with a change in speed-accuracy trade-off and related strategy shifts.

ERP Analyses. In the response-locked ERP waveforms, the negative-going component, peaking approximately 60 ms after the incorrect response, was identified as the ERN/Ne. Inspection of the scalp topographies showed that the ERN/Ne was maximal at Cz; therefore, values obtained from Cz were used for statistical analysis (dependent variables were time-on-task interval (first/second/third/fourth half hour), cue type (colour/hand), and performance accuracy (correct/incorrect hand). The amplitude of the ERN/Ne was defined for each subject as the amplitude of the largest negative peak in the 40-80 ms post-response interval. The proportion of compatible errors relative to the proportion of incompatible errors remained stable during the experiment, allowing us to pool incompatible and compatible trials (Gehring et al., 1993). ERNs/Ne's were observed much more prominently after incorrect compared to correct responses ($F(1,14) = 12.28$, $p = .004$; Fig. 3.1). The ERN/Ne peak amplitude decreased significantly with time-on-task ($F(3,42) = 4.27$, $p = .015$), indicating that performance monitoring is affected by prolonged task performance. As can be seen in Fig. 3.2, this time-on-task effect is due mainly to a decrease in ERN/Ne amplitude from the second and third 30-min interval ($F(1,14) = 8.99$, $p = .010$).

In the stimulus-locked ERP waveforms, no effects of time-on-task were apparent. For instance, as can be seen in Fig. 3.3, the amplitude of the P3 component (largest at Pz, as typical) remained unaffected by time-on-task (Analyses were performed on mean amplitudes in 50 ms windows; between 350-500 ms: $F(3,42) < 1.13$, n.s). This observation attests to the specificity of time-on-task effects on ERN/Ne amplitude.

Corrective Actions. If a reduction of the ERN/Ne component implies a failure of response monitoring, performance adjustments are expected to be less efficient with increasing time-on-task. As a behavioural index of error correction, we first examined the proportion of error trials on which the erroneous response was followed immediately (within 500 ms) by a correct response (Fiehler et al., 2004; Gehring and Knight, 2000; Rabbit, 1966). Of all incorrect responses, 78% was corrected by a subsequent, correct response (SD = 17%). Note that these second responses were true error corrections, as very few *correct* responses were 'corrected' by errors (0.8%, SD = 1.4%). The percentage of corrected errors was smaller for compatible compared to incompatible trials ($F(1,11) = 8.85$, $p = .013$). Remarkably, however, these immediate performance adjustments were unaffected by the time spent on task performance. Thus, the decrease in ERN/Ne amplitude with time-on-task was not accompanied by a corresponding decrease in immediate error corrections with prolonged task performance.

As a second behavioural index of behavioural adjustment after errors, we examined speed/accuracy adjustments in trials subsequent to incorrect trials. In particular, we analysed time-on-task effects on post-error slowing. In correct trials following error trials, subjects slowed down compared with RTs in trials following correct trials ($F(1,14) = 4.70$, $p = .048$). Most important, however, this post-error slowing disappeared with time-on-task (time-on-task x trial type: $F(3,42) = 5.25$, $p = .004$). As can been seen in Fig. 3.4, the post-error slowing observed in the first half hour ($F(1,14) = 12.77$, $p = .003$) had disappeared in all subsequent 30-min intervals (all $F(1,14) < 2.22$, all $p > .05$).

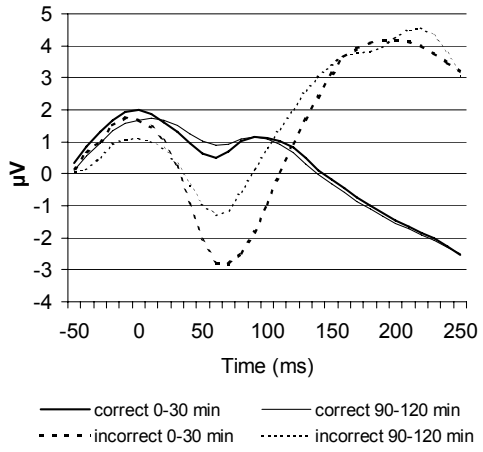

***Figure 3.1**. Response-locked event-related potentials from the vertex (Cz) electrode for correct (straight lines) and incorrect trials (dashed lines) in the 0-30 min interval and in the 90-120 min interval.*

In sum, although the incidence of errors remained stable across prolonged task performance, the amplitude of the ERN/Ne decreased with time on task and performance adjustments subsequent to errors declined with time-on-task, as well. During the first 30-min of task performance errors were followed by post-error slowing, an adjustment that can be interpreted as a transient shift in speed-accuracy balance in an attempt to prevent subsequent errors. This tendency to adopt a more conservative strategy following the occurrence of errors disappeared during the course of prolonged task performance.

Discussion

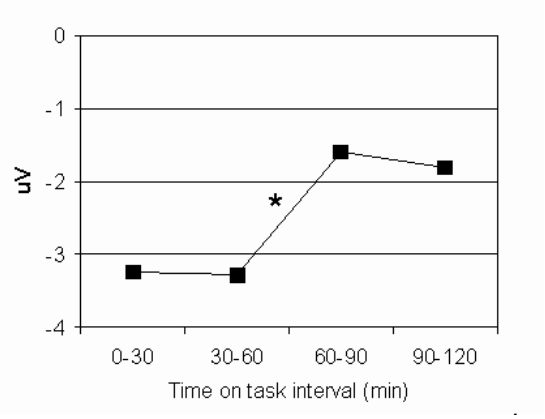

Figure 3.2. *Mean ERN/Ne amplitude for incorrect trials in different time-on-task intervals (asterisk indicates significant difference (p < .01) between ERN/Ne amplitudes in successive time-on-task intervals).*

Although performance detriments as a function of mental fatigue have been documented across a broad spectrum of cognitive tasks (Craig and Cooper, 1992; Van der Linden et al., 2003; Lorist et al., 2000), the neurocognitive mechanisms underlying these effects have remained elusive. Building on the hypothesis that these effects involve mechanisms of cognitive control, we examined the effects of prolonged task performance on error processing. The present study documents that mental fatigue results in compromised error monitoring as reflected in a significant attenuation of the ERN/Ne, as well as in adjustment failures in post-error performance. However, subjects seemed to compensate for the reduction in performance efficiency due to prolonged task performance by increasing RTs, preventing the occurrence of errors and related demands placed on ACC functioning.

Thus, a change in the internal state of humans due to two hours of prolonged task performance has major effects on one of the key features of cognitive control: the extraction of goal-relevant features of past experiences to orchestrate future behaviour in accord with intentions. To verify whether this impairment is specific to error monitoring, it was important to establish that time-on-task uniquely affected ERN/Ne amplitude and did not generalize to other ERP components that are not related tot error processing. In addition, it was important to establish that any effects of mental fatigue on error detection were not contaminated by concomitant reductions in interference control or in accuracy, since the latter affects could potentially mediate the effects on ERN/Ne amplitude (De Bruin et al., 2004; Ridderinkhof et al., 2002). As both conditions were satisfied, the present data reveal that mental fatigue affects the error-monitoring processes expressed in the ERN/Ne.

The capacity to monitor error performance, as reflected in ERN/Ne amplitude, is thought to rely predominantly on intact ACC functioning (Botvinick et al., 2001; Carter et al., 1998; Gehring and Knight, 2000; Holroyd and Coles, 2002; Luu et al., 2000; Ullsperger and Von Cramon, 2003). In addition to the monitor function, the ACC serves to signal the need for enhanced cognitive control after a performance error has occurred. Subjects typically slow down on the trial after an incorrect response (Botvinick et al., 2001; Rabbit, 1966). We observed that these remedial adjustments were limited to the first 30-min period of task performance. Although the precise relationship between the ERN/Ne and subsequent post-error slowing is still unclear (Gehring and Fencsik, 2001; Nieuwenhuis et al., 2001), the present findings suggests that the ability to use information from previous trials to strategically adapt behaviour is severely deteriorated already after half an

hour of task performance. By contrast, remedial actions in the form of immediate corrections were not affected by time-on-task. To understand this differential sensitivity to mental fatigue, note that post-error performance adjustments are subject to strategic modulation (Fiehler et al., 2004; Ridderinkhof et al., 2002) while immediate error correction is a relatively automatic process that cannot be consciously suppressed (Fiehler et al., 2004; Rabbit, 1990). After a premature execution of the first incorrect response tendency, stimulus processing continues and can result in a corrective response. Note that these immediate corrections are based on the stimulus-driven second response tendency, which does not require error detection (Fiehler et al., 2004). The present data provide support for the notion that post-error slowing and overt response correction are different phenomena, and suggest that mental fatigue mainly affects higher-level cognitive control mechanisms, while reflexive reactions seem relatively insensitive to prolonged task performance.

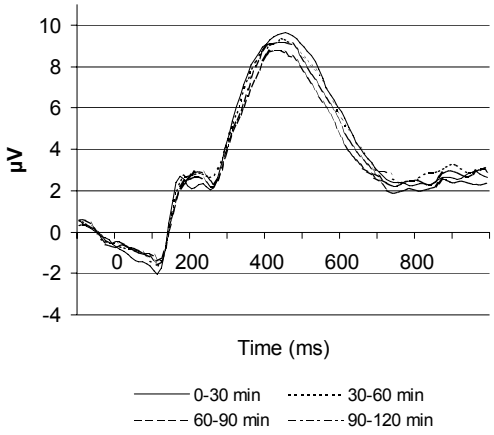

***Figure 3.3**. Stimulus-locked event-related potentials from the parietal (Pz) electrode elicited in different time-on-task intervals.*

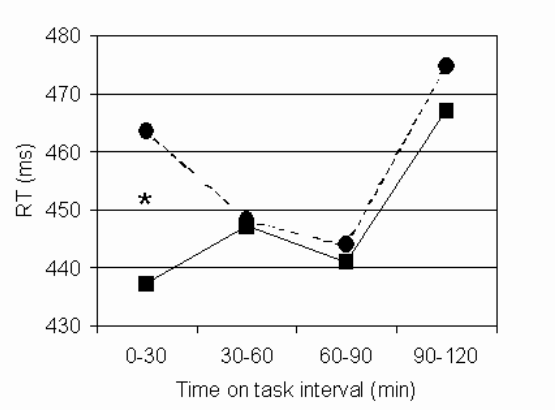

***Figure 3.4.** Mean reaction time for correct trials following a correct response (straight line) and correct trials following an incorrect response (dashed line; asterisk indicates significant difference ($p < .01$) between reaction times in specific time interval).*

Different brain structures are involved in monitoring performance, deciding how and when to allocate attention and for the implementation of control or behavioural adjustments (Kerns et al., 2004; Ridderinkhof et al., 2004). The results of the present study suggest that these different brain areas are differentially sensitive to the effects of mental fatigue. The ERN data indicate that monitoring processes, mediated by the ACC, were compromised after 60 min of continuous task performance. However, the implementation of control, which may be mediated by response preparation areas, seemed more vulnerable to the effects of mental fatigue; post error slowing already was absent after half an hour of task performance.

Taking into consideration the attenuation of the ERN observed after 60 min of task performance, indicating that monitoring processes are compromised with time on task, and the disappearance of strategic behavioural adjustments after half an hour of task performance, it was

surprising that even after two hours no decline in performance accuracy was observed. However, subjects did show a general reduction in speed of performance with time on task, irrespective of accuracy on previous trials.

In previous studies (Lorist et al., 2000) we have observed that subjects seemed to be able to perform at a rather stable speed level during the first hour of task performance; thereafter a sudden increase in RTs was observed. The occurrence of errors, however, increased gradually during the experiment. These results indicate that with time on task, subjects tried to maintain their speed of performance, as was stressed in the task instructions, and in order to do so they sacrificed accuracy. After 60 min of task performance, however, subjects seemed to readjust their strategy; in addition to sacrificing accuracy they also modified their speed levels (Lorist et al., 2000).

In the present study, subjects were able to respond relatively stable for 60 min. of task performance, where after, the ERN amplitude attenuated, indicating that monitoring processes were compromised. The instructions stressed both speed and accuracy; however, subjects were told that they were able to correct incorrect reactions. This additional instruction stressed accuracy. It might be argued that the increase in RTs after 90 min of task performance indicates that subjects sacrificed speed in order to maintain accuracy levels.

Slowing down may allow a more complete accumulation of evidence concerning the correct response, thus preventing premature incorrect reactions. The general slowing observed with time on task thus might be a dynamic adaptation allowing subjects to compensate for the reduction in performance efficiency due to prolonged task performance, and can be considered a functional strategy to cope with sub optimal internal states (i.e., mental fatigue).

Beyond these demonstrations, the present data provide initial support for the notion that mental fatigue involves dopamine-mediated mechanisms of cognitive control, thereby providing the initial contours of a neurocognitive theory of mental fatigue. Although the neuroanatomical pathways and the neurochemical substrates for mental fatigue remain far from clear, the genesis of symptoms related to fatigue has been argued to involve the striatum (Chaudhuri and Behan, 2000). Patients suffering from ischemic vascular diseases involving the basal ganglia or from progressive neurodegeneration affecting the striatum (like in Parkinson’s disease), frequently report symptoms of mental fatigue. Moreover, Falkenstein et al. (2001) have shown that patients with Parkinson's disease have a reduced ERN/Ne (but see 16). These clinical observations suggest the possible involvement of mesencephalic dopaminergic projection systems comprising the striatum and frontal cortical structures, in particular ACC. A role of ACC in mental fatigue is suggested also by reports of modulations in neural activity as a function of time-on-task (Cohen et al., 1988; Paus et al., 1997). The present finding that two key functions of ACC in action monitoring, error detection and signalling the need for remedial action, decline during prolonged periods of demanding cognitive activity, combined with the notion that these monitoring functions of ACC rely on dopaminergic inputs (De Bruin et al., 2004; Holroyd and Coles, 2002), suggest that mental fatigue results from a failure to maintain adequate levels of dopaminergic transmission in the striatum and ACC. The result is

impaired cognitive control, expressed in the present case as compromised performance monitoring and inadequate performance adjustment.

Chapter 4
Mental Fatigue, Motivation and Action Monitoring

Adapted from:
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Mental Fatigue, Motivation and Action Monitoring

In this study we examined whether the effects of mental fatigue on behaviour are due to reduced action monitoring as indexed by the error related negativity (ERN/Ne), N2 and contingent negative variation (CNV) event-related potential (ERP) components. Therefore, we had subjects perform a task which required a high degree of action monitoring, continuously for two hours. In addition we tried to relate the observed behavioural and electrophysiological changes to motivational processes and individual differences.
Changes in task performance due to fatigue were accompanied by a decrease in ERN/Ne and N2 amplitude, reflecting impaired action monitoring, as well as a decrease in CNV amplitude which reflects reduced response preparation with increasing fatigue. Increasing the motivational level of our subjects resulted in changes in behaviour and brain activity that were different for individual subjects. Subjects that increased their performance accuracy displayed an increase in ERN/Ne amplitude, while subjects that increased their response speed displayed an increase in CNV amplitude.

Introduction

Mental fatigue and Action Monitoring. Fatigue due to prolonged task performance is a common phenomenon in our everyday lives. When people become fatigued, they usually experience difficulties in maintaining task performance at an adequate level . This can have major consequences: for example, in a recent study by Campagne et al. (2004) in which subject were required to drive a car (in a simulator) for about 3 hours, it was found that with increasing fatigue, performance deteriorated. Driving errors such as large speed variations and even running of the road became increasingly frequent. Comparable results have been obtained for truck and train drivers (Kecklund et al., 1993; Torswall et al., 1987). It seems that the problems that fatigued people experience in these circumstances result to a large extent from the fact that they monitor their actions insufficiently.

To be able to behave in a coherent and adaptive manner, it is imperative to monitor ones actions (MacDonald et al., 2000). In doing so, information is gained which can be used to adjust ongoing behaviour. To keep with our example: if the subjects in the car simulator would have monitored their actions adequately, they would have detected their deviations in speed and position on the road earlier, resulting in less driving errors.

In the present study we examined the effects of fatigue on action monitoring processes, using event-related potentials (ERPs). Different indices of action monitoring can be discerned in the ERP. The error related negativity (ERN) or error negativity (Ne) consists of a large negative shift in the response locked ERP occurring after subjects made an erroneous response. First reported by Falkenstein et al. (1990) and Gehring et al. (1990), the ERN/Ne was thought to be specifically related to error detection processes, in the sense of a mismatch signal when representations of the actual response and the required response are compared.

Peaking at 50-150 ms after response execution, the ERN/Ne is most prominent at fronto-central scalp positions (e.g., Fz, FCz and Cz). Localization of the ERN/Ne with dipole localization algorithms (BESA) has led most authors to conclude that the ERN/Ne is generated in the Anterior Cingulate Cortex (ACC, Dehaene et al., 1994; Gehring and Knight, 2000). These findings are corroborated with results from fMRI studies (Carter et al., 1998; Kiehl et al., 2000; Van Veen and Carter, 2002a).

A second ERP component associated with action monitoring is the N2 (Van Veen and Carter 2002b). This stimulus locked ERP component has a similar scalp topography as the ERN/Ne and has also been localized in the ACC (Lange et al., 1998; Liotti et al., 2000). In contrast to the ERN/Ne, the N2 occurs prior to response execution on correct trials and is thought to reflect response conflict (Lange et al., 1998; Kopp et al., 1996; Liotti et al., 2000, Swick and Turken, 2002). Response conflict occurs when a stimulus activates more that one response channel (the correct and an incorrect channel).

To resolve the detected conflict, the action monitoring system recruits greater top-down control from other prefrontal structures to improve task performance and thereby reduce conflict (Botvinick et al., 2001; Carter et al, 1998; Gehring and Knight, 2000; Menon et al., 2001). The Contingent Negative Variation (CNV) is thought to reflect anticipatory and preparatory processes, and has been shown to correlate with performance accuracy (Hohnsbein et al., 1998). The CNV is elicited by providing the subject with a warning stimulus (e.g., a cue) followed at some fixed interval by a second 'imperative' stimulus. The CNV is observed as a large negative deflection in the ERP between the warning and the imperative stimulus.

Action monitoring is a prerequisite for the ability to optimize ongoing behaviour. To modify behaviour, remedial actions should be implemented when errors are made. These remedial actions can consist of immediate corrections and/or post error slowing (Rabitt, 1966). Post error slowing refers to the phenomenon that, after making an error, subjects typically respond with increased reaction times on the following trial. This probably reflects a strategic adjustment in response generation. Gehring et al. (1993), noted that the ERN/Ne was larger on trials in which errors were immediately corrected and that larger ERN/Nes were related to a slower response on the subsequent trial (see also Scheffers et al., 1996). Moreover, Fiehler et al. (2004) reported a significantly greater haemodynamic response for corrected than for uncorrected errors in the rostral cingulate zone, an area identified to play an important role in error detection.

To investigate whether action monitoring processes are compromised when people are fatigued, we had subjects perform a task in which response conflict was high and required a high degree of action monitoring, for 2 hours. The task we used was a modified version of the Simon task. In this kind of task, targets which are assigned to different effectuators (in this case hands) are displayed either left or right of fixation. The Simon effect (or congruency effect), first described by Simon and Small (1969) refers to the phenomenon that people respond faster (typically 20 to 30 ms; Lu and Proctor, 1995) when the side of stimulus presentation corresponds to the response side. This kind of task induces response conflict as the presentation of the stimulus automatically activates the spatially corresponding response. In the incongruent condition however, one has to override this automatically

activated response in order to give the required response, which relies heavily on adequate action monitoring.

Mental Fatigue and Motivation. A second important issue we addressed in the current study is the relationship between fatigue and (lack of) motivation to continue task performance. Chaudhuri and Behan (2000) noted that in their patients fatigue is, at least in part, due to a deranged motivation in self-initiated tasks. Tops et al. (2004) proposed that mental fatigue can be viewed as an effort/reward imbalance: as long as one feels that the invested effort in the end will result in sufficient rewards, one will continue working. However, when the perceived effort becomes to great and the reward no longer compares to this, the motivation to continue will dissipate and one will want to disengage from the task, feeling fatigued.

To test this, we manipulated motivation by offering our subjects a certain amount of money if they performed well in the remainder of the task, after they had performed the task for 2 hours. If fatigue can indeed be viewed as an effort/reward imbalance, the increased reward should lead to a better balance between effort and reward, thus counteracting the effects of fatigue. However, there are large individual differences in the way people respond to motivation and what kind of rewards are perceived as motivating. Here, we chose to motivate our subjects by offering them a monetary reward, as well as stressing that their performance would be compared to that of other participants (social comparison). We stressed both accuracy and performance speed, so that subjects were free to choose the way in which they could improve their performance. This allowed us to investigate individual differences in response strategies.

Interestingly, many studies have shown the ERN/Ne to be related to motivational processes: when by task instructions the motivation to perform well is reduced, a reduction in ERN/Ne amplitude can be observed (Gehring et al., 1993). Motivation appears to be essential for observing a robust ERN/Ne (Gehring et al., 1993; Gehring and Knight, 2000; Tucker, 1999; Dikman and Allen, 2000; Luu et al., 2000). Bush et al. (2000) argue that ERN/Ne and related ACC activity represent a general evaluative system that processes the motivational significance of events including, but not limited to errors and conflict. In addition, Falkenstein and colleagues (2003) have shown the CNV to be sensitive to motivational manipulations as well. In their study, CNV amplitude was larger on trials when subjects were asked for an effortful improvement of performance compared to trials when no such performance improvement was demanded.

In this study we will investigate whether the effects of fatigue on behaviour are due to reduced action monitoring as indexed by the ERN/Ne, N2 and CNV ERP components. In addition we will relate these changes to motivational processes.

Methods

Subjects. Nineteen healthy participants (9 males), between 18 and 26 (M=22) years of age, were recruited from the university population. They were paid for their participation and had normal or corrected-to-normal vision. All

participants described themselves as being right handed. None of the subjects worked night shifts or used prescription medication. Written informed consent was obtained prior to the study.

Stimuli. All stimuli were presented white on a black background. The fixation point in de centre of the screen was indicated by an asterisk. Every trial started with the presentation of an arrow cue (150 ms), 0.6 degrees above the fixation point. The arrow indicated the hand that would have to be used for response for the upcoming stimulus. This cue was valid in 80% of the trials. 1000 ms after cue onset, the imperative stimulus was presented. Stimuli consisted of an H or an S (0.5 degrees visual angle). Participants were instructed to make a left-hand button-press response if the stimulus was an H, and a right hand button-press response if the stimulus was an S. Stimuli were presented 2.2 degrees left or right of the fixation point. When stimulus location and response are on the same side, the stimulus is called congruent (for example an H presented on the left side of the screen). When stimulus location and response are on opposite sides, the stimulus is called incongruent (for example an H presented on the right side of the screen). Congruent and incongruent stimuli were equiprobable. Stimuli remained on the screen until a response was made or until 1200 ms had elapsed. After this, there was a 500 ms interval, in which subjects had the opportunity to correct their erroneous response by giving the correct response. Finally, there was an interval of 400-600 ms before the start of the next trial.

Procedure. Subjects were instructed to abstain from alcohol 24 hours before the experiment and from caffeine containing substances 12 hours before the experiment. Subjects were told the study was aimed at investigating the neural correlates of cognitive control, they were unaware the study was about mental fatigue and motivation.

After arrival at the laboratory (between 12 p.m. and 1 p.m.), the subjects surrendered their watches. They had no knowledge of the length of the session other than that it would not last beyond 18.00 hours. Before the start of the experiment, subjects were given written task instructions, where after they were trained in performing the task, for 15 minutes.

Following the application of the electrodes, subjects were seated in a dimly lit, sound-attenuated, electrically shielded room at 0.90 m from a 17” PC monitor. Their index fingers rested on touch-sensitive response boxes. Subjects were instructed to lift their finger from the response button as quickly as possible when a target was presented, maintaining a high level of accuracy. The experiment started between 13.30 and 14.30 hours and lasted for 2 hours and 20 minutes. Subjects completed between 3500 and 4000 trials during the entire experiment. In the first 2 hours subjects performed the task to induce fatigue. Before the start of the last 20 minutes, a text was displayed on screen that informed the subject that from that time on, his performance would be compared to that of other subjects and that the subjects who performed best would receive 25 euros extra payment. No rest pauses were given during task performance.

Recording. The electroencephalogram (EEG) was recorded using 22 Sn Electrodes attached to an electro cap (Electro-Cap International), from

positions F7, F3, Fz, F4, F8, Fc5, Fc1, Fc2, Fc6, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, Oz and O2. All electrodes were referenced to linked earlobes. The electro-oculogram (EOG) was recorded bipolarily from the outer canthi of both eyes and above and below the left eye, using Sn electrodes. Electrode impedance was kept below 5kΩ. EEG and EOG were amplified with a 10s time constant and a 200 Hz low pass filter, sampled at 1000 Hz, digitally low pass filtered with a cut-off frequency of 30 Hz, and online reduced to a sample frequency of 100 Hz.

Data Analysis. To investigate the effects of time on task, the data were divided into six time intervals of 20 minutes each. Data were subjected to SPSS ANOVA for repeated measurements, using the ε-adjustment procedure recommended by Quintana and Maxwell (1994). When the main analysis indicated a significant interaction ($p<.05$) between factors, follow-up analyses were performed, adjusting error rates according to Bonferroni.

Performance. For the different stimulus conditions mean reaction times (RTs) were calculated. Reactions occurring within a 150-1000 ms interval after stimulus presentation were considered as hits. The percentage of misses and false alarms were also determined. We tested the factors time on task (TOT, six levels), cue validity (VAL, two levels) and congruency (CON, two levels).

ERPs. In addition to the ERN/Ne, N2 and CNV, we also measured P3 amplitude and latency. All ERP analyses were performed using the Brain Vision Analyser software (Brain Products). ERPs were averaged off-line. Out of range artefacts were rejected and eye movement artefacts were corrected, using the Gratton and Coles method (Gratton, Coles & Donchin, 1983). A baseline voltage over the 100 ms interval preceding the cue (CNV), stimulus (N2 and P3) or response (ERN/Ne), was subtracted from the averages. The ERPs were averaged over replications and calculated separately for each subject, time on task interval and stimulus category.

Using the grand averages, we determined the electrodes showing the largest amplitudes for each of the ERP deflections of interest (ERN/Ne, N2 and P3). For these electrodes we automatically detected peak amplitudes and latency. Peak detection for the ERN/Ne was performed in the 50-200 ms latency range, N2 peak detection was performed in the 250-350 ms latency range and peak detection for the P3 was performed in the 300 – 600 ms latency range. For the ERN/Ne, N2 and P3, we selected the average amplitude of the respective ERP components in a time window from 20 ms before the peak until 20 after the peak for statistical analysis. For the CNV we tested the amplitude in the 600 ms – 1000 ms time window after cue onset.

The ERN/Ne was maximal on Cz (Fig 4.2). Because of the limited number of errors made by the subjects, these ERPs were averaged over stimulus categories, leaving only the factor TOT for statistical analyses. As the N2 amplitude was maximal on Cz, we used this electrode to test the factors TOT, VAL and congruency CON. For the P3 we tested the same factors on Pz, where this component had its maximum. For the CNV, we tested the factors TOT and CUE (left or right) in the specified time window at electrode Cz, where visual inspection indicated that the CNV was maximal.

Motivation. To investigate the effects of motivation on the behaviour and brain activity of fatigued subjects, we tested the difference on all the measures described above between the last interval before the motivation manipulation

(interval six) and the interval after the motivation manipulation (interval seven). RTs and the proportion of correct responses in interval seven were converted to standard scores for each participant. An index of speed-accuracy trade-off was then calculated according to the method of Nietfeld and Bosma (2003). Based on this index, we divided our subjects (median split) in a group that responded to the motivational instructions with increased accuracy and one that responded with increased speed (the 'accuracy' and the 'speed' group).

Interval	*RT (ms)*	*SD (ms)*	*Errors (%)*
1	457 (13.3)	121 (08.2)	9.2 (1.4)
2	463 (14.8)	129 (09.1)	10.4 (1.3)
3	460 (16.0)	136 (08.9)	11.4 (1.7)
4	464 (14.0)	145 (09.4)	12.2 (1.8)
5	473 (14.5)	156 (12.3)	12.5 (2.0)
6	485 (15.1)	145 (10.2)	12.9 (1.8)
7	463 (14.2)	150 (12.3)	12.7 (1.9)

Table 4.1. *Changes in RT, SD of RTS and Errors with time on task (interval 1-6) and with motivation (interval 7), collapsed over stimulus categories. Standard errors in parenthesis.*

Results

Performance

RTs and Accuracy. Processing speed was reduced by time on task, from 457 ms in the first interval to 485 ms in the sixth interval (Table 1, $F(5,90)=3.03$, $p<0.05$). In addition, we found that RT variability increased with time on task, $F(6,108)=6.18$, $p<.005$ (Table 4.1). Mean correct RTs for incongruent trials were slower, compared to the RTs for congruent stimuli (483 ms vs. 451 ms, ($F(1,18)=48.13$, $p<0.001$).). However, the magnitude of this typical congruency effect was not modulated by time on task (TOTxCON, $F(5,90)=0.69$, ns). The difference in RT for valid (446 ms) and invalidly cued stimuli (488 ms) also proved to be significant ($F(1,18)=21.99$, $p<0.001$). Furthermore, we found an interaction between congruence and validity ($F(1,18)=8.58$, $p<0.01$). The difference in RT between congruent and incongruent stimuli was larger when validly cued (Valid: ($F(1,18)=60.70$, $p<0.001$), Invalid: ($F(1,18)=19.32$, $p<0.001$), although there was a congruency effect in both validity conditions.

Accuracy was determined as percentage incorrect per stimulus category (i.e. false alarms). The performance in terms of accuracy decreased from 9.2% errors in the first interval, to 12.9% errors in the sixth interval (Table 1, $F(5,90)=3.61$, $p<0.05$). Subjects made more errors on incongruent trials (15.3%) than on congruent trials (7.5%, $F(1,18)=34.49$, $p<0.001$). As with the RTs, the magnitude of this congruency effect was not modulated by time on task (TOTxCON, $F(5,90)=1.77$, ns). Validly cued trials resulted in less errors (7.1%) than invalidly cued trials (15.7%, $F(1,18)=17.50$, $p<0.001$). Contrary to what we found for RTs, the difference in percentage of errors between congruent and incongruent trials was larger when invalidly cued,

F(1,18)=17.34, p<0.001, (Valid: F(1,18)=23.87, p<0.001, Invalid: F(1,18)=30.57, p<0.001). Again, we obtained a congruency effect in both validity conditions.

Post Error Slowing and Immediate Corrections. On average, subjects were slower on trials following an erroneous response compared to a correct response (458 vs. 445 ms, F(1,18)=5.44, p<0.05). However, this difference disappeared with time on task (Fig. 4.1, F(5,90)=3.06, p<0.05).

The percentage of immediately corrected responses decreased from 73% in the first interval, to 39% in the sixth interval (F(5,90)=5.43, p<0.01).

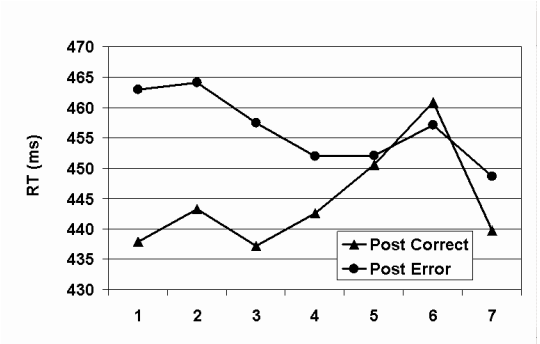

Figure 4. 1. *Changes in post error slowing with time on task (interval 1-6) and with motivation (interval 7), collapsed over stimulus categories.*

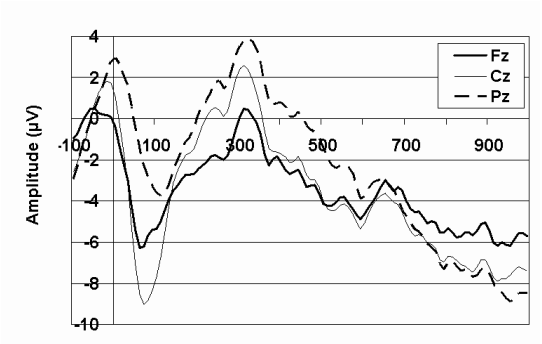

Figure 4. 2. *ERN/Ne amplitude at Fz, Cz and Pz for interval 1. The ERN/Ne had a maximal amplitude at Cz.*

ERPs

ERN/Ne. ERN/Ne amplitude decreased with time on task, (Fig. 4.3; F(5,90)=9.70, p<0.001) from –9.5 μV in interval 1 to –3.5 μV in interval 6. ERN/Ne latency remained unchanged.

N2. N2 latency and amplitude were significantly greater for invalidly cued stimuli compared to validly cued stimuli (296ms vs. 288ms, F(1,18)=9.18, p<0.01; 2.6 μV vs. 1.9 μV, F(1,18)=9.10, p<0.01). N2 amplitude was greater for incongruent stimuli compared to congruent stimuli (2.5 μV vs. 2.0 μV, F(1,18)=7.35, p<0.05). Importantly, the difference in amplitude between congruent and incongruent trials disappeared with time on task (Fig. 4.4), F(5,90)=6.41, p<0.001. Specifically, the N2 amplitude in the incongruent conditions was significantly reduced with time on task (F(5,90)=7.67, p<0.001), while the amplitude in the congruent conditions remained the same across time on task intervals (F(5,90)=.095, ns).

CNV. CNV amplitude was maximal on Cz and decreased with time on task, (Fig. 4.5; F(5, 90)=3.07, p<0.05), from –2.6 μV in interval 1 to –1.2 μV interval 6.

P3. Amplitude of the P3 component was larger for validly cued trials compared to invalidly cued trials (13.6 μV vs. 12.0 μV), F(1,18)=23.03, p<.001. Although P3 amplitude did not change with time on task, P3 latency did change. Latency increased from 381 ms to 399 ms, F(1,18)=5.68, p<.001. Also, P3 latency was greater for invalidly cued trials compared to validly cued trials (402 ms vs. 385 ms), F(1,18)=13.31, p<.005, and for incongruent stimuli compared to congruent stimuli (400 ms vs. 386 ms), F(1,18)=29.09, p>.001.

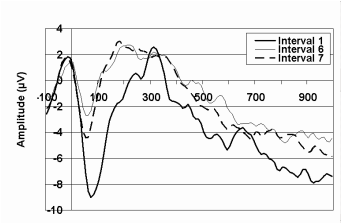

Figure 4.3. *ERN/Ne amplitude for interval 1 (non-fatigued), interval 6 (fatigued) and interval 7 (fatigued and motivated).*

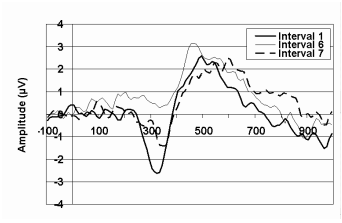

Figure 4.4. *N2 amplitude (difference waves; incongruent - congruent) for interval 1 (non-fatigued), interval 6 (fatigued) and interval 7 (fatigued and motivated).*

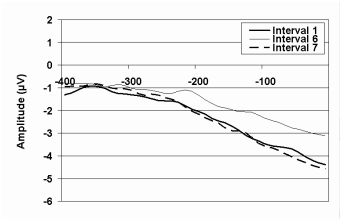

Figure 4.5. *CNV amplitude for interval 1 (non-fatigued), interval 6 (fatigued) and interval 7 (fatigued and motivated).*

Motivation and individual differences. When comparing the last interval before subjects were motivated (interval 6), and the interval after which subjects were motivated (interval 7), a number of changes can be observed. Behaviourally, reaction times decrease (Table. 1; $F(1,18)=10.60$, $p<0.005$), while accuracy remains unaffected (Table 1; $F(1,18)=0.03$, ns). Interestingly, the post error slowing that had disappeared with time on task in the previous intervals once again emerged (Fig. 4.1; $F(1,18)=4.63$, $p<0.05$). Visual inspection of the ERP averages suggests that this increase in post error slowing was accompanied by an increase in ERN/Ne amplitude (Fig. 4.3). However this increase was not significant ($F(1,18)=1.39$, ns). N2 amplitude also did not increase significantly, (Fig. 4.4; $F(1,18)=0.18$, ns.). In contrast, CNV amplitude increased to the level of the first interval after motivation, (Fig. 4.5; $F(1,18)=8.98$, $p<0.01$). P3 amplitude also increased after motivation, $F(1,18)=7.06$, $p<.05$, while latency remained unchanged.

Inspection of the data of the individual subjects revealed that subjects did not all react in the same way to the motivational instructions. The instructions stressed accuracy as well as speed. It appeared that subjects never improved their performance on both speed and accuracy. Instead they chose a strategy for themselves in which they focussed on either speed or accuracy. To investigate whether these different strategies were accompanied by different patterns of brain activity, we divided our subjects in to two groups. One group tended to improve most on speed (n=10), the other most on accuracy (n=9). Subjects in the accuracy group increased their response speed to a much lesser extent than subjects in the speed group ($F(1,17)=3.29$, $p<0.05$, 1-tailed). Moreover, subjects in the accuracy group responded to the motivation with increasing their accuracy, while subjects in the speed group even made more errors than before the motivation (Fig. 4.6; $F(1,17)=10.92$, $p<0.005$, 1-tailed).

At the physiological level, the ERN/Ne amplitude is differentially affected by the motivation manipulation, as indicated by the TOTxGROUP interaction, $F(1,17)=10.32$, $p<0.005$. As show in Figure 4.7, ERN/Ne amplitude increases only for subjects in the accuracy group. The post error slowing seems to follow the same pattern, but the difference between the groups failed to reach significance, $F(1,17)=0.72$, ns. Likewise, the N2 amplitude showed no difference between groups, $F(1,17)=1.38$, ns. In contrast, CNV amplitude increased only for subjects in the speed group,

F(1,17)=9.10, p<0.01. The effect of motivation on P3 amplitude and latency was not different for the two groups.

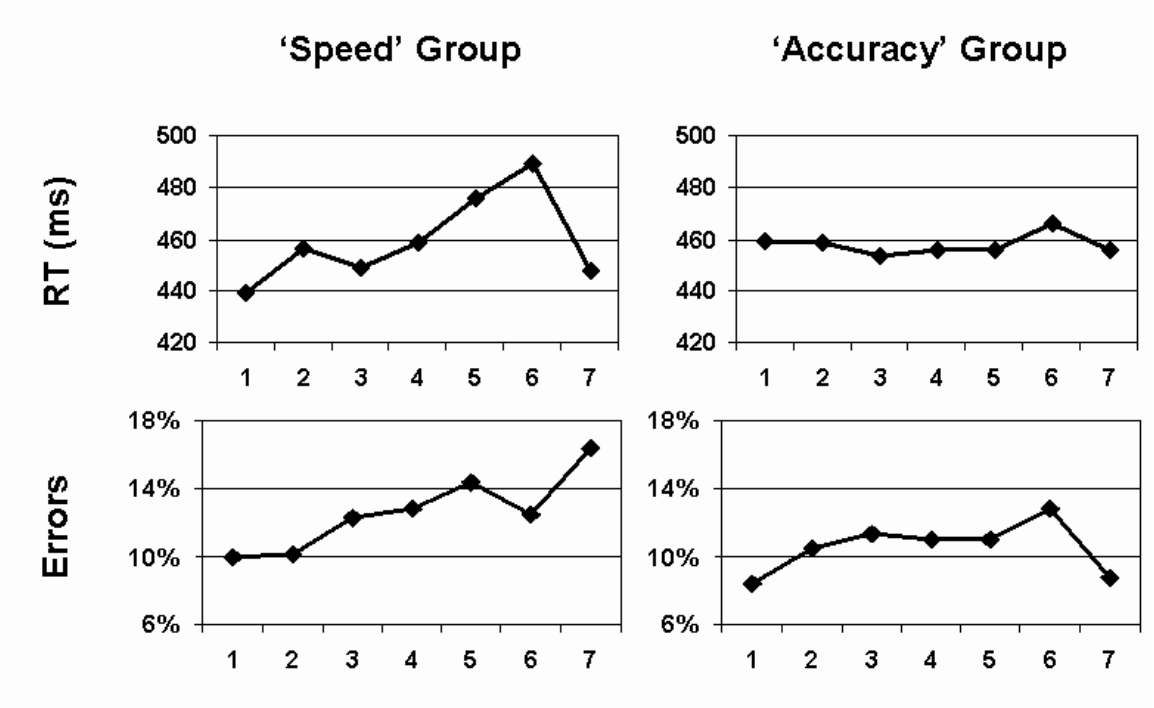

Figure 4.6. *RT (top panels) and errors (lower panels) for subjects in the 'speed' group (left panels) and the 'accuracy' group (right panels). Subjects in the speed group responded to the motivation with decreased RTs, while subjects in the accuracy group responded with increased accuracy.*

Discussion

Mental fatigue and action monitoring. In the following, we will discuss the effects of 2 hours of continued task performance on the behavioural and physiological indices of action monitoring. In addition, the relationship between fatigue, motivation and individual differences will be discussed.
Apparent in ERPs associated with erroneous responses, there was a clear ERN/Ne that had its maximum at fronto central scalp positions. This negative deflection was absent in ERPs associated with correct responses. ERN/Ne amplitude was substantially reduced during the two hours of task performance, indicating that action monitoring is impaired in fatigued subjects (see also Lorist et al., 2005; Scheffers et al., 1999). In addition to reflecting action monitoring, the ERN/Ne also serves to signal the need to initiate performance adjustments after errors (Gehring & Knight, 2000). As a reduction in ERN/Ne amplitude indicates that the cognitive system fails to detect erroneous behaviour, this should have direct consequences for the initiation of remedial actions. Indeed, subjects corrected their incorrect responses less often when they were fatigued. In addition, fatigued subjects no longer slowed down after committing an error. These results suggest that the ability to strategically adjust behaviour after incorrect actions is reduced in fatigued subjects.

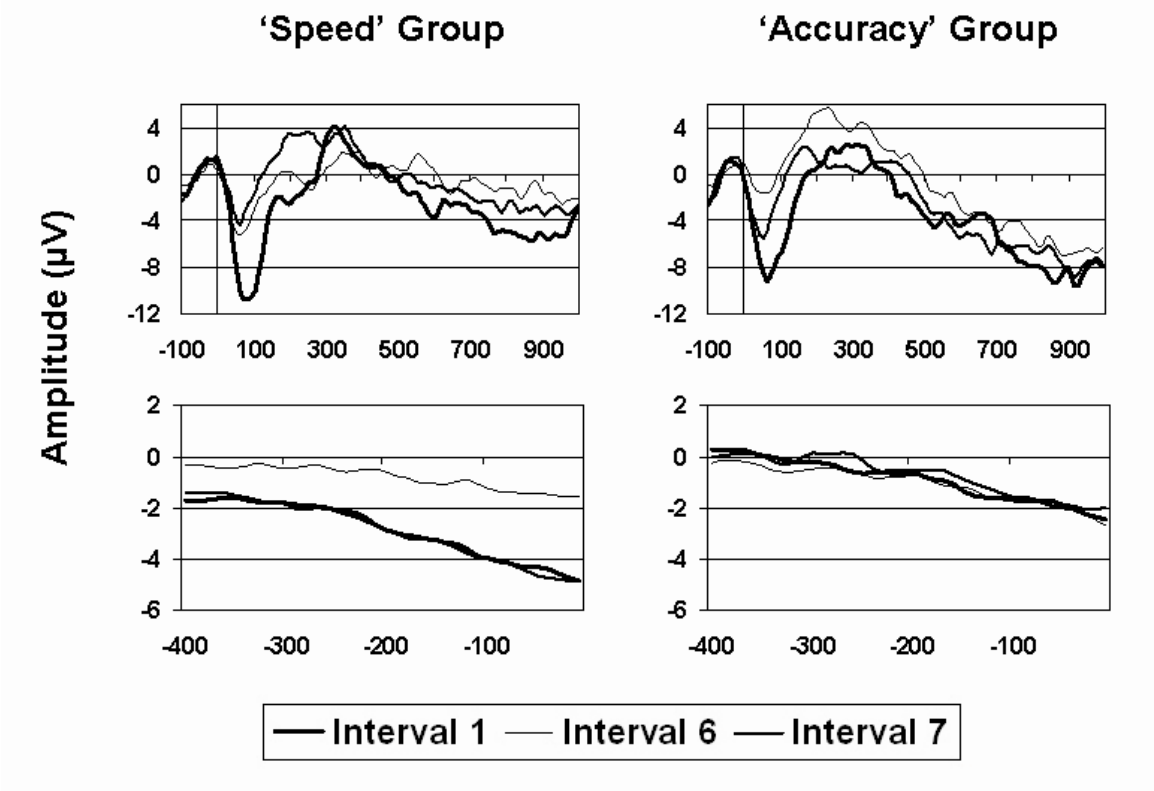

Figure 4.7. ERN/Ne (top panels) and CNV (lower panels) for subjects in the 'speed' group (left panels) and the 'accuracy' group (right panels). Subjects in the speed group responded to the motivation with increased CNV amplitude, while subjects in the accuracy group responded with an increase in ERN/Ne amplitude.

This inability to strategically adjust behaviour with mental fatigue is also reflected in the observed decrease in CNV amplitude. Subjects could use the advance information provided by the cue to prepare themselves for the upcoming stimulus. However, fatigued subjects did not seem to prepare themselves as well for the upcoming trial, resulting in a decrease in response speed and reduced accuracy. This replicates previous findings of Lorist et al. (2000). The validity of the cue influenced the magnitude of the congruency effect. This replicates previous findings: cueing the side of the required response results in an increased congruency effect on validly cued trials (Wascher & Wolber, 2004). This effect of validity however, did not change with time on task.

According to Van Veen and Carter (2002a,b), the N2 reflects the conflict that occurs when an incorrect response is overridden by the correct response. When our subjects were not fatigued, they clearly monitored their actions in terms of detecting the conflict that occurred on incongruent trials. This is reflected by the larger N2 on incongruent compared to congruent trials. On the behavioural level, subjects made more errors on incongruent trials and also RTs were longer on incongruent trials. However, when subjects were fatigued, there no longer was a difference in N2 amplitude between congruent and incongruent trials. More specifically: the N2 amplitude on incongruent trials is reduced to the level of the amplitude observed on congruent trials. So, it seems that the conflict that arises by the activation of the incompatible

responses is no longer detected. Various studies using source localization have found that the N2, like the ERN/Ne is generated in the ACC. The decrease in N2 amplitude together with the decrease in ERN/Ne amplitude can thus be viewed as converging evidence that the action monitoring functions of the ACC are negatively affected by mental fatigue.

Remarkable is that, despite the differential effect of mental fatigue on N2 amplitude in congruent and incongruent trials, the congruency effect at the behavioural level remains unaffected. The decrease in N2 amplitude on incongruent trials suggests that subjects no longer detect the conflict that occurs on these trials. This would result in an increased number of errors and/or greater response latencies on incongruent trials specifically, increasing the congruency effect. This is not what we observe in our data. Instead, subjects increased there response latency on all trials (from 457 to 485 ms) when they became fatigued. Studies on the Simon effect have shown that when subjects postpone their response, the difference in response latency between congruent and incongruent stimuli becomes smaller. In the present study, subjects appear to have used these larger response latencies to counteract the effects of reduced conflict detection to keep performance at an acceptable level. Subjects seemed to have switched from a controlled, effortful strategy, requiring the detection of conflict, to a more passive strategy in which they increased their overall response latency. This increase is probably due to the fact that subjects took more time to evaluate the stimuli, before responding. The finding that P3 latency increases when subjects become fatigued corroborates this interpretation. The latency of the P3 component covaries with target detection processes involved in stimulus evaluation and categorization, with the peak of this component indicating the termination of these evaluation processes (Duncan-Johnson, 1981; Duncan-Johnson & Donchin, 1982).

This kind of strategy change when people become fatigued has been observed in other task situations as well. For example Sperandio (1978) showed that air traffic controllers shifted to cognitively less demanding strategies when they had worked under high workload for a considerable period of time. In the present task however, the effectiveness of the strategy change was limited, as the number of errors still increased as subjects became more fatigued.

Mental fatigue and motivation. As already mentioned in the introduction, there is a strong link between fatigue and motivation: fatigue may be considered a lack of motivation or drive to perform. Tops et al. (2004), have argued that fatigue may result from an ‘effort/reward imbalance’: as long as one feels that the invested effort in the end will result in sufficient rewards, one will continue working. However, when the perceived effort becomes to great and the reward no longer compares to this, the motivation to continue will dissipate and one will want to disengage from the task, feeling fatigued. When our subjects are motivated after 2 hours of task performance by the promise of a financial reward if they perform as well as they possibly can, we observed a number of changes in behaviour and brain activity.

As expected, inspection of the individual data of our subjects revealed that subjects did not all respond to the motivational instructions in the same manner. The instructions stressed both speed and accuracy. Subjects

however, almost never improved both their speed and their accuracy. Instead they chose a strategy for themselves to improve their performance, focussing on either speed or accuracy. Subjects that opted for improving their accuracy showed a remarkable increase in ERN/Ne amplitude, while subjects focussing on speed did not show this increase at all. Conversely, subjects who chose to improve their performance speed instead of their accuracy, exhibited an increase in CNV amplitude, while subjects that focussed on accuracy did not. This dissociation in ERP changes between the two groups of subjects reflects the strategy they chose to improve their performance. The subjects who focussed on accuracy responded to the motivation by the improving the monitoring of their actions (indicated by the increased ERN/Ne amplitude), so that they would produce less errors. The subjects who increased their response speed, however, once again prepared themselves better for the upcoming stimulus (reflected by the increase in CNV).

These findings have some important implications for the concept of mental fatigue. It appears that fatigued subjects, when motivated, could once again monitor their actions adequately. However in doing so, they had to sacrifice their response speed. On the other hand, fatigued subjects that were, when motivated, once again able to aptly prepare for the upcoming stimulus and thus increase their response speed appeared unable to monitor their actions in an adequate manner, resulting in increasing numbers of errors. These results suggest that there is a strong motivational component involved in the processes related to mental fatigue. However this is not the whole story: fatigued, but motivated subjects were unable to improve their performance in terms of both speed and accuracy, opting instead to improving on one measure by sacrificing the other. This implies that fatigue is more than an effort/reward imbalance and involves adaptive strategies to keep performance at an acceptable level under adverse internal circumstances.

In one of our recent studies (unpublished data), we obtained additional support for this notion. The design employed in this study was comparable to the present study, only this time subjects were motivated by rewarding accuracy more than speed. The results showed that under these circumstances, all fatigued subjects chose to improve their performance in terms of accuracy and not in terms of speed. This clearly indicates that fatigue indeed involves adaptive strategies that are, at least to some extend, under voluntary control of subjects.

Returning to the present study: post error slowing increased when subjects were motivated. Although there was no significant difference between the two groups, it appears that only subjects who focussed on accuracy slowed down after making an error. Immediate corrections also follow this pattern: subjects that focussed on accuracy corrected their actions more often when motivated, while subjects who focussed on speed did not. This fits well with the observed increase in ERN/Ne amplitude for these subjects. Because accuracy was most important for these subjects, they monitored their actions better, resulting in more immediate corrections and better strategic adaptation when performance fails in the form of slowing down after having made an error.

Of course, dividing our subjects into two groups results in rather small groups. This results in low statistical power and this is probably the reason that the differences between the groups on corrective behaviour failed to

reach significance. Thus, these data should not be taken as hard evidence, but more as suggestive for underlying processes.

The same caution should be taken concerning the N2 results. Although there is no significant difference in N2 amplitude before and after motivation, visual inspection seemed to indicate that N2 amplitude does increase after motivation. No difference between the two groups of subjects were found. This may suggest that ERN/Ne and N2 are differentially affected by motivation, and may not be viewed as being different measures for the same underlying process (Falkenstein et al., 1999). This is corroborated by fMRI studies (Kiehl et al., 2000; Braver et al., 2001; Ullsperger and von Cramon, 2001) that have shown distinct areas of the ACC to be activated by conflict (N2) and errors (ERN/Ne), suggesting potentially dissociable processes.

A possible mechanism. The finding that there is a relationship between fatigue, motivation/reward and action monitoring (ERN/Ne) may suggest a common neurophysiological mechanism. We suggest that the mechanism underlying mental fatigue may involve a reduction in activity of dopaminergic (DA) projection systems, comprising the basal ganglia (BG) and medial frontal structures such as the ACC. The BG have long been recognized as a structure of central importance for the motivational aspect of behaviour and reward (Nauta, 1986; Schulz, 2000) and neuro-imaging and ERP studies have suggested that the response monitoring functions of the ACC rely on DA input from the BG (Holroyd & Coles, 2002). According to the theory put forward by Holroyd and Coles (2002), a response monitoring system located in the BG produces error signals that activate the mesencephalic DA system, and the ERN/Ne is elicited by the impact of this phasic DA activity on the ACC (Holroyd & Yeung, 2003). The observation that the reduction of ERN/Ne amplitude when people become fatigued can, at least in part, be undone by increasing the rewards, suggests a role of the DA system in mental fatigue.

Indeed, Chaudhuri & Behan (2000) proposed that the symptoms of mental fatigue reported by their neurological patients may be due to a failure of the DA mediated functions of the BG. Moreover, based on animal studies, Nucleus Accumbens (Nac) DA has been proposed to be central in mental fatigue, by regulating the tendency to expend energy (Neill & Justice, 1981; Salamone et al., 1999; Szechtman et al., 1994). Salamone (1999) suggested that the Nac may be involved in some kind of effort/reward analyses, setting constraints on energy expenditure such that DA depletion in the NA biases behaviour towards low effort alternatives (Lorist & Tops, 2003). Moreover, Walton et al. (2003) found that rats with lesions to the ACC, preferably selected low cost – low reward response alternatives, while control animals continued to prefer the high cost – high reward alternatives. In the present study, subjects indeed shifted to a lower demanding strategy (increasing response latency, decreasing action monitoring) when they became fatigued. Although DA turnover was obviously not measured in the present experiment, the results do provide a valuable insight in the underlying mechanisms of mental fatigue that have so far remained elusive.

Summary

Subjects clearly exhibited impaired action monitoring and response preparation when they became fatigued. The observation that this impairment can be alleviated by increasing rewards, suggest that mental fatigue involves an effort/reward imbalance. Continuous task performance over such a prolonged period of time requires an increase in effort of subjects to keep performance at adequate levels. When the observed rewards become insufficient, subjects disengage from the task, feeling fatigued. When rewards are increased at the end of the task, effort and reward are once again balanced, resulting in better performance. The observation that subjects differed in the way they improved their performance after the motivation, suggests that performance under conditions of mental fatigue involves adaptive strategy changes to keep performance at acceptable levels.

Chapter 5
Subcomponents of the ERN/Ne Involved in Fatigue and Motivation

Adapted from:
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Subcomponents of the ERN/Ne Involved in Fatigue and Motivation

Extraction of covert sub-components from the error-related negativity (ERN/Ne) has shown transient frontal-central theta and delta rhythms locked to movement onset that differentiated errors from correct reactions. In the present study we found that the delta component of the ERN/Ne, as well as the error positivity (Pe), was most affected by fatigue and rewards: the delta component of the ERN/Ne and Pe amplitude decreased more strongly with time on task, compared to the theta component and was more enlarged when rewards were increased. Our data further suggests that the ERN/Ne together with the Pe form a complex that is best modelled by filtering the ERP in the delta frequency range. The results suggest that this delta component of the ERN/Ne and Pe reflects the motivational aspects of performance monitoring involving the dopaminergic system, providing us with additional evidence for the involvement of the dopaminergic projection systems in mental fatigue.

Introduction

The detection of errors has a role of central importance in the regulation of cognitive processes. The discovery of the neural correlates of error processing has inspired an abundance of research in recent years. In particular, event-related potential (ERP) studies have revealed a neural response to errors that has been termed the error-related negativity (ERN) or error negativity (Ne). The ERN/Ne consists of a large negative shift in the response locked ERP occurring after subjects have made an erroneous response (Falkenstein et al.,1990; Gehring et al., 1990). Peaking at 50-150 ms after response execution, the ERN/Ne is most prominent at fronto-central scalp positions (e.g., Fz, FCz and Cz). Localization with dipole localization algorithms has led most authors to conclude that the ERN/Ne is generated in the ACC (Dehaene et al., 1994). These findings are corroborated with results from fMRI studies (Ullsperger et al., 2003; Ridderinkhof et al., 2004) that show increased activation of the ACC during error trials, relative to correct trials.

In addition to the ERN/Ne, error trials elicit a clear positive going ERP component following the ERN/Ne: the error positivity (Pe). Although the functional significance of the Pe is far from clear, the Pe has been found to be more pronounced for perceived than for unperceived errors, and has therefore been proposed to reflect conscious error processing (Nieuwenhuis et al., 2001), or updating of error context (Leuthold and Sommer, 1999). The Pe was localized mainly in Brodman area 24 of the ACC (Herrmann et al., 2004), a structure that has been shown to be involved—among other things—in reward-based decision making (Bush et al., 2002), motivational valence assignment (Mesulam, 1990) and reward assessment (Knutson et al., 2000), all of which may well be involved in post-error processing and thus may contribute to the emergence of the Pe.

Recently, independent component analysis, spectral estimation and analysis of single trial EEG traces have been applied to extract covert sub-components from the ERN/Ne (Contreras-Vidal et al., 2004; Luu et al., 2004;

Yordanova et al., 2004). These analyses showed transient frontal-central theta (4-8 Hz), low beta (12-18 Hz) and delta (1.5-3.5 Hz) rhythms locked to movement onset that differentiated errors from correct reactions. Luu et al. (2001; 2004) showed that filtering of the response locked ERP shows that much of the energy of the ERN/Ne is in the theta band (57%), while the remaining energy was predominantly in the lower frequencies (i.e. delta). In addition, Luu et al. (2004) reported that most of the energy of the Pe is concentrated in the delta band (1-3 Hz).

Interestingly, delta- range unit activity has been recorded from subcortical structures known to play a prominent role in reward and motivation, including the nucleus accumbens (Leung and Yim, 1993) and dopamine (DA) neurons in the ventral tegmental area (Grace, 1995). Studies using dipole modelling place the site of delta generation in the anterior medial frontal cortex (Michel et al, 1992, 1993).

This fits well with a recent prominent theory on the ERN/Ne, the reinforcement learning theory of the ERN/Ne (Holroyd and Coles, 2002). These authors proposed a monitoring system located in the basal ganglia that predicts the outcome (positive or negative) of an action, on the basis of information received from the external environment and an 'efference copy' of the action. When events are better or worse than expected, the basal ganglia respond with error signals that are coded as phasic increases and decreases, respectively, of the tonic activity of the mesencephalic DA system (Schulz, 2002). These authors propose that a phasic decrease in activity of mesencephalic DA neurons following the commission of an error, disinhibits the apical dendrites of motor neurons in the ACC, producing the ERN/Ne (Holroyd and Yeung, 2003).

In our previous work, we have demonstrated that the amplitude of the ERN/Ne is reduced in mentally fatigued subjects (Boksem et al., in press; Lorist et al., 2005). In addition we found that increasing the rewards could reverse the effects of fatigue on ERN/Ne amplitude (Boksem et al., in press). We proposed that mental fatigue involves a reduction in activity of DA projection systems, comprising the striatum (part of the basal ganglia) and medial frontal structures such as the ACC, comparable to the monitoring system proposed by Holroyd and Coles (2002).

In the present study, we investigated whether the theta component and delta component of the ERN/Ne and Pe are differentially affected by mental fatigue and reward, providing us with additional evidence for our hypothesis of mental fatigue involving the DA neurotransmitter. Therefore, we had our subjects perform a flanker task for 2 hours, to induce fatigue, followed by 20 minutes of task performance in which subjects could earn extra money (the reward condition). Response locked ERPs were filtered to obtain the delta and theta frequency components of the error related ERP components (ERN/Ne en Pe).

Methods

Subjects. Twenty-four healthy participants (females), between 18 and 26 (M=20, SD=3.4) years of age, were recruited from the university population. They were paid for their participation and had normal or corrected-to-normal

vision. Three participants described themselves as being left handed. None of the subjects worked night shifts or used prescription medication. Written informed consent was obtained prior to the study.

Measures. We used a version of the Eriksen Flanker Task (Eriksen and Eriksen, 1974). On each trail, a five-letter string was presented. The central letter was the target, the remaining letters the flankers. The stimuli used for targets and flankers were the letters H and S. During the entire task a fixation mark was displayed 0.14 degrees above the target letter. On congruent trials the target letter was the same as the flankers (SSSSS of HHHHH); on incongruent trials the target letter differed from the flankers (SSHSS or HHSHH). 40% of the trials consisted of incongruent stimuli and 60% consisted of congruent stimuli. Congruent and incongruent trials were presented in random order.

The stimuli were presented on a 17 inch monitor. The letters were white against a black background and each letter had a height and width of 0.24 degrees visual angle. Eriksen and Eriksen (1974) showed that reaction times and error rates were highest when letters were presented close together. Therefore, we presented letters 0.05 degrees apart. The complete five-letter string had a width of 1.43 degrees visual angle.

In addition, flankers were presented 100 ms prior tot target onset to maximize the expected flanker compatibility effect (Kopp et al., 1996). Target and flankers disappeared simultaneously at the moment a response was made. In case no response was given; targets and flankers disappeared after 1200 ms. The interstimulus interval was 3s. Participants received six blocks of 400 trials. Each block had a total duration of 20 minutes.

After six blocks, participants received additional information by means of a text message on the screen: the reward condition. Participants were informed that they were about to begin the last part of the experiment and that they could earn points by responding correctly. For each correct response, participants would receive 10 points. For every incorrect response, participants would lose 20 points. Responding too slow, or not at all, resulted in no points. Finally, participants were told that their performance would be compared to other participants; the ten participants with the highest score would receive an extra monetary reward of 20 euros. After this information, a last block consisting of 388 trails was presented. After every 97 trials participants received feedback about the number of points they scored. The duration of the complete task was 2 hours and 20 minutes.

Procedure. Subjects were instructed to abstain from alcohol 24 hours before the experiment and from caffeine containing substances 12 hours before the experiment. After arrival at the laboratory at 12.00 hours, the subjects surrendered their watches. They had no knowledge of the length of the session other than that it would not last beyond 18.00 hours. Before the start of the experiment, subjects were given written task instructions where after they were trained in performing the task, for 15 minutes. Following the application of the electrodes, subjects were seated in a dimly lit, sound-attenuated, electrically shielded room at 1.20 m from the screen. Their index fingers rested on touch-sensitive response boxes. Subjects were instructed to

lift their finger from the response button as quickly as possible when a target was presented, maintaining a high level of accuracy.

Electrophysiological recording and data reduction. The electroencephalogram (EEG) was recorded using 4 Sn Electrodes attached to an electro cap (Electro-Cap International), from positions Fz, FCz, Cz and Pz. All electrodes were referenced to linked earlobes. The electro-oculogram (EOG) was recorded bipolarily from the outer canthi of both eyes and above and below the left eye, using Sn electrodes. Electrode impedance was kept below 5kΩ. EEG and EOG were amplified with a 10s time constant and a 200 Hz low pass filter, sampled at 1000 Hz, digitally low pass filtered with a cut-off frequency of 70 Hz, and online reduced to a sample frequency of 250 Hz.

All ERP analyses were performed using the Brain Vision Analyzer software (Brain Products). ERPs were averaged off-line. The data was further filtered with a 0.53 Hz high-pass filter and a slope of 48 dB/oct and a 40 Hz low-pass filter with a slope of 48 dB/oct. Out of range artefacts were rejected and eye movement artefacts were corrected, using the Gratton, Coles and Donchin method (Gratton, Coles and Donchin, 1983). A baseline voltage over the 200 ms interval preceding the response was subtracted from the averages.

To investigate the frequency components of the ERN/Ne and Pe, we further filtered our data. We isolated the theta component of the ERN/Ne and Pe by using a 5 Hz high-pass filter with a slope of 48 dB/oct and a 12 Hz low-pass filter, also with a slope of 48 dB/oct. To isolate the delta component, we used a 1 Hz high-pass filter and a 4 Hz low-pass filter, both with a slope of 48 dB/oct.

Data Analysis. To investigate effects of mental fatigue and reward, the data were divided into seven time intervals of 20 minutes each. Data were subjected to SPSS GLM for repeated measurements, using the ε-adjustment procedure recommended by Quintana and Maxwell (1994). To further investigate observed effects, polynomial, repeated and simple contrasts were analysed. When the main analysis indicated a significant interaction ($p<.05$) between factors, follow-up analyses were performed, adjusting error rates according to Bonferroni.

Performance. For the different stimulus conditions mean reaction times (RTs) were calculated. Correct reactions occurring within a 150-1000 ms interval after stimulus presentation were considered as hits. The percentage of false alarms and misses were also determined. Because misses were very rare, we will focus here on hits and false alarms. To investigate strategic performance changes after error detection, we also analyzed RTs on trials following an error or a correct response (i.e. Post error slowing; Rabbit, 1966).

ERPs. Mean ERN/Ne and Pe amplitude were calculated at Cz, where visual inspection showed these components were maximal. The averaging epoch for the ERN/Ne was between 28 ms and 100 ms post response. The averaging epoch for the Pe was from 164 ms to 360 ms post response. Data were subjected to a repeated measurements GLM with the factor time on task (seven levels). To investigate differences in ERN/Ne and Pe between delta en theta frequency, data were subjected to a separate GLM with the factors time on task (seven levels) and filter (delta or theta, two levels).

EEG Spectral Power Analysis (qEEG). In addition to the ERP analysis, we performed a spectral analysis on the data. Task intervals were segmented into 50% overlapping, 5.12 s segments. After artefact detection and ocular correction as described above, the data was submitted to a fast Fourier transform, using a 100% Hanning window. After averaging, power was determined in two separate frequency bands for each subject, electrode and time on task interval. Average power in these frequency bands was log transformed (ln) for normalization (Gasser et al., 1982). We tested for effects in the delta frequency band (1-4 Hz), and the theta frequency band (5-12 Hz), at Cz.

Results

Performance. *RT.* Analysis revealed a quadratic polynomial contrast between the seven time on task intervals, $F(1,23)=14.45$, $p<.001$, indicating an increase in RTs in the first six intervals (from 464 ms to 514 ms), while RTs decreased in the reward condition (to 469 ms). As expected, RTs were longer on incongruent trials, compared to congruent trials (515 vs. 458 ms), $F(1,23)=241.55$, $p<.001$. There was an interaction between time on task and congruency in interval 6 vs. 7, $F(1,23)=5.97$, $p<.05$: RTs in congruent trails decreased more compared to incongruent trials.
Errors. The number of errors subjects committed changed with time on task, $F(6,138)=4.39$, $p<.01$. This was also revealed to be a quadratic polynomial contrast, $F(1,23)=7.75$, $p<.05$, indicating an increase in errors in the first 6 intervals (from 6.4% to 9.4%), and a decrease from interval 6 to 7 (to 7.1%). Repeated contrasts showed that the changes with time on task were in particular present in interval 1 vs. 2, $F(1,23)=8.39$, $p<.01$ and interval 6 vs. 7, $F(1,23)=7.06$, $p<.05$. As expected, more errors were made on incongruent trials (12.7%), compared to congruent trials (3.9%), $F(1,23)=53.85$, $p<.001$.
Post Error Slowing. Subjects responded significantly slower on trails following a trial in which they made an error, compared to trials following a correct response, $F(1,23)=15.53$, $p<.001$. This post error slowing remained unchanged with time on task.

ERPs. *ERN/Ne.* Amplitude of the ERN/Ne decreased with time on task and increased in the reward condition, as indicated by the quadratic polynomial contrast, $F(1,22)=32.96$, $p<.001$. Repeated contrasts revealed that this effect was predominantly present in interval 1 vs. 2, $F(1,22)=12.05$, $p<.005$, interval 3 vs. 4, $F(1,22)=14.18$, $p<.005$ and interval 6 vs. 7, $F(1.22)=12.00$, $p<.005$.

What is striking in the filtered ERN/Ne data is that the delta component of the ERN/Ne wave is much more reduced in amplitude with time on task compared to the theta component of the ERN/Ne wave, indicated by the interaction between time on task and frequency band, $F(6,138)=3.25$, $p<.01$: Repeated contrasts showed that the delta component is much more reduced in amplitude from interval 1 to 2 compared to the theta component, $F(1,23)=8.61$, $p<.01$. Conversely, the amplitude of the delta component increased more from interval 6 to 7 compared to the theta component, $F(1,23)=7.08$, $p<.05$.

Pe. Different from the ERN/Ne, the Pe showed a cubic increase with time on task, F(1,23)=5.65, p<.05, reflecting a small increase from interval 1 to interval 6 and a subsequent larger increase from interval 6 to 7, although a repeated contrast showed only a marginally significant difference between interval 6 and 7, (F(1,23)=3.31, p=.089. Simple contrasts revealed that intervals 3 to 6 differed from interval 1, F(1,23)=3.77-9.59, p<.05, reflecting an increase in Pe when subjects became fatigued.

Analysis of the filtered Pe data showed that the time on task effects were entirely caused by amplitude changes in the delta component of the Pe, indicated by the time on task interaction with frequency band, F(6,138)=5.04, p<.001 (quadratic, F(1,23)=21.52, p<.001). The delta component changed in amplitude with time on task, F(6,138)=5.28, p<.001. Further analysis revealed a quadratic polynomial contrast, F(1,23)=18.19, p<.001, suggesting a decrease from interval 1 to 6, and a subsequent increase from interval 6 to 7. A simple contrast, however, did not reveal a significant difference between interval 1 and interval 6, while a repeated contrast did reveal an increase in amplitude of the delta component of the Pe wave from interval 6 to 7, F(1,23)=25.08, p<.001.

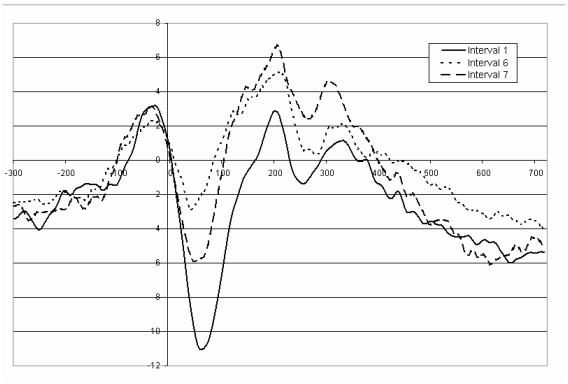

Figure 5. 1. *Unfiltered ERN/Pe.*

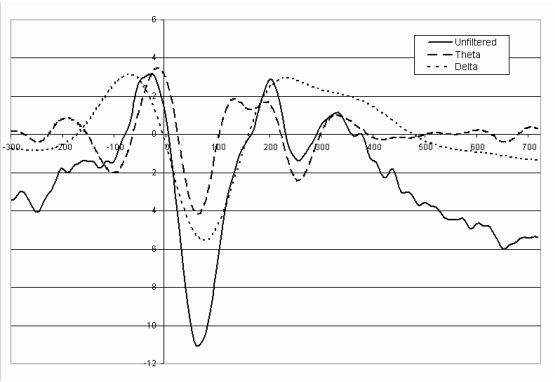

Figure 5.2. *Unfiltered, Theta and Delta components of ERN and Pe in interval 1.*

Performance and ERN/Ne. Analyses of the filtered ERN/Ne data showed that the amplitude of the theta component of the ERN/Ne wave, was positively correlated with post error slowing, r=.49, p<.05. Subjects with a larger amplitude of the theta component of the ERN/Ne slowed down more after committing an error. No such correlation was found for the delta filtered ERN/Ne or the unfiltered ERN/Ne.

qEEG. *Delta.* Power in this frequency band changed with time on task in a quadratic fashion, F(1,23)=14.05, p<.001, indicating an increase in the first six intervals, and a decrease in power from interval 6 to interval 7.
Theta. Similarly, power in the theta band increased in the first six intervals, and decreased after motivation, indicated by the quadratic effect of time on task, F(1,23)=13.51, p<.001.

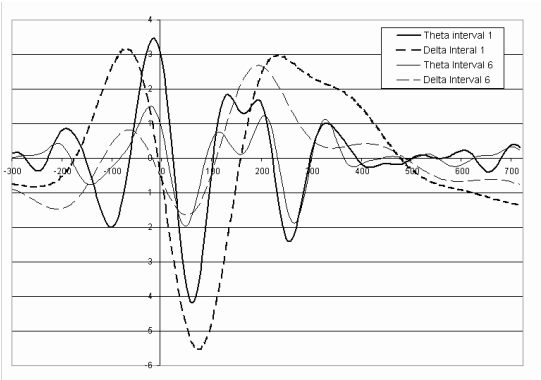

Figure 5.3. *Theta and Delta ERN/Pe in interval 1 and interval 6.*

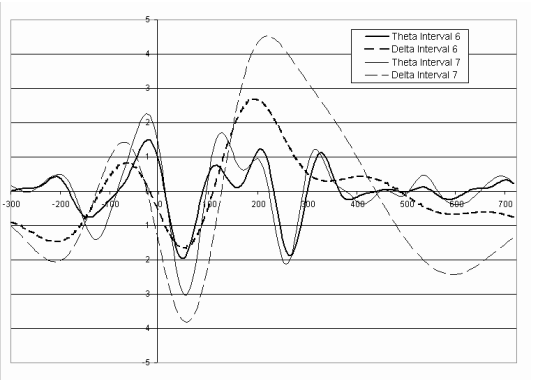

Figure 5.4. *Theta and Delta ERN/Pe in interval 6 and interval 7.*

Discussion

Performance was clearly impaired with time on task: RTs increased during the two hours of task performance, while accuracy decreased. These effects were reversed by rewarding our subjects. In addition, ERN/Ne amplitude decreased with time on task and increased with reward. According to the theory put forward by Holroyd and Coles (2002), the ERN/Ne is elicited by the impact of this phasic DA activity on the ACC (Holroyd & Yeung, 2003). Consistent with observations by Chaudhuri and Behan (2000), who noted that reduced DA activity is common in many disorders involving mental fatigue, our observation that the reduction of ERN/Ne amplitude when people become fatigued can be reversed by increasing the rewards, suggests that the mechanism underlying mental fatigue may involve a reduction in activity of DA projection systems, comprising the basal ganglia and medial frontal structures including the ACC (Lorist et al., 2005; Boksem et al., submitted).

Yordanova et al. (2004) showed that a sub component of the ERN/Ne that was in the delta frequency range was most specific for errors and is elicited by a medial frontal system that is involved in performance monitoring. Importantly, delta activity has been proposed to be elicited by DA activity originating from midbrain structures that are involved in reward-mediated behaviour (Alper, 1999).

The present data shows that it is this delta component of the ERN/Ne and Pe that was most affected by fatigue and the subsequent increased rewards: the delta components of the ERN/Ne and Pe amplitude decreased more strongly with time on task, compared to the theta components and was more enlarged when rewards were increased. Importantly, the observed changes in response locked delta were not the result of an overall change in delta band power. Delta power even showed a pattern of results exactly opposite to what we found for the response locked delta in the ERN/Ne and Pe latency range: delta power increased with time on task in the first six intervals and decreased from interval six to interval seven.

These findings corroborate our hypothesis that a reduction in the activation of the DA projection systems may be involved in mental fatigue. Response locked delta was reduced with time on task, which has been related to a reduction in motivational processes (Reinke et al., 1994), consistent with our observation of the increased response locked delta after

increasing the rewards. We propose that this delta component of the ERN/Ne and Pe reflects the motivational aspects of performance monitoring, that has been suggested by several authors (e.g., Gehring et al., 1990, Pailing and Segalowitz, 2004, Ridderinkhof, 2004), and that this delta activity reflects the involvement of the DA system in performance monitoring.

Our data further suggests that the ERN/Ne together with the Pe form a complex with a common functionality (i.e. performance monitoring or conflict detection; Van Veen and Carter, 2002), that is best modelled by filtering the ERP in the delta frequency range. These findings may explain the inconsistent results in the literature regarding the functionality of the Pe: Fig. 5.3 shows that activity in the theta range causes a negative peak in the Pe latency range. This negativity may interfere with the positivity that results from the response locked delta activity, obscuring the Pe. Here, we found a decrease in unfiltered ERN/Ne amplitude with time on task, while a small increase in the unfiltered Pe was observed (Fig. 5.1). However, Fig 5.3 presents a completely different picture: the changes in amplitude of response locked ERP components with time on task are largely the result of a decrease in amplitude of response locked delta activity. The reverse was true when the reward condition was compared with the final fatigue interval: response locked delta increased, especially in the Pe latency range (Fig. 5.4). We propose that the response locked delta activity that occurs after an erroneous response, reflects the activity of the DA projection system that has been proposed to result from an error in reward prediction (Holroyd and Coles, 2002).

Consistent with findings by other researchers (Luu and Tucker, 2001; Luu et al., 2004; Yordanova et al., 2004; Bernat et al., 2005), we also observed a sub-component of the ERN/Ne that was within the theta frequency range. Yordanova et al. (2004) suggested that this response-synchronized theta activity may subserve a separate system that is involved in movement regulation. Luu and Tucker (2001) proposed that the ERN/Ne reflects theta coordination of the broader activity of the action-regulation circuitry which includes the ACC. The finding that a source within the ACC can generate the frontal midline theta in EEG supports this notion (Pizzagalli et al., 2003). They further suggest that these action regulation processes are regulated by the Acetylcholine (ACh) neurotransmitter system, as the primary pacemaker of theta regions like the ACC, appears to be cholinergic input from the septohippocampus (Chrobak and Buzsaki, 1998).

Our data showed that the ERN/Ne and Pe, as observed in the ERP, are composed of overlapping activities in delta and theta frequency ranges. While response locked delta reflects the activity of the DA system involved in the motivational aspects of performance monitoring, response locked theta reflects inhibitory processes involved in motor regulation (Yordanova et al., 2004), probably mediated by the ACh neurotransmitter (Luu et al., 2001). These two systems may interact in the process of performance monitoring: cholinergic theta activity seems important in withholding responses that were previously associated with reward (Gabriel, 1990; Pribram, 1991).

The present results provide some support for this: although the largest changes in ERN/Ne amplitude with time on task and motivation were observed in the delta frequency range, ERN/Ne amplitude in the theta frequency also changed. In our previous work (Lorist et al., 2005; Boksem et

al., submitted), we have shown that the reduction in ERN/Ne amplitude with time on task was accompanied by a decrease in post error slowing. Although in the present study, we were unable to replicate our effects of time on task on post error slowing, we did observe a positive correlation between post error slowing and theta activity in the ERN/Ne. As post error slowing results from inhibition of fast responses, this indeed suggests that the ACh mediated theta activity in the ERN/Ne is related to the inhibitory aspects of movement regulation, which interacts with the DA mediated motivational aspects of performance monitoring that are reflected in the delta frequency. Performance monitoring appears to be critically dependent on the interplay between these to processes, reflected in the ERN/Ne and Pe.

Chapter 6
General Discussion

General Discussion

The studies presented in the preceding chapters investigated two distinct, but related issues concerning the phenomenon of mental fatigue. The first was whether mental fatigue selectively impairs cognitive control processes, as opposed to affecting cognitive processes requiring little conscious control. The second issue concerned the apparent relationship between fatigue, motivation and reward. Here we will discuss the main results and implications of these studies.

Mental Fatigue. In the experiments described in this thesis, we induced mental fatigue in our subjects by making them perform cognitive tasks for prolonged periods of time. Before reviewing any changes in cognitive functioning and related brain activity resulting from time on task, we had to first make sure that our fatigue manipulation (i.e. time on task) was successful in fatiguing our subjects.

Evidence for this came from our observation that subjects reported increased aversion to continue task performance with time on task (chapter 2). According to Holding (1983) and Hockey (1997), aversion to invest further effort into task performance is the most reliable characterization of mental fatigue. In this view, the observed increase in subjective levels of aversion against continued performance indeed indicate that subjects indeed became more fatigued during task performance.

EEG spectral power provided additional support. In chapter 2, we observed an increase in alpha, theta and beta power during three hours of task performance, indicating a clear increase in fatigue. Importantly, the observed increase in lower alpha power was shown to be significantly correlated with the increase in subjectively reported levels of fatigue. Although we reported data on subjective levels of fatigue and background EEG only in chapter 2, we found this to be a very consistent finding in our experiments. Together, these findings suggest that we were able to induce mental fatigue by using time on task.

In all our experiments, this increase in fatigue was associated with a clear decrement in task performance. Subjects became slower in responding, and the number of mistakes made in each of the experiments increased. However, it is inherently difficult to infer effects on cognitive processes from behavioural measures. Therefore, we will now turn to the effects of fatigue on brain activity, to gain more insight in the cognitive processes involved.

Mental Fatigue: Cognitive Control. In the introduction, we distinguished two aspects of cognitive control: the evaluation of current behaviour, and the implementation of control. We found effects of mental fatigue on both of these aspects of control. The monitoring and evaluation of behaviour is a primary function attributed to the ACC and is reflected in the ERN/Ne and N2 ERP components. In chapters 3, 4, and 5, we obtained convincing evidence that this monitoring function is impaired in fatigued subjects: ERN/Ne and N2 components were reduced when subjects became fatigued.

When performance is no longer appropriately evaluated, this should have significant effects on the implementation of control, which was exactly what we found. Subjects corrected their erroneous responses less often and

post error slowing was reduced in fatigued subjects. Moreover, we showed that subjects prepared themselves less well for the coming response and had increasing difficulties in sustaining attention and ignoring irrelevant information (i.e. increased distractibility), indicating that the top-down influence of the PFC on sensory and motor areas was impaired.

Together these data clearly suggest a problem in the engagement of cognitive control in fatigued subjects. But does this mean that fatigue is a psychophysiological state that inevitably occurs after a prolonged period of work and which only function would be to make people function on a lower level, making them distractible and error prone? In our view, this simplistic conceptualization of fatigue does not do justice to the important function that fatigue has in everyday performance. We propose that fatigue can best be considered as an adaptive signal that the present behavioural strategy may no longer be the most appropriate, because it continues to demand effort while substantial effort has already been invested and the goal evidently has not yet been achieved. Fatigue may provide the cognitive system with a signal that encourages the organism to lower present goals and/or seek lower effort alternative strategies.

Our data presents some evidence for this view. In chapter 3 we argued that, while response monitoring decreased, subjects sacrificed speed in order to maintain accuracy levels. Slowing down may allow a more complete accumulation of evidence concerning the correct response, thus preventing premature incorrect reactions. The general slowing observed with time on task thus might be a dynamic adaptation allowing subjects to compensate for the reduction in performance efficiency due to prolonged task performance, and can be considered a functional strategy to cope with sub optimal internal states (i.e., mental fatigue). The same kind of strategy change was observed in chapter 4, where subjects seemed to have switched from a controlled, effortful strategy, requiring the detection of conflict and the active monitoring of performance, to a more passive strategy in which they, again, increased their overall response latency.

Chapter 4 further revealed that subjects did not all respond to the motivational instructions in the same manner. The instructions stressed both speed and accuracy. Subjects however, almost never improved both their speed and their accuracy. Instead they chose a strategy for themselves to improve their performance, focussing on either speed or accuracy. Subjects that opted for improving their accuracy showed a remarkable increase in ERN/Ne amplitude, while subjects focussing on speed did not show this increase at all. Conversely, subjects who chose to improve their performance speed instead of their accuracy, exhibited an increase in CNV amplitude, while subjects that focussed on accuracy did not.

This dissociation in ERP changes between subjects reflects the strategy they chose to improve their performance. The subjects who focussed on accuracy responded to the motivation by the improving the monitoring of their actions (indicated by the increased ERN/Ne amplitude), so that they would produce less errors. However, the subjects who once again prepared themselves better for the upcoming stimulus (reflected by the increase in CNV), managed to increase their response speed.

Together, these findings demonstrate that fatigue does not just involve a general deterioration of performance. Instead, adaptive strategy changes

are invoked by fatigued subjects that entail minimising the amount of effort that has to be invested in task performance, while keeping performance at acceptable levels.

Having said this, these strategy changes appear to have been only partly effective, as performance always still deteriorated in some way or another. Might it be the case that goal directed behaviour is temporarily suspended when subjects become fatigued (i.e. goal neglect), so that performance is maintained at acceptable levels, but nothing more? Here we argue that this probably would be an over simplification. As already mentioned in the introduction, integration of immediate needs, like rest, is essential for realizing long term goals. Ignoring these short term goals would have major negative consequences for other, less immediate goals. When people are fatigued, these long term goals suffer more and more competition form these short term goals, that are directed at maintaining general wellbeing. In this view, fatigue may not involve an impairment of goal directed behaviour, but instead involve a change in the goals towards which behaviour is directed; from long term goals to more immediate goals.

Mental Fatigue: Costs and Benefits. This brings us to the second issue presented in this thesis, the relationship between the concepts of fatigue, motivation and reward. We proposed that mental fatigue involves a motivational evaluation of current behaviour; the feeling of fatigue may result from a subconscious analysis of costs and benefits of expending energy. The ACC and BG (the NaC in particular) have been shown to be key structures that enable the brain to perform such analyses (Walton et al., 2002; Salamone et al., 1994). As the ERN/Ne is proposed to result from activity in both BG and ACC, we propose that ERN/Ne amplitude reflects this process of evaluation of current behaviour in terms of costs and benefits (Bush et al., 2000). Here we showed that, while ERN/Ne amplitude decreased with fatigue, it recovered after rewards for continuing task performance were increased. This increase in ERN/Ne amplitude was accompanied by a clear improvement in performance.

Thus, mental fatigue may involve a motivational evaluation regarding the costs and benefits of expending energy. This results in the observed change in strategy of fatigued subjects to lower demanding strategies in terms of effort, similar to the change in performance of ACC/NaC lesioned rats reported by Walton et al. (2002) and Salamone et al. (1994).

Mental Fatigue: The Model. Our findings suggest an architecture of mental fatigue in which the decision whether or not to engage in a particular behaviour is strongly dependant upon the balance between the perceived rewards and the perceived effort required to obtain that reward. In Figure 6.1, we present a model of our account of mental fatigue.

First, goals are selected from the potential goals that the current environment supports. This selection is probably based on the relative value of rewards associated with each goal. Now, the organism evaluates whether the available energetical resources are sufficient and if the required effort compares to the expected rewards. When this evaluation turns out to be positive, the organism engages in the required behaviour. While the organism is engaged in this particular behaviour, performance is continuously

evaluated. When performance deviates from the performance that is required to achieve the selected goal, a signal is generated to exert more control over behaviour. At the same time, continued implementation of control and task performance causes energy to decrease and the perceived effort to increase.

This results in an evaluation of current performance that becomes more and more negative with time on task, resulting in a reduced tendency to continue with task performance. In addition, performance goals are increasingly deactivated when effort continues to exceed rewards, which leads the organism to lowering the present goal to one that requires less effort, or even changing goals altogether when the rewards associated with another goal provided by the environment are perceived to correspond better to the energy available and the effort required for attaining that goal. By increasing the rewards associated with current task performance, as we did in chapters 4 and 5, the balance between effort and reward is restored, resulting in a more positive evaluation of current behaviour and enabling subjects to overcome work related costs and continue task performance.

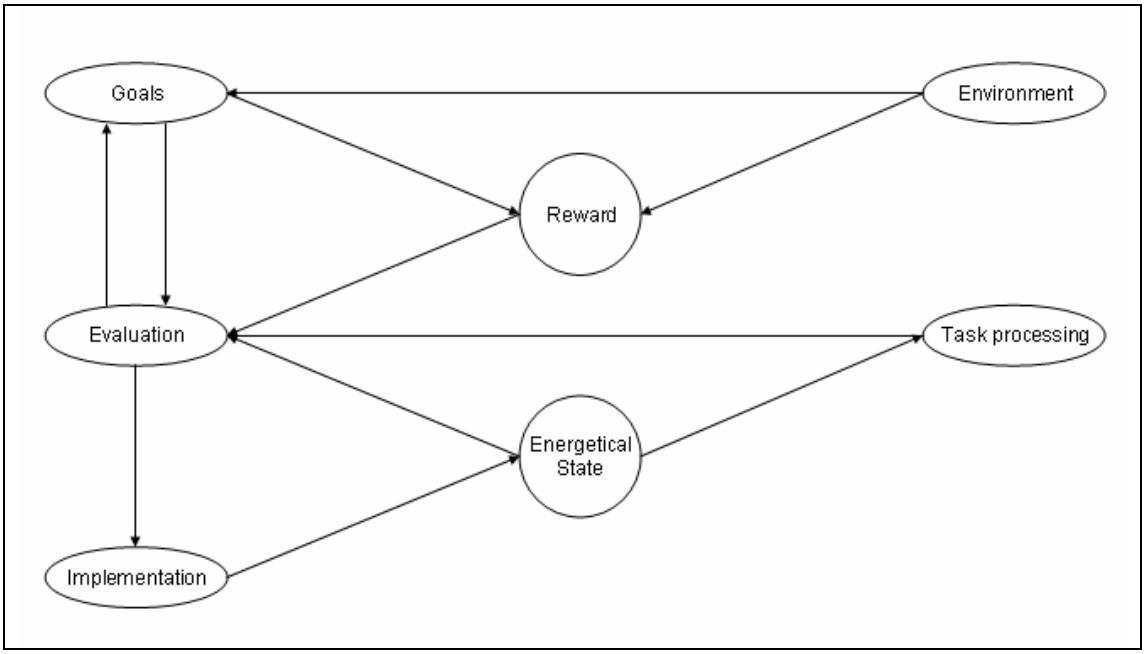

Figure. 6.1. Mental Fatigue, The Model.

Mental Fatigue: The Dopamine Connection. The data reported in this thesis, provide initial support for the notion that mental fatigue involves impaired DA-mediated mechanisms of cognitive control, thereby providing the initial contours of a neurocognitive theory of mental fatigue.

The decision whether or not to expend energy relies heavily on the release of DA in the NaC and its connections with the ACC. As the ERN/Ne is proposed to be elicited by the impact of phasic DA activity on the ACC, our finding that the ERN/Ne is reduced with mental fatigue suggests that the observed strategy change to lower effort alternatives results from reduced DA activity in these mesencephalic dopaminergic projection systems comprising the striatum and frontal cortical structures, in particular the ACC.

Our finding that the effects of fatigue can, at least in part, be reversed by increasing rewards, corroborate this interpretation. BG DA has long been recognized as being of central importance to the motivational aspect of

behaviour and reward (Schulz, 2000). The increased rewards may result in an increase of DA activity that may increase the propensity to expend energy on higher effort demanding behavioural strategies.

Moreover, in chapter 5 we found that it is the DA related delta component of the ERN/Ne that was most affected by fatigue and the subsequent increased rewards, corroborating our hypothesis that a reduction in the activation of the dopaminergic projection systems may be involved in the process of mental fatigue. Although DA turnover was obviously not measured in the present experiments, the results do provide a valuable insight in the underlying mechanisms of mental fatigue that have so far remained elusive.

Before we continue, we would like to point out the functionality of fatigue, which, at first glance may only seem debilitating, However, it would be highly unlikely that such a common phenomenon should not have a useful adaptive function. We propose that the reduced influx of DA into the PFC that occurs with prolonged task performance is adaptive in the sense that it signals the need to change the ongoing behaviour in such a way to promote energy conservation or change the focus of attention to other, perhaps more rewarding behaviours. In everyday life, it is rarely useful to keep attention directed at one particular goal for prolonged periods of time, while rewards remain forthcoming. In this view it may even be considered adaptive that the reduced influx of DA in the PFC results in increased distractibility (i.e. goals become less activated, as suggested in our model in Figure 6.1), which would promote exploratory behaviour in search of other, perhaps more rewarding goals.

Mental Fatigue: A Neurochemical Balance. Although the focus in this thesis has been on the involvement of the DA system in mental fatigue, it is important to consider that one neurotransmitter system never works in a vacuum. For every faculty that emerges, multiple brain structures and neurotransmitter systems have to work in concert. Focussing on the DA system enables us to provide a coherent framework of mental fatigue, but at the same time may present a picture that is to limited in scope.

For example, Bailey and colleagues (1993) have shown that fatigue during prolonged exercise in rats is associated with not only a reduced DA concentration in the brain, but also an increase in serotonin (5-HT) concentrations. Other evidence has also shown an inverse relationship between DA and 5-HT in certain brain areas. This has led several authors (e.g. Newsholme et al., 1987; Davis et al., 2000) to propose that 5-HT may have a role as a possible mediator of mental fatigue.

While the DA projections are involved in behaviour that is aimed at the acquisition of rewards and the expenditure of energy, the 5-HT projections are involved in behaviour that is primarily aimed at energy conservation and withdrawal from energy demanding activities. During prolonged activity, the level of free Triptophane (a precursor to 5-HT) in the blood increases, ultimately resulting in increased 5-HT levels in the brain. This increase in 5-HT is known to have effects on the perception of effort and therefore may provide the evaluative system in the brain with information on the amount of energy that is being spent on the current behaviour. A low ratio of brain 5-HT to DA

may result in increased motivation for action, while high ratios may promote a reduction in activity (Davis et al., 2000).

These ratios of 5-HT and DA may constitute the neurochemical substrate of the effort/reward (im)balance that we propose is central to mental fatigue. During prolonged activity, the level of 5-HT in the brain rises, increasing the perceived effort necessary to continue task performance. This increase in 5-HT may inhibit the DA system, resulting in a reduced motivation to expend energy and increased feelings of fatigue. Indeed, Chaouloff et al. (1989) found increases in 5-HT in the rat midbrain and striatum following 90 minutes of treadmill running. In addition, Bailey (1993) found that DA concentrations in the midbrain and striatum of fatigued rats were reduced, while 5-HT concentrations were elevated.

The 5-HT that builds up during prolonged activity may inhibit the DA system (Bailey et al., 1993; Chaouloff et al.,1989), thus shifting the balance between effort and rewards towards promoting withdrawal from the current activity or changing strategies to lower effort alternatives. Conversely, increasing the rewards would result in elevated levels of DA that may inhibit 5-HT synthesis and metabolism, shifting the balance between efforts and rewards toward energy expenditure and higher effort, higher reward strategies.

Beyond Control. Choosing courses of action based on an analysis of costs and benefits is highly adaptive and efficient, but only when one is free to choose between various action alternatives (i.e. the situation is controllable). In everyday life, especially in the work environment, this control over the situation is often lacking. High workload, high demands on cognitive functions, and fixed production quotas limit the possibilities of employees to choose lower effort alternatives when they perceive effort to become to great compared to the perceived rewards. In other words, they have to override the signal of imminent fatigue that results from an imbalance of perceived costs and benefits.

The ability to override this signal is in itself adaptive as well, for example in emergency situations, in which case the importance of the emergency outweighs the possible costs. However, overriding this signal for prolonged periods of time comes at a price in the form of stress, which in time can lead to damage (McEwen and Wingfield, 2003). This damage takes the form of chronic elevated levels of 5-HT and reduced DA activity, resulting in a permanent decrease in the motivation to expend energy and a withdrawal from the work environment. This may be fundamental to disorders that are characterized by long term fatigue, like burn-out (see Tops et al. (2004) for a more detailed discussion).

Samenvatting

Samenvatting

Mentale vermoeidheid is een psychische klacht die men steeds vaker tegen komt. Deze toename heeft verschillende oorzaken, maar een belangrijke oorzaak is zeker dat het dagelijks werk van mensen in steeds mindere mate fysiek van aard is, terwijl het mentale aspect van arbeid steeds belangrijker wordt. Kijk alleen maar eens naar de toename van het aantal managers, maar ook naar de toename in de mate van automatisering in het hedendaagse productieproces. Dit heeft als neveneffect dat veel mensen vermoeidheidsklachten hebben. In Nederland rapporteert de helft van de vrouwelijke beroepsbevolking en een derde van de mannen dergelijke klachten.
Er is echter nog maar weinig onderzoek gedaan naar de effecten van mentale vermoeidheid op prestaties. Ook de fysiologische basis van vermoeidheid is nog grotendeels onverkend terrein. In dit proefschrift hebben we onderzocht welke aspecten van informatieverwerking en taakgedrag het sterkst beïnvloed worden door mentale vermoeidheid, stellen we theorieen voor omtrent wat er verandert in ons lichaam wanneer we ons vermoeid voelen, en zetten we uiteen wat nu eigenlijk de functie is van dergelijke veranderingen.

Wat het meest in het oog springt bij studies naar de effecten van vermoeidheid is dat mensen steeds minder doelgericht handelen: het evalueren en reguleren van eenvoudige, geautomatiseerde handelingen verloopt steeds minder efficiënt. Psychologen noemen dit een verminderde “cognitieve controle”. Cognitieve controle stelt ons in staat om aangeleerde gedragspatronen, die min of meer automatisch verlopen, bij te sturen of te stoppen. Dit weerhoudt ons ervan om niet simpelweg op alle prikkels uit de omgeving te reageren, maar stelt ons in staat ons gedrag in overeenstemming te brengen met onze lange termijn-doelstellingen.
Uit de experimenten in dit proefschrift blijkt dat vermoeide proefpersonen hun gedrag inderdaad minder goed evalueren. Dit resulteert niet alleen in een toename in het aantal gemaakte fouten, maar ook in een afname in het bijsturen van het gedrag nadat een fout gemaakt is: fouten worden minder vaak gecorrigeerd. Ook is het voor vermoeide proefpersonen erg moeilijk om hun aandacht bij de taak te houden; ze lijken verhoogd afleidbaar.
Deze bevindingen suggereren inderdaad een probleem in de cognitieve controle. Het is echter belangrijk om ons te realiseren dat vermoeidheid niet slechts een vervelend fenomeen is dat er voor zorgt dat mensen verhoogd afleidbaar worden en meer fouten gaan maken. In tegendeel; uit onze experimenten blijkt dat vermoeidheid gezien kan worden als een adaptief signaal, dat ons er toe moet bewegen om van strategie te veranderen om op een acceptabel niveau te kunnen blijven functioneren. Het nadeel van het intensief evalueren en reguleren van gedrag is namelijk dat het erg veel energie kost. Als mensen lang bezig zijn met een bepaalde taak, raakt deze energie langzaam maar zeker op, waardoor het steeds minder goed mogelijk wordt om deze cognitieve controle toe te passen.
Wat we zien in onze experimenten is dat mensen van strategie veranderen als ze vermoeid raken. In het algemeen schakelen mensen over op een strategie die hen minder energie kost: in plaats van het actief evalueren en reguleren van hun gedrag, gaan vermoeide mensen hun reactiesnelheid terug

brengen. Door langzamer te reageren, nemen ze meer tijd om informatie tot zich te nemen, wat hen beter in staat stelt om de juiste respons te selecteren. Het is zelfs zo dat de gekozen strategie afhankelijk is van individuele voorkeuren van proefpersonen. Proefpersonen die veel waarde hechten aan het maken van weinig fouten, proberen het aantal fouten op peil te houden, wat ten koste gaat van hun reactiesnelheid. Omgekeerd proberen mensen die veel waarde hechten aan snelheid, hun reactietijd laag te houden, wat ten koste gaat van het aantal fouten dat zij maken.

Het is echter een misverstand om te veronderstellen dat vermoeidheid er toe leidt dat mensen hun doelgerichte handelen tijdelijk stop zetten. Dit zou vanuit een functioneel evolutionair oogpunt ook verre van adaptief zijn: een organisme dat zijn doelen negeert, is ten dode opgeschreven. Het is veeleer het geval dat mensen hun doelen veranderen, dan dat zij deze doelen helemaal uit het oog verliezen. Namelijk, vermoeide mensen lijken niet meer te werken voor lange termijn-doelen, maar zich juist te richten op meer korte termijn-doelen, zoals de behoefte aan rust. Integratie van deze korte termijn-doelen in de sturing van gedrag is natuurlijk essentieel voor het bereiken van de lange termijn-doelstellingen: het organisme zou omkomen van honger, dorst en uitputting voordat welk langer termijn doel dan ook bereikt zou kunnen worden.
In dit proefschrift stellen we daarom voor dat al ons gedrag berust op een impliciete afweging tussen de kosten en de baten van een bepaalde handeling. Wegen de kosten (in termen van de hoeveelheid energie die de handeling zal vergen) op tegen de baten (in termen van het te bereiken voordeel voor het organisme), dan zal het organisme in actie komen. Is dit niet het geval, dan zal het organisme kiezen voor een alternatief gedrag dat wellicht meer op zal leveren.

Onze theorieën over mentale vermoeidheid zijn gebaseerd op experimenten die in dit proefschrift worden beschreven en die een afname van de “Error Related Negativity” (ERN of Ne) laten zien wanneer mensen vermoeid worden. Deze ERN/Ne is waarneembaar als mensen een fout maken en manifesteert zich als een negatief electrisch veld dat met behulp van electrodes op de schedel gedetecteerd kan worden. De ERN/Ne wordt gegenereerd in de Anterieure Cingulate Cortex (ACC), in de mediale frontale hersenschors. Er wordt verondersteld dat in de ACC de hierboven genoemde kosten/baten-analyse plaats vindt. Onze bevinding dat de ERN/Ne sterk in amplitude afneemt wanneer mensen vermoeid raken (en in amplitude toeneemt als mensen extra beloond worden), is een sterke aanwijzing dat vermoeidheid samenhangt met een verandering in de kosten/baten-analyse van de huidige taak.

De neurotransmitter dopamine lijkt in dit proces een belangrijke rol te spelen. De beslissing om wel of geen energie te investeren, hangt sterk samen met het vrijkomen van dopamine in de middenhersenen en de neurale verbindingen met de ACC. Aangezien de ERN/Ne, zoals we die meten op de schedel, veroorzaakt wordt door dopaminerge activiteit in de ACC, lijkt het er sterk op dat de keuze van vermoeide mensen voor gedragsstrategieën die minder energie kosten, veroorzaakt wordt door een verlaagde dopaminerge

activiteit in de hersenen van deze mensen. Deze reductie in dopaminerge activiteit (overigens in combinatie met een toename in activiteit van andere neurotransmitters), zou het neurale signaal kunnen zijn dat het organisme er toe aan zet om te stoppen met het huidige gedrag omdat de kosten te hoog worden en de baten klaarblijkelijk uitblijven. Dit signaal zorgt er voor dat het organisme rust gaat zoeken, of juist de aandacht verplaatst naar doelen die gemakkelijker te bereiken zijn of voordelen opleveren. Dit signaal, dat wij vermoeidheid noemen, is uiterst functioneel en adaptief.

Het is belangrijk hier te vermelden dat het kiezen voor een bepaalde vorm van gedrag op basis van kosten/baten-analyses efficiënt is zolang men vrij is om te kiezen tussen verschillende alternatieven in gedrag. In het dagelijks leven, in het bijzonder in de werksituatie, heeft men deze vrijheid over het algemeen echter niet: hoge werkdruk, vastgestelde productiequota, en werk dat een continu beroep doet op hogere cognitieve functies, beperken de vrijheid van werknemers om terug te vallen op strategieën die minder energie kosten. Met andere woorden: zij moeten het signaal van vermoeidheid negeren.
Het feit dat mensen dit signaal kunnen negeren, is op zichzelf ook adaptief, bijvoorbeeld in noodgevallen, wanneer de urgentie van het noodgeval de mogelijke kosten overstijgt. Echter, het voor langere tijd negeren van dit signaal kan leiden tot stress en een chronische verstoring van de neurotransmitter- en hormoonhuishouding in het lichaam. Dit zou kunnen leiden tot permanente schade aan het organisme en zou de basis kunnen zijn van vermoeidheidsstoornissen, zoals burn-out.

Literature

Literature

Alper, K.R. (1999). The EEG and cocaine sensitization: a hypothesis. *Journal of Neuropsychiatry and Clinical Neuroscience, 11*, 209-221.

Bartlett, F.C. (1943). Fatigue following highly skilled work, *Proceedings of the Royal Society, B131*, 247-257.

Bailey, S.P., Davis J.M., & Ahlborn, E.N. (1993). Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. *Journal of Applied Physiology, 74*, 3006-3012.

Berendse, H.W., Galis-de Graaf, Y., & Groenewegen, H.J. (1992). Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. J*ournal of Comparative Neurology, 316*, 314-347.

Bernat, E.M., Williams, W.J., & Gehring, W.J. (2005). Decomposing ERP time-frequency energy using PCA. *Clinical Neurophysiology, 116*, 1314-1344.

Boksem, M.A.S., Lorist, M.M., & Meijman, T.F. (2005). Effects of mental fatigue on attention: an ERP study. *Cognitive Brain Research, in press*.

Boksem, M.A.S., Meijman, T.F., & Lorist, M.M. (2005). Mental fatigue, motivation and action monitoring. *Biological Psychology*, in press.

Boksem, M.A.S., Wester, A.E., Tops, M., Meijman, T.F., & Lorist, M.M. (2005). Subcomponents of the ERN/Ne involved in fatigue and reward motivation. *Submitted for publication.*

Borg, G. (1978). Subjective aspects of physical and mental load. *Ergonomics, 21(3)*, 215-220.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108*, 624-652.

Brown, I.D. (1994). Driver Fatigue. *Human Factors, 36*, 298-314.

Bruce, M., Scott, N., Lader, M., & Marks, V. (1986). The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. *British Journal of Clinical Pharmacology, 22*, 81-87.

Bruijn, de, E. R. A., Hulstijn, W., Verkes, R. J., Ruigt, G. S. F., & Sabbe, B. G. C. (2004). Drug-induced stimulation and suppression of action monitoring in healthy volunteers. *Psychopharmacology, 177*, 151-160.

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*, 215-222.

Bush G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., & Rosen, B.R. (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences of the USA, 99*, 523–528.

Campagne, A., Pebayle, T., & Muzet, A. (2004). Correlation between driving errors and vigilance level: Influence of the driver's age. *Physiology and Behavior, 80*, 515-524.

Carter, C.S., Braver, T.S., Barch, D.M., Botvinick, M.M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science, 280*, 747-749.

Chaouloff, F., Laude, D., & Elghozi, J.L. (1989). Physical exercise: evidence for differential consequences of tryptophan on 5-HT synthesis and metabolism in central serotonergic cell bodies and terminals. *Journal of Neural Transmission, 78 (2)*, 121-130.

Chaudhuri, A. & Behan, P.O. (2000). Fatigue and Basal Ganglia. *Journal of the Neurological Sciences, 179*, 34-42.

Chrobak, J.J., & Buzsaki, G. (1998). Operational dynamics in the hippocampal-entorhinal axis. *Neuroscience and Biobehavioral Reviews, 22*, 303-310.

Cohen, R.M., Semple, W.E., Gross, M., Holcomb, H.H., Dowling, M.S., & Nordahl, T.E. (1988). Functional localization of sustained attention: comparison to sensory stimulation in the absence of instruction. *Neuropsychiatry and Neuropsychological Behavioral Neurology, 1*, 3-20.

Cohen, J.D., & Servan-Schreiber, D. (1992). Context, cortex and dopamine: a connectionist approach to behavior and biology in schizophrenia. *Psychological Review, 99*, 45-77.

Cohen, J.D., Botvinick, M.M., & Carter, C.S. (2000). Anterior cingulate and prefrontal cortex: who's in control? *Nature Neuroscience, 3* , 421-423.

Contreras-Vidal, J.L., & Kerick, S.E. (2004). Independent component analysis of dynamic brain responses during visuomotor adaptation. *Neuroimage, 21(3)*, 936-945.

Cook, I.A., O'Hara, R., Uijtdehaage, S.H.J., Mandelkern, M., & Leuchter, A.F. (1998). Assessing the accuracy of topographic EEG mapping for determining local brain function. *Electroencephalography and Clinical Neurophysiology, 107*, 408-414.

Corbetta, M., & Shulman, G.L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*, 201-215.

Corr, P.J., Kumari, V. (2000). Individual differences in mood reactions to d-amphetamine: A test of three personality factors. *Journal of Psychopharmacology, 14(4)*, 371-377.

Craig, A. & Cooper, R.E. (1992). Symptoms of acute and chronic fatigue. In: A.P. Smith and D.M. Jones (Eds), *Handbook of human performance, Vol. 3: State and trait* (pp. 289-339). San Diego: Academic Press.

Dalley, J.W., Chudasama, Y., & Theobald, D.E. (2002). Nucleus accumbens dopamine and discriminated approach learning: Interactive effects of 6-hydroxydopamine lesions and systemic apomorphine administration. *Psychopharmacology, 161(4)*, 425-433.

Davis, J.M., Alderson, N.L., & Welsh, R.S. (2000). Serotonin and central nervous system fatigue: nutritional considerations. *American Journal of Clinical Nutricion, 72 (2 Suppl)*, 573S-578S.

Dehaene, S., Posner, M.I., & Tucker, D.M. (1994). Localization of a neural system for error detection and compensation. *Psychological Science 5*, 303–305.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annual Reviews of Neuroscience, 18*, 193-222.

Dikman, Z.V. & Allen, J.J. (2000). Error monitoring during reward and avoidance learning in high- and low- socialized individuals. *Psychophysiology*, *37*, 43-54.

Dosher, B.A., & Lu, Z.L, (2000). Mechanisms of perceptual attention in precueing of location. *Vision Research, 40*, 1269-1292.

Duncan, J., Emslie, H., Williams, P., Johnson, R., & Freer, C. (1996). Intelligence and the frontal lobe: the organization of goal-directed behavior. *Cognitive Psychology, 30*, 257-303.

Duncan-Johnson, C.C. (1981). Young Psychophysiologist Award address, 1980. P300 latency: a new metric of information processing. *Psychophysiology*, *18(3)*, 207-215.

Duncan-Johnson, C.C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. *Biological Psychology*, 14(1-2), 1-52.

Durstewitz, D., Kelc, M., & Gunturkun, O. (1999). A neurocomputational theory of the dopaminergic modulation of working memory functions. *Journal of Neuroscience, 19*, 2807-2822.

Durstewitz, D., Seamans, J.K., & Sejnowski, T.J. (2000). Dopamine-mediated stabilization of delay-period activity in a network model of the prefrontal cortex. *Journal of Neurophysiology, 83*, 1733-1750.

Eason, R.G. (1981). Visual evoked potential correlates of early neural filtering during selective attention. *Bulletin of the Psychonomic Society, 18*, 203-206.

Eason, R.G., Oakley M., & Flowers, L. (1983). Central neural influences on the human retina during selective attention. *Physiological Psychology, 11*, 18-28.

Eimer, M. (1993). Spatial cueing, sensory gating and selective response preparation: an ERP study on visuo-spatial orienting. *Electroencephalography and Clinical Neurophysiology, 88*, 408-420.

Eriksen, B.A., & Eriksen, C.W. (1974). Effects of noise letters upon the identification of target letters in visual search. *Perception and Psychophysics, 16*, 142-149.

Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1990). Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: C.H.M. Brunia, A.W.K. Gaillard, & A. Kok (Eds.). *Psychophysiological Brain Research* (pp. 192–195). Tilburg: Tilburg University Press.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). EKP-Korrelate der Fehlerverarbeitung in Abhängigkeit von Alter und Ermüdung. In: M. Falkenstein, J. Hohnsbein and P. Ullsperger (Eds). *Cognitive Changes due to Aging and Fatigue as revealed in the Electrical Brain Activity* (pp. 57-66). Dortmund: Wirtschaftsverlag NW.

Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sundermann, B., & Hohnsbein, J. (2001). Action monitoring, error detection, and the basal ganglia: an ERP study. *NeuroReport, 12*, 157-161.

Falkenstein, M., Hoormann, J., Hohnsbein, J., & Kleinsorge, T. (2003). Short-term mobilazation of processing resources is revealed in the event-related potential. *Psychophysiology*, *40*, 914-923.

Fiehler, K., Ullsperger, M., & Von Cramon, D.Y. (2004). Neural correlates of error detection and error correction: is there a common neuroanatomical substrate? *European Journal of Neuroscience, 19 (11)*, 3081-3087.

Fuster, J.M. (1989). *The Prefrontal Cortex*. New York: Raven Press.

Gabriel, M. (1990). Functions of anterior and posterior cingulate cortex during avoidance learning in rabbits. *Progress in Brain Research, 85*, 467-482.

Gasser, T., Bacher, P., & Mocks, J. (1982). Transformations towards the normal distribution of broad band spectral parameters of the EEG. *Electroencephalography and Clinical Neurophysiology, 53*, 119-124.

Gehring, W.J., Coles, M.G.H., Meyer, D.E. & Donchin, E. (1990). The error-related negativity: an event-related brain potential accompanying errors. *Psychophysiology, 27*, S34.

Gehring, W.J., Goss, B., Coles, M.G.H., Meyer, D.E., & Donchin, E. (1993). A neural system for error detection and compensation. *Psychological Science, 4*, 385–390.

Gehring, W.J., & Knight, R.T. (2000). Prefrontal-cingulate interactions in action monitoring. *Nature Neuroscience*, *3*, 516-520.
Gehring, W.J., & Fencsik, D.E. (2001). Functions of the medial frontal cortex in the processing of conflict and errors. *Journal of Neuroscience, 21*, 9430-9437.

Gehring, W.J., & Willoughby, A.R. (2002). The medial frontal cortex and the rapid processing of monetary gains and losses. *Science, 295(5563)*, 2279-2282.

Gold, P.W., Chrousos, G.P. (1998). The endocrinology of melancholic and atypical depression: Relationships to neurocircuitry and somatic consequences. *Proceedings of the Association of American Physicians, 111(1)*, 22-34.

Goldman-Rakic, P.S. (1987). In F. Plum (Ed.). *Handbook of Physiology: The Nervous System* (pp 373-417). Bethesda: American Physiological Society.

Grace, A.A. (1995). The tonic/phasic model of dopamine system regulation: its relevance for understanding how stimulant abuse can alter basal ganglia function. *Drug and Alcohol Dependance, 37(2)*, 111-129.

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, *55*, 468-484.

Haber, S.N., Kunishio, K., Mizobuchi, M., & Lynd-Balta, E. (1995). The orbital and medial prefrontal circuit through the primate basal ganglia. *Journal of Neuroscience, 15 (7 Pt 1)*, 4851-4867.

Hajcak, G., McDonald, N., & Simons, R.R. (2003). Anxiety and error-related brain activity. *Biological Psychology*, *64*, 77-90.

Heinze, H.J., Luck, S.J., Mangun, G.R., & Hillyard, S.A. (1990). Visual event-related potentials index focussed attention within bilateral stimulus arrays: I. Evidence for early selection. *Electroencephalography and Clinical Neurophysiology, 75*, 511-527.

Heinze, H.J., & Mangun, G.R. (1995). Electrophysiological signs of sustained and transient attention to spatial locations. *Neuropsychologia, 33*, 889-908.

Herrmann, M.J., Rommler, J., Ehlis, A.C., Heidrich, A., & Fallgatter, A.J. (2004). Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). *Cognitive Brain Research, 20(2)*, 294-299.

Hillyard, S.A., & Münte, T.F. (1984). Selective attention to colour and location: An analysis with event-related brain potentials. *Perception and Psychophysics, 36*, 185-198.

Hillyard, S.A., Münte, T.F., & Neville, H.J. (1985). Visual-spatial attention, orienting and brain physiology. In: M.I. Posner & O.S.M. Marin (Eds). *Attention and Performance XI* (pp. 63-84). Hillsdale, N.J: Erlbaum.

Hillyard, S.A., Mangun, G.R., Luck, S.J., & Heinze H.J. (1990). Electrophysiology of visual attention. In: E.R. John, T. Harmony, L.S. Pricheb, M. Valdez, & P.A. Valdez (Eds.). *Machinery of Mind*. Boston, M.A: Birkhauser.

Hockey, G.R.J. (1993). Cognitive-energetical control mechanisms in the management of work demands and psychological health. In*:* A.D. Baddeley, L. Weiskrantz (Eds.). *Attention: Selection, awareness, and control: A tribute to Donald Broadbent* (pp. 328-345). New York, NY: Clarendon Press/Oxford University Press.

Hockey, G.R.J. (1997). Compensatory control in the regulation of human performance under stress and high workload: A cognitive energetical framework. *Biological Psychology, 45*, 73-93.

Hohnsbein, J., Falkenstein, M., & Hoormann, J. (1998). Performance differences in reaction tasks are reflected in event-related brain potentials (ERPs). *Ergonomics, 41*, 622-633.

Holding, D. (1983). Fatigue. In: G.R.J. Hockey (Ed.). *Stress and fatigue in human performance* (pp. 145-164). Durnham: John Wiley & Sons.

Holroyd, C.B., & Coles, M.G. (2002). The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychological Review*, *109*, 679-709.

Holroyd, C.B., & Yeung, N. (2003). Alcohol and error processing. *Trends in Neuroscience, 26*, 402-404.

Hommel, B., Ridderinkhof, K.R., & Theeuwes, J. (2002). Cognitive control of attention and action: Issues and trends. *Psychological Research, 66*, 215-219.

Ito, S., Stuphorn, V., & Brown, J.W. (2003). Performance Monitoring by the Anterior Cingulate Cortex During Saccade Countermanding. *Science, 302(5642)*, 120-122.

Jonides, J. (1980). Towards a model of the mind's eye's movement. *Canadian Journal of Psychology, 34*, 103-112.

Kanwisher, N., & Wojciulik, E. (2000). Visual attention: insights from brain imaging. *Nature Reviews Neuroscience, 1 (2)*, 91-100.

Kastner, S., Pinsk, M.A., De Weerd, P., Desimone, R., & Ungerleider, L.G. (1999). Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron, 22*, 751-761.

Kecklund, G., & Akerstedt, T. (1993). Sleepiness in long distance truck driving: an ambulatory EEG study of night driving. *Ergonomics, 36*, 1007-1017.

Kenemans, J.L., & Lorist, M.M. (1995). Caffeine and selective visual processing. *Pharmacology Biochemistry and Behavior, 52(3)*, 461-471.

Kerns, J.G., Cohen, J.D., MacDonald, A.W., Cho, R.Y., Stenger, V.A., & Carter, C.S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science, 303*, 1023-1026.

Kiehl, K.A., Liddle, P.F., & Hopfinger, J.B. (2000). Error processing and the rostral anterior cingulate: an event-related fMRI study. *Psychophysiology*, *37*, 216-223.

Klimesh, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Research Brain Research Reviews, 29*, 169-195.

Knutson, B., Westdorp, A., Kaiser, E., & Hommer, D. (2000). fMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage, 12*, 20–27.

Kopp, B., Mattler, U., Goertz, R., & Rist, F. (1996). N2, P3 and the lateralized readiness potential in a nogo task involving selective response priming. *Electroencephalography and Clinical Neurophysiology, 99*, 19-27.

Kopp, B., Rist, F., Mattler, U. (1996). N200 in the flanker task as a neurobehavioral tool for investigating executive control. *Psychophysiology, 33*, 282-294.

Lafrance, C. & Dumont, M. (2000). Diurnal variations in the waking EEG: comparison with sleep latencies and subjective alertness. *Journal of Sleep Research, 9*, 243-248.

Lange, J.J., Wijers, A.A., Mulder, L.J.M., & Mulder, G. (1998). Color selection and location selection in ERPs: differences, similarities and 'neural specificity'. *Biological Psychology*, *48*, 153-182.

Laufs, H., Kleinschmidt, A., Beyerle, A., Eger, E., Salek-Haddadi, A., Preibisch, C., & Krakow, K. (2003). EEG-correlated fMRI of human alpha activity. *Neuroimage, 19*, 1463-1476.

Leung, L.S., & Yim, C.Y. (1993). Rhythmic delta-frequency activities in the nucleus accumbens of anesthetized and freely moving rats. *Canadian Journal of Physiology and Pharmacology, 71*, 311-320.

Leuthold, H., & Sommer, W. (1999). ERP correlates of error processing in spatial S-R compatibility tasks. *Clinical Neurophysiology, 110*, 342–357.

Linden, van der, D., Frese, M., & Meijman, T.F. (2003). Mental fatigue and the control of cognitive processes: effects on perseveration and planning. *Acta Psychologica, 113*, 45-65.

Linden, van der, D. (2004). Mentale vermoeidheid en doelgericht handelen: Effecten van taakcontext op de sturing van gedrag. = Mental fatigue and goal-oriented behaviour: Effects of task context on behaviour guidance. *Gedrag en Organisatie, 17(4)*, 252-271.

Liotti, M., Woldorff, M.G., Perez, R., III, & Mayberg, H.S. (2000). An ERP study of the temporal course of the Stroop color-word interference effect. *Neuropsychologia*, *38*, 701-711.

Lorist, M.M., Snel, J., Kok, A., & Mulder, G. (1994). Influence of caffeine on selective attention in well-rested and fatigued subjects. *Psychophysiology, 31*, 525-534.

Lorist, M.M., Klein, M., Nieuwenhuis, S., De Jong, R., Mulder, G., & Meijman, T.F. (2000). Mental fatigue and taks control: planning and preparation. *Psychophysiology, 37*, 614-625.

Lorist, M.M., & Tops, M. (2003). Caffeine, fatigue, and cognition. *Brain and Cognition*, *53*, 82-94.

Lorist, M.M., Boksem, M.A.S., & Ridderinkhof, K.R. (2005). Impaired control and reduced cingulate activity during mental fatigue. *Cognitive Brain Research, 24*, 199-205.

Lu, C.H., & Proctor, R.W. (1995). The influence of irrelevant location information on performance: a review of the simon and spatial stroop effects. *Psychonomic Bulletin & Review, 2,* 174-207.

Luck, S.J., Heinze, H.J., Mangun, G.R., & Hillyard, S.A. (1990). Visual event-related potentials index focussed attention within bilateral stimulus arrays: II. Functional dissociation of P1 and N1 components. *Electroencephalography and Clinical Neurophysiology, 75*, 528-542.

Luck, S.J. (1995). Multiple mechanisms of visual-spatial attention: recent evidence from human electrophysiology. *Behavioral Brain Research, 71*, 113-123.

Luck, S.J., & Hillyard, S.A. (1995). The role of attention in feature detection and conjunction discrimination: An electrophysiological analysis. *International Journal of Neuroscience, 80*, 281-297.

Luu, P., Collins, P., & Tucker, D.M. (2000). Mood, personality, and self-monitoring: negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology General*, *129*, 43-60.

Luu, P., Flaisch, T., & Tucker, D.M. (2000). Medial frontal cortex in action monitoring. *Journal of Neuroscience, 20*, 464-469.

Luu, P., & Tucker, D.M. (2001). Regulating action: alternating activation of midline frontal and motor cortical networks. *Clinical Neurophysiology, 112*, 1295-1306.

Luu, P., Tucker, D.M., & Makeig, S. (2004). Frontal midline theta and the error-related negativity: neurophysiological mechanisms of action regulation. *Clinical Neurophysiology, 115(8)*, 1821-1835.

MacDonald, A.W., III, Cohen, J.D., Stenger, V.A., & Carter, C.S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, *288*, 1835-1838.

Mangun, G.R., & Hillyard, S.A. (1988). Spatial gradients of visual attention: Behavioral and electrophysiological evidence. *Electroencephalography and Clinical Neurophysiology, 70*, 417-428.

Mangun, G.R., & Hillyard, S.A. (1990). Allocation of visual attention to spatial locations: Trade-off functions for event-related brain potentials and detection performance. *Perception and Psychophysics, 47*, 532-550.

Mangun, G.R., & Hillyard, S.A. (1991). Modulations of sensory-evoked brain potentials indicate changes in perceptual processing during visual-spatial priming. *Journal of Experimental Psychology: Human Perception and Performance, 17*, 1057-1074.

Mangun, G.R., Hillyard, S.A., & Luck, S.J. (1993). Electrocortical substrates of visual selective attention. In: S. Kornbloum and D.E. Meyer (Eds). *Atttention and Performance XIV* (pp. 219-243). Hillsdale, N.J.: Erlbaum.

Mangun, G.R. (1995). Neural mechanisms of visual selective attention. *Psychophysiology, 32*, 4-18.

McEwen, B.S., & Wingfield, J.C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior, 43*, 2-15.

Meijman, T.F. (2000). The theory of the stop-emotion: On the functionality of fatigue. In D. Pogorski & W. Karwowski (Eds.). *Ergonomics and safety for global buisiness quality and production* (pp. 45-50). Warschaw: CIOP.

Mesulam, M.M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology, 28*, 597–613.

Michel, C.M., Lehmann, D., Henggeler, B., & Brandeis, D. (1992). Localization of the sources of EEG delta, theta, alpha and beta frequency bands using the FFT dipole approximation. *Electroencephalography and Clinical Neurophysiology, 82*, 38-44.

Michel, C.M., Henggeler, B., Brandeis, D., & Lehmann, D. (1993). Localization of sources of brain alpha/theta/delta activity and the influence of the mode of spontaneous mentation. *Physiological Measurement, 1*, A21-A26.

Milham, M.P., Banich, M.T., Claus, E.D., & Cohen, N.J. (2003). Practice-related effects demonstrate complementary roles of anterior cingulate and prefrontal cortices in attentional control. *NeuroImage, 18*, 483-493.

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nature Reviews Neuroscience, 1*, 59-65.

Miller, E.K., & Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. *Annual Reviews of Neuroscience, 24*, 167-202.

Menon, V., Adleman, N.E., White, C.D., Glover, G.H., & Reiss, A.L. (2001). Error-related brain activation during a Go/NoGo response inhibition task. *Human Brain Mapping, 12*, 131-143.

Murray, S.O., & Wojciulik, E. (2004). Attention increases neural selectivity in the human lateral occipital complex. *Nature Neuroscience, 7(1)*, 70-74.

Nauta, W.H.J. (1986). Circuitous connections linking cerebral cortex, limbic system and corpus striatum. In: B.K. Doane, & K.E. Livingstone (Eds). *The limbic system: functional organization and clinical disorders* (pp. 43-54). New York: Raven Press.

Neill, D.B., & Justice, J.B. (1981). An hypothesis for a behavioral function of dopaminergic transmission in nucleus accumbens. In: R.B. Chronister, & J.F. DeFrance (Eds.). *The neurobiology of the nucleus accumbens*, (pp. 343–350). Brunswick, ME: Haer Institute for Electrophysiological Research.

Newman, F., Stein, M.B., Trettau, J.R., Coppola, R., & Uhde, T.W. (1992). Quantitative electroencephalographic effects of caffeine in panic disorder. *Psychiatry Research, 45(2)*, 105-113.

Newsholme, E.A., Acworth, I.N., Blomstrand, E. (1987). Amino acids, brain neurotransmitters and a functional link between muscle and brain that is important in sustained exercise. In: *Advances in myochemistry* (pp. 127-133). London: John Libbey Eurotext.

Nietfeld, J., & Bosma, A. (2003). Examining the self-regulation of impulsive and reflective response styles on academic tasks. *Journal of Research in Personality*, *32*, 118-140.

Nieuwenhuis, S., Ridderinkhof, K.R., Blom, J., Band, G.P.H., & Kok, A. (2001). Error-related brain potentials are differentially related to awareness of response errors: evidence from an antisaccade task. *Psychophysiology*, *38*, 752-760.

Oken, B.S. & Salinsky, M. (1992). Alertness and attention: Basic science and electrophysiologic correlates. *Journal of Clinical Neurophysiology, 9(4)*, 480-494.

Okita, T., Wijers, A.A., Mulder, G., & Mulder, L.J.M. (1985). Memory search and visual spatial attention: an event-related brain potential analysis. *Acta Psychologica, 60*, 263-292.

Pailing, P.E., & Segalowitz, S.J. (2004). The error-related negativity as a state and trait measure: motivation, personality, and ERPs in response to errors. *Psychophysiology, 41*, 84-95.

Pandya, D.N., & Barnes, C.L. (1987). In: E. Percman (Ed.). *The Frontal Lobes Revisited* (pp. 41-72). New York: IRBN Press.

Paus, T., Zatorre, R.J., Hofle, N., Caramanos, Z., Gotman, J., Petrides, M., & Evans, A.C. (1997). Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task. *Journal of Cognitive Neuroscience, 9(3)*, 392-408.

Pizzagalli, D.A., Oakes, T.R., Davidson, R.J. (2003). Coupling of theta activity and glucose metabolism in the human rostral anterior cingulate cortex: an EEG/PET study of normal and depressed subjects. *Psychophysiology, 40*, 939-949.

Posner, M.I., Snyder, C.R.R., & Davidson, B.J. (1980). Attention and the detection of signals. *Journal of Experimental Psychology, 109*, 160-174.

Pribram, K.H. (1991). *Brain and Perception: Holonomy and Structure in Figural Processing.* Hillsdale, NJ: Erlaum.

Quintana, S.M., & Maxwell, S.E. (1994). A Monte Carlo comparison of seven adjustment procedures in repeated measures designs with small sample sizes. *Journal of Educational Statistics, 19*, 57-71.

Rabbitt, P.M.A. (1966). Errors and error correction in choice reaction tasks. *Journal of Experimental Psychology, 71*, 264–272.

Rabbitt, P. M. A. (1990). Age, IQ and awareness, and recall of errors, *Ergonomics, 33*, 1291-1305.

Reinke, W., Westphal, K.P., Diekmann, V., Grozinger, B., & Kornhuber, H.H. (1994). Changes in functionally determined order processes of the EEG in a motor task due to various dosages of biperidene. *Neuropsychobiology, 29*, 194-201.

Ridderinkhof, K.R., Ullsperger, M., Crone, E.A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. *Science, 306*, 443-447.

Ridderinkhof, K.R., de Vlugt, Y., Bramlage, A., Spaan, M., Elton, M., & Snel J. (2002). Alcohol consumption impairs detection of performance errors in mediofrontal cortex. *Science, 298,* 2209-2211.

Rugg, M.D., Milner, A.D., Lines, C.R., & Phalp, R. (1987). Modulation of visual event-related potentials by spatial and non-spatial visual selective attention. *Neuropsychologia, 25*, 85-96.

Rushworth, M.F., Walton, M.E., Kennerley, S.W., & Bannerman, D.M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences, 8(9)*, 410-417.

Salamone, J.D., Cousins, M.S., & Bucher, S. (1994). Anhedonia or anergia?. Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behavioural Brain Research, 65(2)*, 221-229.

Salamone, J.D., Aberman, J.E., Sokolowski, J.D., & Cousins, M.S. (1999). Nucleus accumbens dopamine and rate of responding: Neurochemical and behavioral studies. *Psychobiology*, *27*, 236-247.

Scheffers, M.K., Coles, M.G., Bernstein, P., Gehring, W.J., & Donchin, E. (1996). Event-related brain potentials and error-related processing: an analysis of incorrect responses to go and no-go stimuli. *Psychophysiology*, *33*, 42-53.

Scheffers, M. K., Humphrey, D. G., Stanny, R. R., Kramer, A. F., & Coles, M. G. (1999). Error-related processing during a period of extended wakefulness. *Psychophysiology, 36*, 149-157.

Schultz, W. (2000). Multiple reward signals in the brain. *Nature Reviews Neuroscience*, *1*, 199-207.

Schultz, W. (2002). Getting formal with dopamine and reward. *Neuron, 36*, 241-263.

Simon, J.R., & Small, A.M.J. (1969). Processing auditory information: Interference from an irrelevant cue. *Journal of Applied Psychology, 53,* 433-435.

Smulders, F.T.Y., Kenemans, J.L., Jonkman, L.M., & Kok, A. (1997). The effects of sleep loss on task performance and the electroencephalogram in young and elderly subjects. *Biological Psychology, 45*, 217-239.

Sperandio, J.C. (1978). The regulation of working methods as a function of work-load among air traffic controllers. *Ergonomics*, *21*, 195-202.

Sugrue, L.P., Corrado, G.S., Newsome, W.T. (2005). Choosing the greater of two goods: Neural currencies for valuation and decision making. *Nature Reviews Neuroscience, 6(5)*, 363-375.

Swick, D., & Turken, A.U. (2002). Dissociation between conflict detection and error monitoring in the human anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the USA*, *99*, 16354-16359.

Szechtman, H., Talangbayan, H., Canaran, G., Dai, H., & Eilam, D. (1994). Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. *Psychopharmacology (Berl)*, *115*, 95-104.

Tanaka, H., Hayashi, M., & Hori, T. (1997). Topographical characteristics and principal component structure of the hypnagogic EEG. *Sleep, 20*, 523-534.

Tieges, Z., Ridderinkhof, K.R., Snel, J., & Kok, A. (2004). Caffeine strengthens action monitoring: evidence from the error-related negativity. *Cognitive Brain Research, 21*, 87-93.

Tops, M., Lorist, M.M., Wijers, A.A., & Meijman, T.F. (2004). To stress or relax: neurochemical aspects of activity and rest. *Gedrag en Organisatie*, *17*, 32-42.

Torswall, L., & Akerstedt, T. (1987). Sleepiness on the job: continuously measured EEG changes in train drivers. *Electroencephalography and Clinical Neurophysiology, 66 (6)*, 502–511.

Tremblay, L., & Schultz, W. (1999). Relative reward preference in primate orbitofrontal cortex. *Nature, 398*, 704-708.

Ullsperger, M., & von Cramon, D.Y. (2003). Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional resonance imaging. *Journal of Neuroscience, 23*, 4308-4314.

Tucker, D.M., Hartry-Speiser, A., McDougal, L., Luu, P., & deGrandpre, D. (1999). Mood and spatial memory: Emotion and right hemisphere contribution to spatial cognition. *Biological Psychology*, *50*, 103-125.

Ullsperger, M., & von Cramon, D.Y. (2003). Error monitoring using external feedback: specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional resonance imaging. *Journal of Neuroscience, 23*, 4308-4314.

Ullsperger, M., & von Cramon, D. Y. (2004). Neuroimaging of performance monitoring: Error detection and beyond. *Cortex, 40,* 593-604.

Van Veen, V., & Carter, C.S. (2002a). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology and Behavior, 77*, 477-482.

Van Veen, V., & Carter, C.S. (2002b). The timing of action-monitoring processes in the anterior cingulate cortex. *Journal of Cognitive Neuroscience*, *14*, 593-602.

Vogel, E.K., & Luck, S.J. (2000). The visual N1 component as an index of a discrimination process. *Psychophysiology, 37(2)*, 190-203.
Walton, M.E., Bannerman, D.M., & Rushworth, M.F.S. (2002). The Role of Rat Medial Frontal Cortex in Effort-Based Decision Making. *Journal of Neuroscience, 22(24)*, 10996-11003.

Walton, M.E., Bannerman, D.M., Alterescu, K., & Rushworth, M.F.S. (2003). Functional specialization within medial frontal cortex of the anterior cingulate for evaluating effort-related decisions. *The Journal of Neuroscience*, *23(16)*, 6475-6479.

Wascher, E. & Wolber, M. (2004). Attentional and intentional cueing in a Simon task: an EEG-based approach. *Psychological Research*, *68*, 18-30.

Watanabe, M. (1990). Prefrontal unit activity during associatieve learning in the monkey. *Experimental Brain Research, 80*, 296-309.

Watanabe, M. (1992). Frontal units of the monkey coding the associative significance of visual and auditory stimuli. *Experimental Brain Research, 89*, 233-247.

Watanabe, M. (1996). Reward expectancy in primate prefrontal neurons. *Nature, 382*, 629-632.

Wesensten, N.J., Belenky, G., Kautz, M.A., Thorne, D.R., Reichardt R.M., & Balkin, T.J. (2002). Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharmacology, 159*, 238-247.

Wijers, A.A., Mulder, G., Okita, T., Mulder, L.J.M. & Scheffers, M.K. (1989). Attention to colour: An ERP-analysis of selection, controlled search, and motor activation. *Psychophysiology, 26(1)*, 89-109.

Wijers, A.A., Lamain, W., Slopsema, S., Mulder, G., & Mulder, L.J.M. (1989). An electrophysiological investigation of the spatial distribution of attention to coloured stimuli in focussed and divided attention conditions. *Biological Psychology, 29*, 213-245.

Wijers, A.A., Mulder, G., Gunter, Th.C., & Smid, H.G.O.M. (1996). Brain potential analysis of selective attention. In: A.F. Sanders & O. Neumann (Eds). *Handbook of Perception and Action, volume 3* (pp. 333-387). San Diego, CA: Academic Press.

Wijers, A.A., & Boksem, M.A.S. (2005). Selective attention and error processing in an Illusory conjunction task: An event-related brain potential study. *Journal of Psychophysiology, 19(3)*, 216-231.

Yamagychi, S., Tsuchiya, H., & Kobayashi, S. (1995). Electrophysiologic correlates of visuo-spatial attention shift. *Electroencephalography and Clinical Neurophysiology, 94*, 450-461.

Yordanova, J., Falkenstein, M., Hohnsbein, J., & Kolev, V. (2004). Parallel systems of error processing in the brain. *Neuroimage, 22(2)*, 590-602.

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Nu mijn promotietraject volledig acher de rug is (heb jem? Achter de RuG? Hahaha. Dus…) kan ik oprecht zeggen dat ik er met tevredenheid op terugzie. Natuurlijk is achteraf bijna alles leuk, dus dit wil niet zeggen dat het allemaal van een leien dakje is gegaan. Dit is dan ook niet zo. Ik herinner mij lange uren in de EEG ruimte in de kelder van het Heymans gebouw, verstoken van elk zonlicht of contact met de buitenwereld. Ik herinner mij uren achter de PC, de EEG data voor de zoveelste keer heranalyseren. Ik herinner mij manuscripten die telkens weer met commentaar terug kwamen, soms nuttig soms niet, maar altijd tegenstrijdig.
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Maarten,

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