Caffeine and cognitive control : behavioral and electrophysiological studies

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Ter nagedachtenis aan mijn vader

Contents

1

General Introduction

1.1 Introduction

"Coffee leads men to trifle away their time, scald their chops, and spend their money, all for a little base, black, thick, nasty, bitter, stinking nauseous puddle water"

(The Women's Petition Against Coffee, 1674)

Coffee is a beverage known all over the world; millions of people drink it everyday. In addition to the social aspects related to coffee drinking and its beloved taste and smell, the perceived stimulating effect of coffee is probably among the main reasons for its widespread use. Coffee is a complex beverage with several hundreds of identified different compounds, many of which are formed during roasting (e.g., Viani, 1993). A significant proportion of the behavioral and physiological effects of coffee is related to the actions of caffeine (1,3,7-trimethylxanthine), the main component of coffee.

While the largest intake of caffeine has always been through coffee, it is also present in other dietary sources such as tea, chocolate, soft drinks (e.g., energy drinks and cola), and in some medicines, in particular analgetics. As such, it is undoubtedly the most widely consumed psychoactive compound in the world (Fredholm, Battig, Holmen, Nehlig, & Zvartau, 1999).

Because of its widespread use and its perceived activating effects, the relation between caffeine and cognitive functions has long been a topic of scientific interest. However, following nearly a century of systematic studies on the cognitive effects of caffeine, peaking in the last two decades, it is hard to arrive at a coherent account of its effects on cognition. In other words, it is not yet clear which, how, and to what extent cognitive functions are specifically affected by caffeine. Surely, the large number of studies has added to the knowledge of what these effects are (see section 1.1.1). At the same time, however, inconsistent findings have always characterized the research on caffeine. Results among studies vary because of methodological factors such as dosage, time of assessment, and cognitive test. Other factors are related to the subjects including habitual caffeine use, metabolic rate, mood, expectations, and age (Fredholm et al., 1999; Nehlig, 1999; Rogers & Dernoncourt, 1998). Clearly more research is needed in order to reveal the nature of caffeine's actions.

Consequently, the aim of the present thesis is to gain a more detailed insight into the effects of caffeine on cognitive functioning. The focus is on effects of caffeine on higher-order processing, also referred to as 'cognitive control' (see section 1.2). Consider, for example, driving a car while operating a cellular telephone. Does caffeine influence the ability to flexibly switch between these various actions? Or when pushing the gas pedal in response to a green traffic light, and suddenly a child jumps onto the street, does caffeine alter the speed with which you switch to slam on the brakes? Questions like these will be addressed in the present thesis.

But first, let us take a closer look at caffeine's mechanisms of action.

BOX 1. History of coffee and caffeine

Among the many accounts that have developed concerning the origins of coffee, one well-known legend has it that coffee was discovered by an Ethiopian goatherd named Kaldi, who lived around AD 850. One day his goats were behaving frenetically after chewing red berries from a local shrub (a berry contains two beans). Kaldi tried a few himself and his tiredness quickly disappeared. Instead, he felt a fresh burst of energy. The daily habit that Kaldi soon developed was observed by a monk from a local monastery. He boiled the berries to make a drink that helped the other monks stay alert during their long prayers at night (Luttinger & Dicum, 2006).

Around AD 1100, the first coffee trees were planted in Arabia and the Arabs started making a beverage that would be the forerunner of our cup of coffee. In 1616, the first coffee beans were smuggled out from Mocha to Europe by a Dutch trader. By 1706, coffee beans had been brought to Amsterdam, along with a coffee plant for the Amsterdam Botanical Garden, and subsequently the Dutch established plantations in the Dutch East Indies. Coffee was now in the hands of enough different interests to make its spread around the world inevitable. Nowadays, coffee is cultivated in a belt of countries situated around the equator, and an estimated average of 2.25 billion cups of coffee is consumed in the world each day.

Despite the fact that coffee drinking had been a part of everyday life for centuries, caffeine as a discrete entity was not discovered until the beginning of the nineteenth century. To be precise, caffeine was first isolated from green coffee beans in Germany by Ferdinand Runge in 1820. In 1911, the first systematic experimental study on caffeine was performed by psychologist Harry Hollingworth. He was hired by the Coca-Cola company to examine the effects of caffeine on humans, because the company was facing a trial on charges that they had marketed a beverage with a deleterious ingredient, namely, caffeine (for details see Benjamin et al., 1991).

For more facts, figures and general information about the coffee industry the interested reader is referred to e.g. Luttinger and Dicum (2006).

1.1.1 Caffeine

Already known to the Arab world until the fifteenth century, coffee entered Europe and soon after, the United States (for an overview of coffee's history, see Box 1). Presently, coffee is the second largest export product worldwide after oil. According to recent surveys, the top coffee consuming countries are Sweden and Finland (263.6 and 207.3 liter per capita per year, respectively), while 130.6 liter per capita per year is consumed in the Netherlands and only 63.0 liter in the United States (*World Drink Trends*, 2005). See Luttinger and Dicum (2006) for more facts about coffee.

In pure form, caffeine is a white crystalline powder that tastes very bitter. The amount of caffeine in a single serving of coffee ranges from about 60 to 160 mg. This varying amount depends on certain factors, such as the variety of the coffee bean, the level of grind, how the product is manufactured, the method of preparation, and the size of the serving.

Caffeine is considered a mild stimulant acting on the central nervous system. While coffee usually makes people feel more energetic –it helps them "wake up"- too much coffee can have unfavorable consequences on the body as well; for example, a trembling feeling and deterioration of fine motor co-ordination. Nevertheless, caffeine is a substance that is normally considered as "self-regulating", meaning that most people know when they took enough coffee and usually stop drinking at that point. Indeed, whereas the classical drugs of abuse induce quite specific increases in dopamine (DA) release in the shell of the nucleus accumbens (the key structure for reward, motivation, and addiction), habitual caffeine doses do not produce these effects (Acquas, Tanda, & Di Chiara, 2002). Accordingly, caffeine as a substance does not meet the criteria of an addictive drug. Still, coffee consumption is habit forming and some people may experience mild withdrawal effects (headache, fatigue, or drowsiness) after an abstinence of 24 h or more (Nehlig, 1999).

Most research has focused on caffeine's effects on health. Despite previous controversy on the subject, the current prevailing opinion is that a moderate amount of caffeine has no clinically significant effects on the human body. Specifically, moderate daily caffeine intake at a dose level up to 400 mg day is not associated with adverse effects on cardiovascular functioning, bone status and calcium balance, blood pressure, and increased incidence of cancer, while caffeine consumption should preferrably be moderated before or during pregnancy (Nawrot et al., 2003). Interestingly, the effect on cholesterol levels mainly depends on the brewing method, given that boiled unfiltered coffee, but not filtered coffee, appears to have a cholesterol increasing effect. Health effects of caffeine continue to be the topic of popular and scientific debate.

Another branch of research has dealt with caffeine-induced changes in behavior and cognitive functions. Most of these studies show a beneficial influence of moderate amounts of caffeine on reaction time (RT); that is, it speeds up information processing. In addition, accuracy levels and perceptual sensitivity seem to be higher under caffeine taken innormal amounts. Also, the electroencephalogram (EEG) generally shows a heightened cortical arousal level by caffeine conditions as shown from an increase in the alpha frequency band (e.g., Barry et al., 2005). It should be noted, however, that the evidence supporting these views is still somewhat inconsistent.

1.1.2 How caffeine works

For a critical interpretation of experimental results concerning the effects of caffeine, some idea of the pharmacology of caffeine is required.

1.1.2.1 Absorption and pharmacokinetics

After oral ingestion, caffeine is rapidly and almost completely (99%) absorbed from the gastrointestinal tract into the bloodstream. After only 15 minutes the first traces of caffeine can be found in the blood, with peak plasma levels about 30-60 minutes after ingestion. Caffeine is widely distributed throughout the body and easily passes the blood-brain barrier. The half-life of caffeine (in doses lower than 10 mg/kg) ranges from 2.5-4.5 h, but individual clearance rates vary considerably, depending on several endogenous and exogenous factors (Fredholm et al., 1999; Nehlig, 1999). For example, pregnancy as well as the use of oral contraceptives are associated with slower elimination of caffeine, whereas nicotine speeds up the clearance rate by 30-50%. No differences in the metabolic pattern between men and women have been observed. The elimination of caffeine occurs mainly by metabolism in the liver, and its breakdown products are excreted through the kidneys. Only about 5% is excreted unchanged in the urine. The concentration of caffeine in plasma or serum and saliva correlates highly, and the half-life of caffeine is comparable in the two fluids (e.g., Fenske, 2007).

1.1.2.2 Mechanisms of action

Currently, three main mechanisms are accepted as underlying the pharmacological effects of caffeine on the central nervous system: (1) antagonism of adenosine receptors, (2) inhibition of phosphodiesterase, and (3) mobilization of calcium. It is now well established that mechanism (1) underlies the effects of moderate caffeine consumption. Mechanisms (2) and (3) are not likely candidates for mediating caffeine's effects in humans, since the blood concentrations of caffeine needed to activate these mechanisms are relatively high - roughly 100 times the caffeine levels observed in the brain after ingestion of doses typical for man (Fredholm et al., 1999).

Adenosine decreases the firing rate of neurons and exerts an inhibitory effect on synaptic transmission and on the release of most neurotransmitters (Dunwiddie & Masino, 2001). By caffeine intake, the modulatory effects of adenosine on ongoing neural activity are reduced and the levels of the neurotransmitters acetylcholine, noradrenaline, dopamine, and serotonin may be increased.

There are three main classes of adenosine receptors: A_1, A_{2A}, and A_3. In doses that are normally consumed, caffeine blocks inhibitory adenosine A_1 and A_{2A} receptors, and hence increases central nervous system activity. In fact, caffeine occupies about 50% of the adenosine receptors after intake of only a few cups of coffee. The A_3 receptor seems to be largely insensitive to its blockade by xanthines (of which caffeine is one), at least in rodents (Daly, Shi, Nikodijevic, & Jacobson, 1994). Adenosine A_1 receptors are widely distributed throughout the brain with high levels in the hippocampus, cortical layers, and striatum. Conversely, A_{2A} receptors are almost exclusively located in the striatum, nucleus accumbens, and olfactory tubercle. In the striatum, the tonically active A_{2A} receptors are co-

localized with DA receptors (Acquas et al., 2002; Ferré, Fredholm, Morelli, Popoli, & Fuxe, 1997). Stimulation of DA activity through these antagonistic A_{2A}-DA receptor-receptor interactions might underlie some of the behavioral effects of caffeine (Garrett & Griffiths, 1997).

For more elaborate reviews about the pharmacology of caffeine, the reader is referred to Fredholm et al. (1999), Garattini (1993), Nehlig (1999), or Snel and Lorist (1998).

1.1.3 Neurocognitive effects of caffeine

Effects of caffeine have been found in various domains of cognition. The majority of research up till now exclusively used behavioral measurements like response times and error rates. More recent investigations have used event-related potential (ERP) measurements in addition to behavioral measures (see Box 2). This ERP approach has the advantage that it provides insight into the ongoing neural and cognitive processes in the brain.

From a series of such electrophysiological studies (Lorist, 1995; Ruijter, 2000), in which specific stages of information processing were systematically manipulated, it was concluded that the perceptual, attentional, and response stages of information processing were susceptible to caffeine. These conclusions support behavioral studies on caffeine (e.g., Barthel et al., 2001; Warburton, Bersellini, & Sweeney, 2001). While the focus of these studies has been on lower-level processing, caffeine-induced improvements in behavior might also, at least in part, result from changes in central (higher-level) processing stages.

This notion has been investigated by Lorist (1995). Specifically, she studied effects of caffeine on a subset of processes from the broad range of functionally different processes that occur during the central processing stage, namely serial comparison, binary decision making, and response selection (as measured by changing memory/display load, target detection, and stimulus-response compatibility, respectively). It turned out that the evidence for caffeine on central processes was limited to an effect of caffeine on display load, with subjects reacting faster after caffeine compared to placebo, but only in a low (not high) display load condition (Lorist, Snel, Kok, & Mulder, 1996). Consequently, Lorist (1995) concluded that higher mental functions were not sensitive to caffeine. It must be kept in mind, though, that the experimental tasks used in these studies were not specifically designed to measure central processes, and might therefore not represent a suitable tool for studying caffeine's effects on these processes.

Since the time of Lorist's studies, research on higher mental functioning has evolved rapidly, and the focus has shifted towards processes such as planning, action monitoring, task switching, and response inhibition. These higher-level functions require a strict cognitive control. The recent interest with respect to cognitive control is accompanied by a scala of new, or rediscovered paradigms to investigate these processes. The present thesis is aimed at using these *cognitive control* paradigms to gain a better understanding of caffeine's actions on higher-level processing.

BOX 2. Event-related potentials

Event-related brain potential (ERP) measurements provide a powerful tool for investigating the timing and organization of neurocognitive processes. ERPs reflect small changes in brain electrical activity time-locked to the occurrence of a particular event (such as a stimulus or the response to a stimulus). More specifically, ERPs represent the summation of electromagnetic activity generated by large populations of neurons arranged in an open field (i.e. their geometric configuration must be such that their activity summates). This electrical activity, together with the background activity of the brain and noise, is recorded from electrodes placed across the scalp. Although the recordings made from scalp electrodes predominantly reflect cortical processing in the immediate environment of the electrode, earlier components reflecting subcortical processing can also be distinguished.

ERPs are derived from the electroencephalogram (EEG). Time-locked signal averaging is used to extract the very small ERPs from the much larger background EEG activity. As such, this averaging procedure (alignment) washes out variations, noise or larger spontaneous brain activity that are unrelated to the event of interest. The resulting ERP waveform consists of a series of voltage oscillations (or components) that reflect the time course of neuronal activity with a resolution in the order of milliseconds. Because of its low spatial resolution, however, this method is less suited for localization of brain activity.

The polarity (positive or negative), amplitude (peak height), latency (time in milliseconds relative to the onset of a stimulus), and scalp distribution of the successive components can be used to measure the time course of ongoing cognitive processing. Specifically, it has been argued that the *latencies* of different ERP components reflect the timing of information processing, while the *amplitude* of ERP components has been found to be very sensitive to changes in the mobilization of energetical mechanisms involved in task performance. For reviews about the ERP technique, see e.g. Handy (2005).

The (visual) ERP components that are identified in Chapters 2 to 4 require a brief introduction. It should be kept in mind that the precise functional significance of a specific component depends, in part, on the context in which it is elicited (i.e. the properties of the experimental task).

P2: The P2 has been interpreted as reflecting selective attention and basic perceptual processing *(*e.g., Luck & Hillyard, 1994; see Figure 1). Interestingly, it has been repeatedly shown (e.g., Ruijter, 2000) that caffeine enhances a fronto-central P2 compared to placebo in visual attention paradigms. It has been suggested that these P2 effects might reflect caffeine-induced modulations of higher-level control processes.

N2 (or N2b): The N2b component has been associated with selective processing of relevant stimuli (Figure 1). Specifically, it has been interpreted as being a phasic alerting reaction that facilitates further controlled processing of relevant information in the limited capacity system (Naätanen & Picton, 1986). Moreover, this component is sensitive to the state of the subject and to resource allocation (Gunter et al., 1987). It usually peaks around 200 ms after stimulus onset and has a frontocentral voltage distribution. In many circumstances, this component appears to covary with a later positive component, the P3.

P3 (or P3b): The P3 is a posteriorly distributed, positive deflection linked to stimulus evaluation (Figure 1). P3 latency has been argued to reflect stimulus evaluation time, whereas P3 amplitude has been interpreted as the amount of energetical resources required for stimulus evaluation. Observations of increased P3 amplitude in caffeine conditions (relative to placebo) are in agreement with these generally accepted viewpoints of the P3 (e.g., Lorist, 1995; Ruiter, 2000). However, other interpretations of the functional significance of the P3 have

been put forward as well. For instance, P3 amplitude may reflect task load (or task difficulty), a process affected by working memory resources. In fact, it has been pointed out that the P3 does not appear to be a unitary component but, instead, represents the activity of a widely distributed system whose constituent parts may be more or less coupled depending on the situation (see Polich & Kok, 1995 for a review).

Contingent Negative Variation (CNV): The CNV is a slow negative brain potential that is traditionally observed during the foreperiod on forewarned reaction time situations (Walter et al., 1964; Figure 1). Thus, this component is typically observed in paradigms involving the presentation of pairs of stimuli, separated by a time interval. The CNV consists of two components, an early and frontocentrally distributed wave and a later centroparietally distributed wave (cf. Rohrbaugh & Gaillard, 1983). Traditionally, the early CNV wave is taken to reflect the orienting activities to the warning signal, whereas the late CNV wave is thought to reflect effortful motor preparation. Other studies have indicated non-motoric processes like stimulus anticipation and working memory to contribute to the late CNV (e.g., Ruchkin et al., 1995; van Boxtel & Brunia, 1994a).

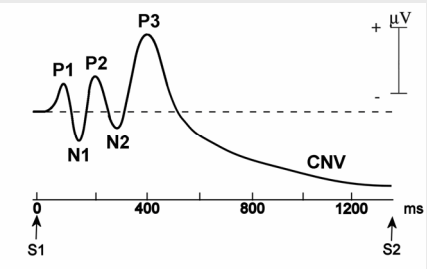

Figure 1. Components of a hypothetical ERP waveform, elicited between two stimuli (S1 and S2).

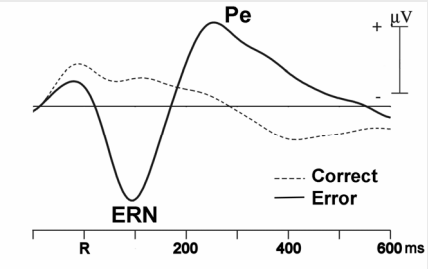

Figure 2. Components of response-locked ERPs during correct responses (dashed lines) and errors (thick lines).

Error Related Negativity (ERN): The ERN (Gehring et al., 1993) or error negativity (Ne; Falkenstein et al., 1991) constitutes a psychophysiological index of action monitoring (see Figure 2). It is a sharp negative deflection in the ERP with a fronto-central distribution, that peaks within 100 ms after an incorrect response. The ERN reflects preconscious detection of errors and response conflicts (Botvinick et al., 2001; Falkenstein et al., 2000) as well as appraisal of the affective or motivational significance of detected errors (Yeung, 2004). It most likely originates in the anterior cingulate cortex (e.g., van Veen & Carter, 2002), which appears to be an essential component of the neural circuit for action monitoring.

Error Positivity (or Pe): The ERN is sometimes followed by a slower positive potential labeled error positivity (Pe), peaking at centro-parietal electrode positions at approximately 200-500 ms after the erroneous response (Figure 2). The ERN and Pe differ in terms of timing and scalp distribution, and studies that examine individual differences in, and/or the effects of experimental manipulations on both the ERN and the Pe often report these effects to be dissociated (Overbeek et al., 2005 for a review). There is evidence to suggest that the Pe is related to conscious recognition of an error (Nieuwenhuis et al., 2001). Moreover, the Pe may constitute a P3b associated with the motivational significance of the error, a notion supported by the finding that some of the main regions involved in the generation of the P3 appear also to be active when a Pe is observed (Hester et al., 2005).

Before introducing this thesis, some general remarks concerning effects of caffeine on cognitive processing and performance should be made. It seems that the influence of caffeine on performance typically is (1) of a modest size; (2) selective, in that some aspects of performance are more sensitive than others; (3) complex, perhaps representing patterns of behavioral facilitation and interference; and (4) not constant, in that it can be moderated by a wide variety of variables. Furthermore, the efficacy of caffeine to reduce impairments in mental efficiency under states of reduced arousal (i.e., fatigue and reduced alertness) is one of the most consistent general findings in caffeine research. The results, however, are not exclusively limited to suboptimal conditions, since benefits of caffeine have also been observed under optimal alertness conditions (Lorist, Snel, & Kok, 1994).

For reviews about the cognitive effects of caffeine, see e.g., Garattini (1993), and Snel, Lorist, and Tieges (2004).

1.2 Cognitive control

Cognitive control refers to the ability to orchestrate thought and action in accordance with changing environmental demands and internal goals, leading to purposeful behavior (Miller & Cohen, 2001). That is, cognitive control processes supervise and organize the operation of more specialized cognitive processes. Typical situations that require a high degree of control include situations that elicit a tendency to commit an inappropriate action, or in which the task is novel, or in which multiple tasks need to be managed at the same time. As an example of the latter case, the need for cognitive control is apparent to anyone who has tried to talk on the phone and read e-mail at the same time.

Numerous attempts have been made to explain the control and co-ordination of subprocesses during the performance of complex cognitive tasks (for an overview, see Monsell, 1996). Early theoretical frameworks have postulated the existence of some type of "executive system" that resides in the prefrontal cortex and presides over behavior, especially in novel situations (e.g., Baddeley, 1986; Norman & Shallice, 1986). The latter authors described a higher-level of control called the "supervisory attentional system" that overrides routine execution of learned behaviors when novel circumstances require modified actions. It thus provides a mechanism for favoring certain actions, to reflect the demands of the situation or to emphasize some goals over others.

In contrast to these unitary views on cognitive control, more recent approaches have emphasized a complex interplay between several subprocesses. That is, they have dismissed the notion of a single control system (e.g., Miller & Cohen, 2001). Instead, these models of control are much more computationally and/or anatomically explicit about the principles of control recruitment and intervention (e.g., Cohen, Dunbar, & McClelland, 1990). Importantly, cognitive control functions such as error monitoring, task-set reconfiguration, context updating, or interference control, should not necessarily be considered as basic mental functions, supported by specific dedicated neural circuits, as

implied by earlier models (e.g., Norman & Shallice, 1986). Instead, they might be thought of as emergent functions, arising from dynamic interactions between existing subordinate processes (Hommel, Ridderinkhof, & Theeuwes, 2002). In other words, only a concert of many processes may create the emergent property of being the "controller" or "executive".

Cognitive control is most commonly associated with the anterior part of the brain, the (pre)frontal cortex (PFC; Chao & Knight 1995; Miller & Cohen 2001; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004b). This is not surprising given its extensive connectivity with other brain regions and specialized processing capabilities. The importance of the PFC for cognitive control becomes apparent in those instances when its function is compromised. For instance, frontal lobe damage generally causes loss of the ability to solve problems and to plan and initiate actions, such as crossing the street. Nevertheless, the ability for cognitive control no doubt involves neural circuitry that extends over much of the brain, including both cortical and subcortical areas (e.g., Aron & Poldrack, 2006; Monchi, Petrides, Strafella, Worsley, & Dovon, 2006).

Cognitive control can be divided into two main components: Executive (or "regulative") control and evaluative control. *Executive* control refers to the ability of the cognitive system to configure itself to perform specific tasks through adjustments of perceptual selection, biasing of response selection, and the maintenance of contextual information over temporally extended periods. In other words, executive control is responsible for the activation and implementation of control processes in order to co-ordinate and adjust goal-directed behavior. *Evaluative* control, on the other hand, refers to the ability of the cognitive system to monitor the internal and external environment for signals that indicate the demand for increased executive control. As such, it is responsible for monitoring the need for executive control and signaling when adjustments in control are needed (Ridderinkhof et al., 2004b).

1.2.1 Evaluative control: Action monitoring and error-related negativity (ERN)

Action monitoring refers to a mechanism in the cognitive system that involves the ability to monitor and evaluate ongoing information processing for signs of conflict or erroneous outcome. Accordingly, these control processes are being alerted if information processing does not proceed adequately, which may lead to adaptations in future behavior. As such, action monitoring is considered a major aspect of evaluative control.

Converging evidence suggest that the medial frontal cortex, especially the anterior cingulate cortex (ACC), is involved in action monitoring. Specifically, the detection of unfavorable outcomes, response errors, response conflict, and decision uncertainty elicits largely overlapping clusters of activation foci in or very near the ACC (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004a).

Holroyd and Coles (2002) have proposed an influential neurobiological model that captures the role of the ACC in coding outcome- and error-related information. According to

this model, errors in reward prediction are coded by phasic changes in activity of the mesencephalic DA system: A phasic increase or decrease when ongoing events are suddenly better or worse (respectively) than expected. These phasic DA signals are communicated to the ACC and give rise to the ERN, a psychophysiological index of action monitoring (see Box 2), which in turn utilizes the signal to modify task performance. The notion of DA involvement in action monitoring is supported by pharmacological studies showing enhanced ERN amplitudes after administration of d-amphetamine (de Bruijn, Hulstijn, Verkes, Ruigt, & Sabbe, 2004) and reduced ERN amplitudes with alcohol (Ridderinkhof et al., 2002).

1.2.2 Executive control: Proactive versus reactive control

With respect to executive control, Braver et al. (in press) proposed a "dual-process" framework that makes a distinction between proactive and reactive control. The model suggests that cognitive control may not only be achieved by *proactive* mechanisms but also through *reactive* mechanisms. In their view, *proactive* control is a resource demanding type of control concerned with preparation and maintaining goals in working memory; *reactive* control deals with a stimulus-driven, conflict-resolving type of control. They further state that proactive control is metabolically costly and is most likely to be used if sufficient capacity is available. Comparable distinctions have been made by others (e.g., early and late correction, Jacoby, Kelly, & McElree, 1999).

The proactive-reactive distinction can be clarified by the following example. Suppose someone decides in the morning to stop by at the post office after work to post a package. A proactive control strategy would require the goal information to be actively sustained from the time the intention is formed until the goal is satisfied (e.g., stopping by at the post office and having posted the package). The usefulness of such a proactive strategy is that plans and behaviors can be continually adjusted to facilitate optimal completion of the goal (e.g., leaving work a little earlier and not scheduling a late appointment). In contrast, with a reactive control strategy the goal would only be transiently activated at the time of intention, and then need to be reactivated again by an appropriate trigger event (e.g., the package left on the car seat might trigger your memory). Because of this need for repeated re-activation, there is greater dependence on the trigger events themselves. When these are insufficiently salient or discriminative they will not drive re-activation. Thus, proactive control requires the presence of predictive contextual cues. Moreover, it is metabolically costly and is prohibitive with very long intervals. In contrast, reactive control is stimulus-driven rather than intention-driven (Braver et al., in press).

It should be noted that reactive control is engaged after, rather than before the occurrence of some imperative event. Furthermore, reactive control mechanisms are engaged only as needed, on a "just-in-time" basis rather than consistently and in advance of critical events. Therefore, reactive control can be thought of as a suboptimal strategy. Nevertheless, the default mode for the cognitive system is probably one favoring reactive control, given its

greater utilization in more situations and lower demands on metabolic resources. Both forms of control strategy may be used during performance of many cognitive tasks, but subtle task and individual difference factors may affect their relative weighing. In the next section, the paradigms as used in the present thesis will be described and classified along the proactive-reactive control distinction.

1.2.3 Research paradigms of executive control

1.2.3.1 Task-switching paradigm

In everyday life, cognitive control is highly dynamic. People move from one task to the next, and new goals replace old ones. Hence, cognitive control must be highly flexible. These dynamic control processes have been extensively studied using the task-switching paradigm. The first systematic study on task switching dates back to the year 1927. In that year, the educational psychologist Arthur Jersild compared the time subjects needed to alternate between subtraction and addition of numbers from a list of two-number digits to the time needed to perform just one task. In the past decade, new interest in the task-switching paradigm has led to the development of several new paradigms to investigate dynamic cognitive control.

Task-switching paradigms typically require participants to rapidly switch back and forth between two or more choice-RT tasks afforded by the same class of stimuli. In order to succeed, subjects must internally represent and rapidly update task-set information about each task, that is, the appropriate rules that govern the mapping between stimuli and responses. As such, proactive control is highly involved during task switching.

Within these paradigms, the central observation is that the changing of task incurs a switch cost. That is, when the task changes, mean RT is longer (and error rate usually greater) than when the same task is repeated. The task to be performed on a given trial may be determined by a fixed order (e.g., the alternating-runs paradigm in which participants switch tasks every second trial; Rogers & Monsell, 1995), or by an explicit cue presented prior to the stimulus (e.g., Meiran, 1996).

Another observation is that responses on repeat trials within mixed blocks (in which participants have to switch between two task-sets) are still slower than when one task is performed throughout a block (single-task block). This “mixing cost” results from a higher working memory load in mixed blocks compared to single-task blocks (one task-set), and thus reflects the ability to maintain and co-ordinate multiple task sets during task switching (Kray & Lindenberger, 2000).

The switch cost can be reduced when participants are given sufficient time to prepare for the impending task (Rogers & Monsell, 1995). A “residual” cost remains that is immune to elimination by further lengthening of the preparation interval. In addition to preparation time, other factors affecting the size of the switch cost include the overlap between stimulus and response attributes, prestimulus cueing, factors encouraging advance

preparation, and relative task strength or familiarity (Monsell & Driver, 2000). Moreover, it has been shown that the switch cost is increased in certain patient groups, such as those suffering from Parkinson's disease (e.g., Cools, Barker, Sahakian, & Robbins, 2001).

A number of explanations have been offered for the switch cost, as reviewed by Monsell (2003). Some authors have suggested a distinction between endogenous or top-down controlled processes (e.g., 'task-set reconfiguration', Rogers & Monsell, 1996; 'goal shifting', Rubinstein, Meyer, & Evans, 2001) and exogenously controlled processes (e.g., 'stimulus-cued completion of reconfiguration', Rogers & Monsell, 1995; 'rule activation', Rubinstein et al., 2001). In contrast, De Jong (2000) conceptualized preparation as a probabilistic all-or-none process. That is, participants will prepare in advance on some trials but not on others, depending on task parameters and participant variables.

In general, the diminution of the switch cost is said to result from an active process of advance reconfiguration or updating of the task set (Meiran, 1996; 2000; Rogers & Monsell, 1995; Rubinstein et al., 2001), from slowly decaying interference from the previously relevant task set (Allport, Styles, & Hsieh, 1994; Allport & Wylie, 1999), or from long-term priming due to associative retrieval of conflicting task sets (Allport & Wylie, 1999, 2000; Rogers & Monsell, 1995). This priming can be quite stimulus-specific (Waszak, Hommel, & Allport, 2003), such that stimuli acquire associations (i.e., "bindings") with the tasks in which they occur. When the current task activation is weak, as is the case on switch trials, the target stimuli can trigger retrieval of the residually associated, competing task, provoking larger time costs. While most researchers agree that both bottom-up, stimulus-driven processes and top-down control processes contribute to task switching (e.g., Ruthruff, Remington, & Johnston, 2001), there is still disagreement about the exact blend.

Neuro-imaging studies have revealed that task switching involves an extensive neural network, including regions of lateral PFC and parietal cortical areas, the pre-supplementary motor area (pre-SMA), and the ACC (e.g., Braver, Reynolds, & Donaldson, 2003; Dreher & Berman, 2002; Kimberg, Aguirre, & D'Esposito, 2000). In addition, some recent studies have used ERP measurements to examine the cognitive processes that underlie task switching (e.g., Karayanidis, Coltheart, Michie, & Murphy, 2003; Kieffaber & Hetrick, 2005; Lorist et al., 2000; Nicholson, Karayanidis, Bumak, Poboka, & Michie, 2005).

1.2.3.2 The stop-signal paradigm

One of the key aspects of cognitive control is the ability to suppress or override competing behavioral response tendencies in order to resolve conflicts and, ultimately, achieve flexible goal-directed behavior. Inhibitory control is invoked when the tendency to make a reflex-like, premature, inappropriate, or incorrect response must be suppressed. Stopping comes into play when the current course of planned thought and action is no longer appropriate (Logan, 1994; Ollman, 1973). As environmental conditions change, new goals are set which demand that current courses of thought and action are inhibited, and that is switched to alternative courses of action in line with current goals. Stopping (or response inhibition) is

an extreme case of executive intervention, and is usually triggered by external demands (such as an alarm bell or a red light). As such, reactive control is highly engaged in stopping.

An adequate tool to investigate stopping is the stop-signal paradigm. In this paradigm, comparisons between conditions with or without response inhibition can be thoroughly investigated (e.g., Logan & Cowan, 1984). The stop signal requires subjects to withhold the initiated response to the choice RT task. Interestingly, the stop task yields an estimate of the duration of the covert response-inhibition process, termed the stop-signal RT.

1.2.3.3 The flanker paradigm

Dealing with conflicting response tendencies is an important step towards goal-directed behavior, and is thought of as another key aspect of cognitive control. The flanker task, as introduced by Eriksen and Eriksen (1974), provides a means to selectively manipulate the presence or absence of response competition while keeping other task demands constant. In conflict tasks, the designated response is indicated by one aspect of the stimulus, but competing response tendencies may be elicited by other aspects of the stimulus, even if the latter are to be ignored. For example, on an incongruent trial, a target arrow may point to the left, while the flankering arrows point to the right. Responses are typically slowed when the irrelevant stimulus features elicit the response opposite to the one elicited by the target stimulus feature (the congruency effect). Adequate performance in the flanker task relies on effective engagement of interference control processes, such as the selective inhibition of inappropriate responses.

Note that interference control can only occur in response to, and after presentation of the imperative stimulus, and thus requires a high degree of reactive control.

1.2.3.4 The continuous performance test

The continuous performance test (CPT) was developed in 1956 by Rosvold and colleagues to study vigilance or sustained attention. In the original CPT, letters were presented visually one at a time, at a fixed rate. The subject's task was to respond by pressing a lever whenever the letter X, designated as the target, appeared and to inhibit a response when any other letter was presented. Since then, many variations of the CPT have been developed, including a cueing variant of the AX-CPT (e.g., Braver, Barch, & Cohen, 1999).

In this cued version of the CPT, the target is the letter X, but only if the X is preceded by the letter A. Participants are instructed to respond to the sequence A-X by pressing a target button. A nontarget response has to be made to all other letter combinations, i.e., AY, BY, and BX (where cue B and probe Y refer to the collection of letters other than A and X).

The high probability of AX (target) trials (usually 70%) induces two types of bias in participants. The first is to make a target response to the occurrence of any X probe. On those trials in which a target response should not be made to the X probe (i.e., BX trials),

context information provided by the cue must be used in an inhibitory fashion to suppress the production of a false alarm. The second bias involves an expectancy to make a target response following the occurrence of an A cue. On those trials in which the cue is an invalid predictor of the response (i.e., AY trials), this attentional function of context creates the tendency to produce a false alarm (Braver et al., 1999). Efficient AX-CPT performance likely involves both proactive and reactive control. For instance, context representations in the AX-CPT can be engaged proactively and reactively (Braver et al., in press).

1.3 Dose

Many studies have shown that the effects of caffeine are dose-dependent, which might be linked to the finding that different brain areas are differentially sensitive to caffeine (Nehlig & Boyet, 2000). However, other studies report a flat dose-response relationship, with no differences between lower and higher doses of caffeine on cognitive functioning (Lieberman, Wurtman, Emde, Roberts, & Coviella, 1987; Robelin and Rogers, 1998). Still, a generally accepted view is that favorable subjective and performance-enhancing stimulant effects occur at low to intermediate caffeine doses, whereas high doses produce impairments or no effects on performance. In other words, performance improves as long as energetical supplies increase up to a certain peak, beyond which it deteriorates ("inverted-U" hypothesis; Yerkes & Dodson, 1908).

The doses used in research on caffeine vary substantially. Some report administration of a single, large dose of caffeine (up to 600 mg) that is not representative of the manner in which caffeine is usually ingested. On the opposite, the use of very small quantities has been reported as well (Lieberman et al., 1987; Smit & Rogers, 2000). Still other studies have concentrated on the effects of moderate, normal daily doses of caffeine (comparable to about two cups of coffee).

The matter of what dose should be used is closely linked to the interests of the researcher. If her main goal is to learn about caffeine's actions on daily life activities, it is best to use a habitual dose of caffeine. On the other hand, when one is primarily interested in the dose at which various brain areas are activated by caffeine, it might be best to use a number of doses including a very small and progressively larger doses of caffeine.

The present research is mainly motivated by the first goal. Consequently, for daily life relevance of the studies presented in this thesis, the effects of habitual amounts of caffeine are evaluated in regular coffee consumers. Specifically, a dose of 3 mg/kg body weight (BW), which is comparable to two cups of coffee and therefore in the range of normal coffee consumption, is included in all studies. This is a commonly used dose in research on caffeine, which has the additional advantage of facilitating comparison of the present results with findings of other studies.

In addition to a dose of 3 mg/kg BW, we decided to administer a second, higher dose of caffeine (except for the study described in Chapter 5). The rationale behind this

approach is related to the fact that the present studies are among the first to study caffeine's actions on processes like action monitoring, task switching, and response inhibition. Consequently, we do not know if such processes are sensitive to caffeine, let alone what dose is required for stimulating them. On the one hand, it has been argued that a lower level of arousal is needed for optimal performance in more difficult tasks than easier tasks, perhaps because the former are intrinsically motivating and would therefore increase the subject's arousal by itself. This would imply that a relatively low dose of caffeine is optimal in the tasks used in the present studies. On the other hand, there is evidence to suggest that complex tasks benefit from relatively high doses of caffeine. For instance, Ruijter, Lorist, and Snel (1999) investigated multiple doses of caffeine in a complex dual-task study, and found a linear decline in RT on both tasks with increasing caffeine dose up to 7.5 mg/kg BW, accompanied by an increasing P3 amplitude.

Thus, in addition to a dose of 3 mg/kg BW, we administered a dose of 5 mg/kg BW (Chapters 2 and 3) and 6 mg/kg BW (Chapter 4) to participants. These amounts are equivalent to about 4 and 5 cups of coffee, respectively (for a person weighing 70 kg and a cup of coffee containing 85 mg caffeine).

1.4 Outline of this thesis

The present thesis comprises four empirical studies, all aiming to understand the effects of caffeine on evaluative and executive cognitive control by using varieties of the four tests that were mentioned before. These studies revolve around the three following research questions, using behavioral measurements and high-density ERP recordings.

(1) Does caffeine influence evaluative control, as involved in action monitoring, and what neural mechanisms underlie these possible effects of caffeine? This research question is addressed in Chapter 2. A double-blind, placebo-controlled, within-subjects experiment is reported, in which two caffeine doses (3 and 5 mg/kg body weight) and a placebo were administered to 18 nonsmoking, habitual coffee drinkers. This study provides support for an effect of caffeine on evaluative control. Specifically, it will be shown that consumption of a few cups of coffee strengthens the monitoring of ongoing cognitive processes for signs of erroneous outcomes, as evidenced by caffeine-induced enhancements in ERN amplitude. However, ERN amplitudes were not different for low and high caffeine conditions, consistent with previous studies showing a flat dose-response relationship in mood and psychomotor performance (e.g., Robelin & Rogers, 1998).

(2) Does caffeine influence executive control, as involved in task switching, and what neural mechanisms underlie these possible effects of caffeine? This issue is addressed in Chapters 3 and 4.

In Chapter 3 we explore the effects of a 3 and 5 mg/kg BW dose of caffeine and a placebo on behavioral and ERP measures of task switching, using the same experimental design as described in Chapter 2. The effects of caffeine on task switching and task maintenance are investigated using a modified version of the alternating-runs paradigm (Lorist et al., 2000). Two types of blocks are presented: Mixed-task (AABB) blocks, in which participants alternate predictably between two tasks, and single-task (AAAA, BBBB) blocks. While switch costs refer to longer RTs on task-switch trials (e.g., AB) compared to task-repeat trials (e.g., BB); mixing costs refer to longer RTs in task-repeat trials compared to single-task trials. Furthermore, preparation time is manipulated, in order to test whether caffeine has a specific effect on anticipatory processes involved in task switching. The behavioral and ERP results provide the first evidence that coffee consumption improves task-switching performance, in particular by enhancing anticipatory processing.

In Chapter 4, these caffeine-induced effects of caffeine on task switching are explored in greater detail, using unpredictable (cued) rather than predictable switches. As such, it is possible to explore the exact timing of anticipatory task-switching processes, without being confounded by response-related processing (which was the case in the study as described in Chapter 2). Specifically, the goal of the study is to further examine whether effects of caffeine on task switching result from caffeine-induced improvements in task-nonspecific anticipatory processes (e.g., actively maintaining the task set in working memory and protecting it against interference) or improvements in task-specific processes (e.g., rule-based response selection). It is predicted that effects of caffeine on task switching are task-specific, and hence should be related to the characteristics of the tasks that have to be switched. To this end, the extent to which the task appeals to anticipatory processing is manipulated by varying the number of task items that have to be prepared (mapping rule, response effectors, or both). Moreover, in a further attempt to check for dose-dependent effects, the high dose is enhanced to 6 mg/kg BW caffeine. The findings of this study suggest once more that caffeine improves task-switching performance by enhancing anticipatory processes, but it appears to do so by affecting task-nonspecific processes (contrary to our hypothesis). These findings are then discussed with respect to brain areas that are involved in the neural circuits underlying task switching and that are sensitive to caffeine.

(3) Does caffeine influence executive control, as involved in response inhibition? At first glance, we would expect caffeine to strengthen inhibitory control, consistent with the role of striatal DA activity in response inhibition (see Cropley, Fujita, Innis, & Nathan, 2006) and in mediating behavioral effects of caffeine (Fredholm et al., 1999). However, previous reports of stimulant effects on inhibitory processes have been inconsistent (e.g., Marczinsky & Fillmore, 2003). In Chapter 5, three behavioral experiments are described in which the effects of a 3 mg/kg BW dose of caffeine and a placebo on different aspects of response inhibition are examined.

The first experiment employs a modified version of the AX-CPT (Braver et al., 1999). In this task, the need for response inhibition is invoked mainly on trials in which the cue is an invalid predictor of the response, which creates the tendency to produce a false alarm. In the second experiment, a stop-signal task is used to assess effects of caffeine on general aspects of response inhibition (i.e. serving to inhibit any ongoing motor activity; Logan & Cowan, 1984). The third experiment employs a flanker task to study caffeine's effects on more specific aspects of response inhibition (inhibiting the activation for one response but not the other; Eriksen & Eriksen, 1974). Collectively, the findings show that the presently studied domains of response inhibition are not susceptible to effects of caffeine.

The four empirical chapters are published in, or have been submitted to, international journals. They have been inserted in this thesis in their original submitted or accepted form. In particular to acknowledge the important contributions of the co-authors, a list of references is presented below:

Tieges, Z., Ridderinkhof, K.R., Snel, J., & Kok, A. (2004). Caffeine strengthens action monitoring: Evidence from the error-related negativity. Cognitive Brain Research, 21(1), p. 87-93. (Chapter 2)

Tieges, Z., Snel, J., Kok, A., Wijnen, J.G., Lorist, M.M., & Ridderinkhof, K.R. (2006). Caffeine improves anticipatory processes in task switching. Biological Psychology, 73(2), 101-113. (Chapter 3)

Tieges, Z, Snel, J., Kok, A., Plat, N., & Ridderinkhof, K.R. (2007). Effects of caffeine on anticipatory control processes: Evidence from a cued task-switch paradigm. Psychophysiology, 44(4), 561-578. (Chapter 4)

Tieges, Z., Snel, J., Kok, A., & Ridderinkhof, K.R. No effects of caffeine on response inhibition. Manuscript submitted for publication. (Chapter 5)

Other publications related to the present thesis:

Snel, J., Lorist, M.M., & Tieges, Z. (2004). Coffee, caffeine, and cognitive performance. In A. Nehlig (Ed.), Coffee, Tea, Chocolate, and the Brain (pp.53-72). Florida: CRC Press

Snel, J., Tieges, Z., & Lorist, M.M. (2004). Effects of caffeine on sleep and wakefulness. In A. Nehlig (Ed.), Coffee, Tea, Chocolate, and the Brain (pp.13-34). Florida: CRC Press

2

Caffeine strengthens action monitoring: Evidence from the error-related negativity

The medial frontal cortex, especially the anterior cingulate cortex (ACC), is involved in action monitoring. We studied the role of moderate amounts of caffeine in action monitoring as expressed by the error-related negativity (ERN), an event-related brain component that reflects ACC activity. In a double-blind, placebo-controlled, within-subjects experiment, two caffeine doses (3 and 5 mg/kg body weight) and a placebo were administered to habitual coffee drinkers. Compared with placebo, both caffeine doses enlarged the ERN. Amplitudes of the P2 and P3 components were not affected by caffeine. Thus, the enlarged ERN after caffeine reflects a specific effect on action monitoring. We conclude that consumption of a few cups of coffee strengthens central information processing, specifically the monitoring of ongoing cognitive processes for signs of erroneous outcomes. Brain areas related to action monitoring such as the ACC presumably mediate these caffeine effects.

Chapter 2 has led to the following publication:

Tieges, Z., Ridderinkhof, K.R., Snel, J., & Kok, A. (2004). Caffeine strengthens action monitoring: Evidence from the error-related negativity. Cognitive Brain Research, 21(1), p. 87-93.

2.1 Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed psychoactive substance in the world. While it is present in a number of dietary sources such as tea, chocolate, and soft drinks, the largest intake of caffeine has always been through coffee. Caffeine, in doses that are normally consumed, blocks inhibitory adenosine A_1 and A_{2A} receptors throughout the brain, which increases central nervous system activity. Adenosine receptors are widely distributed throughout the brain, A_1 receptors being present mostly in cortical layers and striatum, and A_{2A} receptors being co-localized with dopamine (DA) receptors in the striatum (Acquas et al., 2002; Ferré, Fredholm, Morelli, Popoli, & Fuxe, 1997). Most behavioral effects of caffeine are caused by stimulation of dopaminergic activity through these antagonistic A_{2A}-DA receptor-receptor interactions (Fredholm et al., 1999; Garret & Griffiths, 1997; Nehlig, 1999).

Caffeine up to doses of 3 mg/kg body weight (BW) leads to subtle improvements in cognitive operations, the most reported of which are faster reactions, sometimes accompanied by fewer errors (Lorist & Snel, 1997; Ruijter, de Ruiter, & Snel, 2000a). These improvements result from both general caffeine effects on arousal, such as enhanced alertness and wakefulness, and from more specific effects on perceptual (feature extraction), attentional (selective attention), and motor (response preparatory) processes (Lorist et al., 1994; Ruijter et al., 2000a; Ruijter, de Ruiter, Snel, & Lorist, 2000b). In contrast, sensitivity of central higher-order processes to caffeine has received little emphasis. Therefore, we set out to investigate if caffeine influences these central processing stages. More specifically, we tested the assumption that caffeine improves action monitoring, which involves the ability to monitor ongoing processing in the cognitive system for signs of conflict or erroneous outcome. An essential component of the neural circuit for action monitoring is the anterior cingulate cortex (ACC; Carter et al., 1998; Luu, Flaisch, & Tucker, 2000; Nieuwenhuis et al., 2002).

A psychophysiological index of action monitoring is the error-related negativity (ERN; Gehring, Goss, Coles, Meyer, & Donchin, 1993) or error negativity (Ne; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991), a sharp negative deflection in the event-related brain potential (ERP) with a frontocentral distribution, that peaks within 100 ms after an incorrect response. The ERN reflects preconscious detection of errors and response conflicts (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000) as well as appraisal of the affective or motivational significance of detected errors (Yeung, 2004). It most likely originates in the ACC (Nieuwenhuis et al., 2002; Ullsperger & von Cramon, 2001; van Veen & Carter, 2002). According to Holroyd and Coles' theory (2002), the ERN is generated when a negative reinforcement-learning signal is conveyed from the mesencephalic dopamine system to the ACC, which utilizes the signal to modify task performance.

Indirect support suggesting dopaminergic involvement in action monitoring comes from studies showing enhanced ERN amplitudes after administration of d-amphetamine (de

Bruijn et al., 2004) and reduced ERN amplitudes with alcohol (Ridderinkhof et al., 2002).

Since caffeine partly antagonizes alcohol-induced impairments in certain aspects of driving performance (Liguori & Robinson, 2001) and psychomotor speed (Drake, Roehrs, Turner, Scofield, & Roth, 2003; Marczinsky & Fillmore, 2003), we expect that caffeine consumption yields enlarged ERN amplitudes, reflecting strengthened action monitoring. This suggestion is further supported by rat studies showing that moderate amounts of caffeine increased activation in medial prefrontal cortex (Acquas et al., 2002), specifically the ACC (Nehlig & Boyet, 2000). To test our hypothesis, we used a paradigm in which participants performed a switching task after a low and high caffeine dose and placebo, and examined ERPs recorded during hand errors. We expected larger ERN amplitudes in both caffeine conditions compared to placebo, and a larger ERN for high dose than low dose conditions.

2.2 Methods

2.2.1 Participants

Fifteen healthy, nonsmoking undergraduate students (8 males, 7 females) participated in this study. Age ranged from 18 to 26 (mean = 20.40, SD = 2.29). Their daily habitual coffee consumption was between 1.51 and 5.38 cups (mean = 3.66, SD = 1.24), which corresponds to a range from 154 to 549 mg caffeine (mean = 374, SD = 127). They were right-handed, had normal or corrected-to-normal vision, did not use prescription medication except for birth control, and reported no history of brain damage or psychiatric illness. Course credits were obtained for their participation.

2.2.2 Treatment manipulation

A double-blind, placebo-controlled, cross-over design was used. Each participant completed three experimental sessions, in which 3 mg/kg BW lactose (placebo), 3 mg/kg BW caffeine (low dose), and 5 mg/kg BW caffeine (high dose) dissolved in a cup of decaffeinated coffee was administered. The order of these sessions was counterbalanced across participants. They abstained from caffeine-containing foods and beverages for 12 h prior to the experiment. Compliance was checked through analysis of caffeine in saliva.

2.2.3 Subjective measures

Two questionnaires were used to measure subjective feelings before, during, and after the experimental blocks. Changes in mood were measured with the short version of the profile of mood states (POMS; Wald & Mellenbergh, 1990). Participants indicated how they felt at that moment for each of 32 adjectives on a 5-point scale ranging from 0 (not at all) to 4 (very

much). The five clusters of adjectives represented specific mood states: Depression, anger, fatigue, vigor, and tension. The Activation-Deactivation Activation Checklist (AD-ACL; Thayer, 1967) was used to measure various transitory arousal states.

2.2.4 Task

Participants completed a version of the alternating runs task (Lorist et al., 2000; Rogers & Monsell, 1995), in which they had to switch between two simple tasks in a predictable manner (AABB). This paradigm allowed us to test various hypotheses about the actions of caffeine on information processing; here we focus on action monitoring.

After the task instructions, a grey square (4 cm^2), subdivided into four quadrants (2 cm^2 each), was displayed continuously at the center of a black screen. Stimuli appeared, one by one, in the center of one of these quadrants in a clockwise fashion. They consisted of red and blue letters, randomly chosen from the set A, E, O, U, G, K, M, and R, and printed in an uppercase Arial font (0.5 x 0.8 cm). Half of the participants was instructed to judge the color of the letter (color task) if the letter appeared in either of the upper squares, and to judge whether the letter was a consonant or a vowel (letter identity task) if the letter appeared in the two lower squares, or vice versa. The other half of the participants was instructed to perform the color task if the letter appeared in either of the two left squares, and the letter identity task if it appeared in the two right squares, or vice versa. Stimuli remained on the screen until participants gave a response or until 2500 ms had elapsed. After a response-stimulus interval (RSI) of 150, 600, or 1500 ms (selected randomly but equiprobably) the next letter appeared on the screen. Stimulus-response mappings were counterbalanced across participants. Speed and accuracy were equally emphasized.

2.2.5 EEG recording

The electroencephalogram (EEG) was recorded with a 64-channel tin-electrodes Quikcap (Neuroscan, Inc.) referenced to the left earlobe. Impedance was kept below 5 kΩ. Eye movements were recorded from bipolar tin electrode pairs placed above and below the left eye, and left and right of the outer canthi of both eyes. EEG signals were amplified by SynAmps amplifiers (Neuroscan, Inc) and online filtered with a time constant set to 5 seconds and a low pass of 35 Hz. The data were digitized at 250 Hz.

2.2.6 Procedure

In an intake session, the intention and possible consequences of the experiment were explained to the participants and they filled out an informed consent form. This was followed by a training session, in which they completed three blocks of 194 trials (the first two trials of each block were instruction trials).

Next participants completed three experimental sessions of 3 h each, which were

identical except for treatment. All experimental sessions started at 9.30 a.m. Upon arrival the first saliva sample was taken, and participants were asked to fill out the POMS and AD-ACL. Then they completed three practice blocks. The experimental task started about 45 minutes after drinking the coffee at which point the second saliva sample was taken to check the caffeine manipulation, and both questionnaires were filled out for the second time. A total of twelve blocks were presented, with a short break after the sixth block. The task lasted about 90 minutes, after which the third saliva sample was taken and questionnaires were completed once more.

Saliva samples were centrifuged for 3 minutes at 10,000 rpm and about 1 ml of the supernatant was stored at –20 C° for caffeine analysis (Medical Laboratories Dr Stein, Maastricht, Netherlands).

All experimental procedures were conducted in compliance with relevant laws and institutional guidelines, and were approved by the departmental ethical committee.

2.2.7 Data reduction

Responses were defined as correct when made with the correct hand between 100 ms and 2500 ms after stimulus onset. Errors were defined as responses made with the wrong hand, regardless of speed. The mean number of erroneous trials that was averaged into the ERN was 50.60 (SD = 28.64), 43.27 (SD = 26.05) and 39.33 (SD = 26.12) for the placebo, low dose, and high dose, respectively.

Single trial epochs with 4096 ms duration were extracted offline. EEG was corrected for eye movement artifacts, using the algorithm described by Woestenburg, Verbaten, and Slangen (1983), and filtered offline at a 10 Hz low-pass cutoff frequency. Then, for each participant and for each condition, the EEG epochs were averaged synchronized to response onset in order to obtain response-locked waveforms and aligned to a baseline from 150-50 ms preceding the response, in accordance with standard procedures (e.g., Ridderinkhof et al., 2002). In order to include sufficient numbers of trials with erroneous responses into the ERPs, trials were pooled across RSIs and (color and letter-identity) tasks, separately for correct and incorrect responses. However, we selected only those trials that were followed by a 600 or 1500 ms RSI, in order to eliminate contaminating effects in the ERP due to processing of the subsequent stimulus. To obtain stimulus-locked waveforms, for each participant and for each condition, the EEG epochs were synchronized to stimulus onset and aligned to a 100 ms pre-stimulus baseline. The latter waveforms were computed only for the 1500 ms RSI condition, since this allowed examining stimulus-locked ERP components without contamination by ERP reflections of processes related to the preceding response.

2.2.8 Statistical analyses

Individual averages for subjective measures, error rates, reaction times (RT), and ERP component amplitudes were analyzed with repeated measures analyses of variance (ANOVA). Performance data were analyzed with the factors treatment (placebo, low dose, and high dose) and correctness (correct vs. incorrect). Response-locked ERN amplitudes were analyzed only for error trials; stimulus-locked P2, N2, and P3 amplitudes were analyzed only for correct trials. To correct for violations of the sphericity assumption in the ANOVA, degrees of freedom were corrected using the Huynh-Feldt method whenever appropriate. Corrected p-values but uncorrected df values are reported, the latter to facilitate interpretation of the data. Statistically significant main effects of caffeine were followed up by Helmert contrasts analyses, involving two orthogonal contrasts. The first contrast evaluates placebo against the mean of the two caffeine conditions; the second contrast tests the low dose against the high dose condition.

To check whether the saliva caffeine level differed between treatment conditions, separate repeated measures ANOVAs were performed for each sample point, again using Helmert contrasts.

2.3 Results

2.3.1 Saliva caffeine levels

Differences between caffeine and placebo conditions were not significant in pretreatment samples, but they were so for the posttreatment samples. For the former, mean caffeine levels were all <1.00 mg/l, which demonstrated compliance to the abstinence instructions ($F(2,28) = 2.23$, ns). For the second sample, mean caffeine levels were 1.00, 6.38 and 12.09 mg/l for placebo, low dose, and high dose respectively ($F(2,28) = 71.43$, $p < .001$). Contrasts indicated differences between caffeine compared to placebo ($F(1,14) = 23.88$, $p < .001$), and between low and high dose ($F(1,14) = 33.27$, $p < .001$). For the third sample, mean caffeine levels were <1.00, 3.10 and 5.95 mg/l for placebo, low and high dose, respectively ($F(2,28) = 76.24$, $p < .001$). Contrasts again indicated differences between caffeine conditions compared to placebo ($F(1,14) = 85.50$, $p < .001$), and between low and high dose ($F(1,14) = 62.44$, $p < .001$). Thus, saliva caffeine levels differed between placebo, low dose, and high dose conditions only after substance administration, both at the beginning and at the end of task performance.

2.3.2 Subjective data

Participants reported no differences between caffeine and placebo conditions on mood (POMS) or arousal (AD-ACL) upon arrival. Averaged over treatment conditions, they

reported increased fatigue after testing compared to before (fatigue subscale of the POMS) which did not interact with treatment. As for the AD-ACL, a decrease in reported feelings of general activation ($F(1,14) = 7.41$, $p < .05$) and high activation ($F(1,14) = 5.06$, $p < .05$) were found after testing compared to before, as well as a trend toward enhanced feelings of deactivation/sleep ($F(1,14) = 3.65$, $p = .082$). Again, no treatment effects were observed.

2.3.3 Behavioral data

As shown in Table 1, caffeine dose affected RTs ($F(2,28) = 5.88$, $p < .01$) and error rates ($F(2,28) = 4.46$, $p < .05$). Helmert contrasts revealed shorter RTs ($F(1,14) = 9.79$, $p < .01$) and lower error rates ($F(1,14) = 4.63$, $p < .05$) with caffeine compared to placebo. Low dose and high dose conditions differed marginally in accuracy, with fewer errors after a high dose than after a low dose ($F(1,14) = 3.54$, $p = .08$).

Participants responded on average 184 ms slower after error trials than after correct trials ($F(2,28) = 157.58$, $p < .001$). This post-error slowing, which reflects a change in strategy after an incorrect response to prevent future errors (Rabbit, 1966), was however not affected by treatment ($F(2,28) = .14$, ns).

2.3.4 ERN

Consistent with previous studies, the ERN was largest on frontocentral scalp sites and attained its maximum within 100 ms after the erroneous response (see Figure 1). ERN amplitude was defined as the negative peak value relative to baseline between 0-150 ms following the erroneous response in the response-locked ERP.

As shown in Figure 2, the amplitude of the ERN was affected by caffeine ($F(2,28) = 4.06$, $p < .05$). Helmert contrasts confirmed a larger ERN for caffeine conditions than for placebo ($F(1,14) = 17.17$, $p = .001$). Low and high caffeine conditions did not show any difference ($F(1,14) = .33$, ns).

Since caffeine intake yielded slightly but significantly reduced error rates (see Table 1), it could be argued that this accounted for the amplitude effects in the ERN. We used the difference in error rate between each caffeine condition and placebo as a covariate, and entered the covariates in two repeated measures ANOVAs in which the low dose and the high dose were each compared to placebo. Both low dose ($F(1,14) = 4.73$, $p < .05$) and high

	Placebo		Low dose		High dose	
Reaction times	619	(95)	567	(98)	555	(81)
Incorrect trials (%)	5.64	(3.10)	4.95	(2.83)	4.57	(2.66)

Table 1. Mean reaction times in milliseconds (standard deviations) for correct and incorrect responses in placebo, low dose, and high dose conditions.

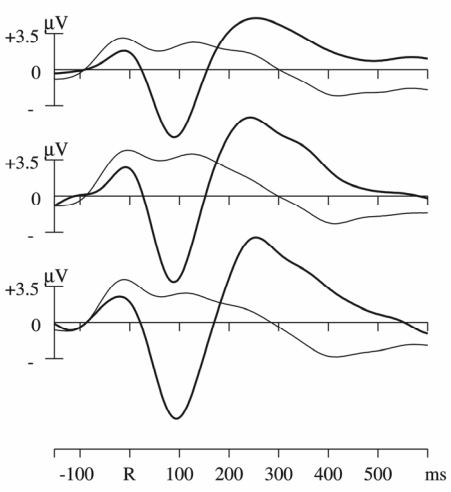

Figure 1. Response-locked grand-average ERPs recorded from FCz during correct responses (thin lines) and errors (thick lines), at placebo, low dose, and high dose (top, middle, and bottom, respectively). R denotes the time of the response.

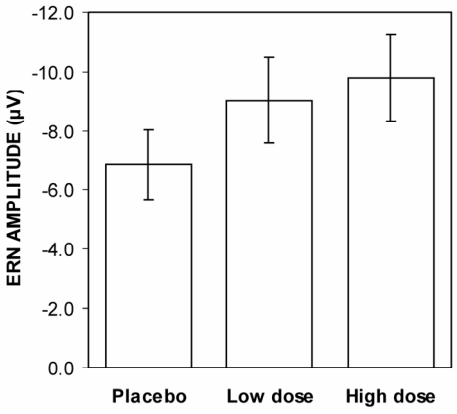

Figure 2. ERN amplitude at lead FCz associated with incorrect responses under various doses of caffeine. Error bars reflect standard errors.

dose ($F(1,14) = 9.28$, $p < .01$) effects on the ERN remained intact. Therefore, the enlarged ERN amplitude in caffeine conditions could not be explained merely by reduced error rates after caffeine intake.

Following the ERN, a clear positivity was observed after incorrect responses under placebo with a frontocentral peak around 300 ms, which has been referred to as the error positivity or Pe (Falkenstein et al., 2000). There is some evidence to suggest that this component reflects the conscious recognition of an error as such (Nieuwenhuis, Ridderinkhof, Blom, Band, & Kok, 2001).

Pe amplitude was defined as the positive peak value between 200-400 ms following the erroneous response in the response-locked ERP. The Pe was affected by treatment condition as well ($F(2,28) = 6.04$, $p < .01$). Helmert contrasts confirmed a larger Pe for caffeine conditions than for placebo ($F(1,14) = 16.04$, $p < .002$), whereas no difference between low and high dose conditions was found ($F(1,14) = .01$, ns).

Again, we entered the difference in error rate as a covariate in repeated measures ANOVAs separately for low and high conditions (compared to placebo). Both low dose ($F(1,14) = 9.95$, $p < .01$) and high dose effects ($F(1,14) = 14.14$, $p < .005$) remained intact.

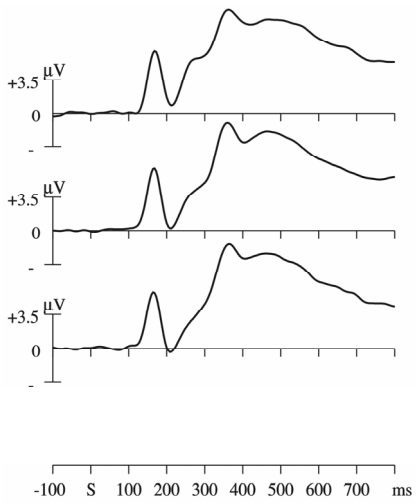

Figure 3. Stimulus-locked grand-average ERPs recorded from Pz during correct responses, at placebo, low dose, and high dose (top, middle, bottom, respectively). S denotes the time of the stimulus.

2.3.5 P2, N2, and P3

To ensure that the treatment effects on the ERN reflect effects specific to error processing rather than general changes in arousal or in perceptual or cognitive processes, stimulus-locked P2, N2, and P3 amplitudes in the three treatment conditions were compared (see Figure 3). P2 and P3 were defined as the positive peaks in the segments 100-200 ms (P2) and 300-600 ms (P3) poststimulus, while N2 was defined as the negative peak in the segment 150-300 ms poststimulus. No significant effect of treatment was observed (P2: $F(2,28) = .72$; N2: $F(2,28) = 3.13$; P3: $F(2,28) = .48$; the effect on N2 being marginally significant). The fact that caffeine affected the ERN but not other endogenous components, suggests that ERN amplitude was selectively enlarged by caffeine, reflecting strengthened action monitoring rather than general arousal changes.

2.4 Discussion

The present study demonstrated that ERN amplitude was enlarged in caffeine conditions compared to placebo. This finding could not be attributed to the slightly smaller number of errors made after caffeine, as verified by including error rate as a covariate in the analyses. In addition, the caffeine effect on the ERN cannot be understood as reflecting general caffeine-induced enhancements in ERP components, since P2 en P3 amplitudes were not affected by caffeine. Rather, the larger ERN in caffeine conditions has a specific cause. The

Pe, which followed the ERN, was also increased after caffeine. Considerable debate remains about the functional significance and neural sources of this component, although there is evidence to suggest that the Pe is related to conscious recognition of an error (Nieuwenhuis et al., 2001). Taken together, the data support our hypothesis that caffeine strenghtens the monitoring function of the mediofrontal cortex, as reflected in ERN amplitude. Whereas previous studies have shown that caffeine consistently facilitates input (perceptual, attentional) and output (motor-related) processes, our data indicate that caffeine also intensifies central, higher-order control processes, specifically action monitoring.

The present findings are in line with previous studies showing changes in action monitoring after administration of psychoactive substances that modulate dopaminergic activity (d-amphetamine; Stahl, 1999, alcohol; Eckardt et al., 1998; Hirvonen, Jaaskelainen, Naatanen, & Sillanaukee, 2000).

Boosting the mesencephalic dopaminergic system, more specifically the ventral tegmental area (VTA), may result in strengthening the error signal carried to the ACC. By analogy, reduced ERN amplitudes in older compared to young adults were shown to be caused primarily by age-related decline in dopaminergic projections to ACC (Nieuwenhuis et al., 2002). This idea is supported by increased glucose utilization found after moderate doses of caffeine in the VTA of rats (Nehlig & Boyet, 2000). Another possibility is that caffeine directly targets the ACC, which is supported by a study showing that caffeine selectively stimulates dopaminergic transmission in the medial prefrontal cortex, but not the nucleus accumbens of rats (Acquas et al., 2002). These authors note, however, that whether this change is the cause or the effect of the psychostimulant properties of caffeine remains unclear.

ERN amplitudes were not different for low and high caffeine conditions, which is consistent with previous studies showing a flat dose-response relationship in mood and psychomotor performance (Lieberman et al., 1987; Robelin & Rogers, 1998). Two explanations can be given for this lack of dose-specific effects. First, while caffeine effects are especially found in suboptimal arousal conditions such as boredom and fatigue (Lorist et al., 1994), arousal levels of the participants in our study were possibly close to optimal during testing (in accordance with the inverted U-shaped function between arousal and performance), since the switch task was demanding and intrinsically motivating. Secondly, the between-subjects variability in reported daily caffeine intake from coffee, ranging from 154 to 549 mg, could have resulted in performance deterioration in low users after a high dose due to induced arousal levels beyond the optimum, whereas high users benefited from the high dose, since they have a higher tolerance to caffeine than low users. Thus, variability in arousal levels after consumption of the high caffeine dose could have caused divergent effects. Although visual inspection of the ERP waveforms for low and high users (based on a median split) indeed suggested a dose-related increase in ERN amplitude in high users, but a decrease in low users, sample sizes were too small to corroborate this observation with reliable statistical analyses.

To summarize, our results show that caffeine strengthens monitoring of ongoing processing in the cognitive system for signs of erroneous outcome. In daily life situations, prevention of errors is crucial, and coffee may help.

3

Caffeine improves anticipatory processes in task switching

We studied the effects of moderate amounts of caffeine on task switching and task maintenance using mixed-task (AABB) blocks, in which participants alternated predictably between two tasks, and single-task (AAAA, BBBB) blocks. Switch costs refer to longer reaction times (RT) on task-switch trials (e.g., AB) compared to task-repeat trials (e.g., BB); mixing costs refer to longer RTs in task-repeat trials compared to single-task trials. In a double-blind, within-subjects experiment, two caffeine doses (3 and 5 mg/kg body weight) and a placebo were administered to 18 coffee drinkers. Both caffeine doses reduced switch costs compared to placebo. Event-related brain potentials revealed a negative deflection developing within the preparatory interval, which was larger for switch than for repeat trials. Caffeine increased this switch-related difference. These results suggest that coffee consumption improves task-switching performance by enhancing anticipatory processing such as task-set updating, presumably through the neurochemical effects of caffeine on the dopamine system.

Chapter 3 has led to the following publication:

Tieges, Z., Snel, J., Kok, A., Wijnen, J.G., Lorist, M.M., & Ridderinkhof, K.R. (2006). Caffeine improves anticipatory processes in task switching. Biological Psychology, 73(2), 101-113.

3.1 Introduction

3.1.1 Neurocognitive processes involved in task switching

Task-switching paradigms typically require participants to switch back and forth between two choice-reaction time (RT) tasks afforded by the same class of stimuli. In order to react quickly to a switch of task, task set information about each task, that is, the appropriate rules that govern the mapping between stimuli and responses, must be internally represented and updated. The changing of tasks incurs a "switch cost", that is, mean RT is longer and error rate usually greater with a change of task than when the same task is repeated. The task to be performed on a given trial may be determined by a fixed order (e.g., the alternating-runs paradigm in which participants switch tasks every second trial; Rogers & Monsell, 1995), or by an explicit cue presented prior to the stimulus (e.g., Meiran, 1996).

Another observation is that responses on repeat trials within these mixed-task blocks are slower than when one task is performed throughout a block (single-task block). This "mixing cost" results from a higher working-memory load in mixed-task blocks (two task sets) compared to single-task blocks (one task set), and thus reflects the ability to maintain and co-ordinate multiple task sets during task switching (Kray & Lindenberger, 2000).

The switch cost can be reduced (although not eliminated) when subjects are given ample time to prepare for the upcoming task switch (Rogers & Monsell, 1995). This diminution may result from an active process of advance reconfiguration or updating of the task set (Meiran, 1996, 2000; Rogers & Monsell, 1995; Rubinstein et al., 2001), from slowly decaying interference from the previous task set (Allport et al., 1994; Allport & Wylie, 1999), or from long-term priming due to associative retrieval of task sets that are associated with the current stimulus (Allport & Wylie, 1999, 2000; Rogers & Monsell, 1995), which can be quite stimulus-specific (Waszak et al., 2003).

Neuro-imaging studies have revealed that task switching involves an extensive neural network, including regions of lateral prefrontal cortex (PFC) and parietal cortical areas, the pre-supplementary motor area (pre-SMA), and the anterior cingulate cortex (e.g., Braver et al., 2003; Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Dreher & Berman, 2002; Kimberg et al., 2000; Konishi et al., 1998; Luks, Simpson, Feiwell, & Miller, 2002). Specifically, fMRI studies that have attempted to isolate brain activity associated with preparing for a shift of task report heterogeneous preparation-related activation in PFC and parietal cortex (Luks et al., 2002; MacDonald, Cohen, Stenger, & Carter, 2000; Sohn, Ursu, Anderson, Stenger, & Carter, 2000).

Several studies have used event-related brain potentials (ERP) to examine the processes that underlie task switching, which may provide more detailed information about the timing of neurocognitive processes than fMRI data. Some of these studies have attempted to isolate processes associated with anticipatory preparation for an impending switch of task (Karayanidis et al., 2003; Kieffaber & Hetrick, 2005; Lorist et al., 2000;

Miniussi, Marzi, & Nobre, 2005; Moulden et al., 1998; Nicholson, Karayanidis, Poboka, Coltheart, & Michie, 2005; Rushworth, Passingham, & Nobre, 2002; Wylie, Javitt, & Foxe, 2003). Lorist et al. (2000) observed a build-up of a slow negativity in the interval between the preceding response and the onset of the next stimulus (the response-stimulus interval, RSI). Relative to repeat trials, switch trials were associated with a reduced negative peak at parietal electrode sites, but this pattern reversed at frontal sites (such that switch trials were associated with enhanced negativities). In a comparable paradigm, Karayanidis et al. (2003) observed a similar build-up of slow negativity, peaking about 400 ms within the RSI. At parietal sites, like Lorist et al. (2000), these authors found that task-alternation trials were associated with a reduced negative peak, but this pattern reversed during the slower portion of the negativity. In a cueing variant of the task-switching paradigm, Rushworth et al. (2002) used a cue to signal subjects to either repeat the task or to switch to the reverse stimulus-response mapping. Again, a late slow negativity was observed within the cue-period of 1400 ms, which turned more negative for switch trials compared to repeat trials around 600 ms postcue at frontal sites.

In sum, the ERP studies described above consistently show a slow negative ERP component differentiating between switch and repeat conditions, which might indicate that the neural circuitry involved in task-set preparation is more strongly activated on switch compared to repeat trials. These components might be generated in prefrontal and/or parietal cortical areas involved in the internal updating of goals and linking this to the appropriate stimulus-response mappings (Brass & von Cramon, 2004; Braver et al., 2003).

The decrease of switch costs with increasing preparatory interval length reflects anticipatory processes that may be facilitated by dopamine (DA)-active agents such as caffeine. The involvement of DA neurotransmission in task preparation is suggested by the observation of impaired task-switching performance after administration of the DA receptor antagonist sulpiride (Mehta, Manes, Magnolfi, Sahakian, & Robbins, 2004). Moreover, patients with Parkinsons' disease, who suffer from DA depletion, exhibit task-switching deficits as well (Cools et al., 2001; Marie et al., 1999; Monchi et al., 2004). However, behavioral indices of switch costs do not in themselves specify which of the component processes involved in task switching are affected by DA-modulating substances. In the present study, we investigated the effects of the DA-active agent caffeine (Fredholm et al., 1999) on both behavioral and ERP indices of task switching, which might provide more specific cues with respect to the nature of neurocognitive processes underlying task switching.

3.1.2 Neurocognitive effects of caffeine

Caffeine (1,3,7-trimethylxanthine) is the best-known pharmacologically active constituent of coffee. In doses that are normally consumed, caffeine blocks inhibitory adenosine A_1 and A_{2A} receptors, which increases central nervous system activity. While adenosine A_1 receptors are present in almost all brain areas, A_{2A} receptors are found mainly in the DA-rich

regions of the brain (e.g., striatum) where they are co-localized with DA receptors (Acquas et al., 2002; Ferré et al., 1997). Most behavioral effects of caffeine are caused by stimulation of DA activity through these antagonistic A_{2A}-DA receptor-receptor interactions (Garrett & Griffiths, 1997).

In doses up to 3 mg/kg body weight (BW), caffeine leads to subtle improvements in cognitive operations, the most consistently reported of which are faster reactions, sometimes accompanied by fewer errors. These improvements result from both general caffeine effects on arousal, such as enhanced alertness and wakefulness, and from more specific effects on perceptual (feature extraction), attentional (selective attention), and motor (response preparatory) processes (Barthel et al., 2001; Lorist & Snel, 1997; Ruijter et al., 2000a, 2000b; Snel et al., 2004; Warburton et al., 2001).

Recently, caffeine has been shown to strengthen action monitoring (Tieges, Ridderinkhof, Snel, & Kok, 2004), which refers to the ability to monitor ongoing cognitive processing for signs of conflict or erroneous outcome (for a review see Ridderinkhof et al., 2004b) and that depends on DA projections from the basal ganglia to the medial frontal cortex (Holroyd & Coles, 2002; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). Expressions of action monitoring are intensified after administration of DA agonists (de Bruijn et al., 2004) and impaired after administration of DA antagonists (de Bruijn et al., 2004; Ridderinkhof et al., 2002). Accordingly, the effects of caffeine on action monitoring have been interpreted in terms of an agonistic effect on the midbrain DA system (Tieges et al., 2004).

3.1.3 Neurocognitive effects of caffeine on task switching

Several studies have shown that caffeine counteracts the detrimental effects of fatigue (Lorist et al., 1994; Lorist & Tops, 2003). Lorist et al. (1994) compared effects of caffeine between groups of well-rested and fatigued participants, and concluded that caffeine interacts with fatigue, such that caffeine and fatigue affect the same neural mechanisms but in an opposite manner. The ERP expressions of differential engagement of anticipatory processes in switch and repeat trials were observed to be reduced with mental fatigue (Lorist et al., 2000). Generalizing from the notion that caffeine tends to counteract the effects of mental fatigue, we would expect consumption of caffeine to boost anticipatory task-preparation processes, as expressed in an enhancement of the switch-differential ERP negativity in the preparatory interval. This hypothesis is informed also by the finding that task-switching performance is impaired by DA antagonists (Mehta et al., 2004) and thus may benefit from the DA agonist function of caffeine.

Caffeine may affect either the specific preparatory processes engaged in incurring a shift of one task set to another, or the more general processes involved in maintaining the prepared state, or both. Under sustained preparation, behavior may become increasingly susceptible to situational or external trigger conditions, as might be the case in mentally fatigued participants (Lorist et al., 2000; Lorist & Tops, 2003). The resulting decline in task-

switch performance may be countered by the general arousing effects of caffeine. Such an effect of caffeine would become manifest in switch costs when long RSIs are used, but especially in mixing costs, as mixed-task situations place higher demands on task set maintenance than do single-task situations. If, however, caffeine more specifically targets the neurocognitive processes involved in task-set updating (as reviewed above), then the beneficial effects would be expressed in switch costs but not in mixing costs.

3.1.4 The present study

In the present study, we examined the effects of a low and high caffeine dose on behavioral and ERP measures of task switching. To test our hypothesis, participants performed a modified version of the alternating runs paradigm (Lorist et al., 2000) with mixed and single-task blocks. Switch costs were defined as the difference in performance measures between switch and repeat trials within a mixed-task block, whereas mixing costs were defined as the difference between repeat trials (mixed-task blocks) and single-task trials (single-task blocks). We expected that caffeine would specifically enhance anticipatory control processes in task switching. If so, then the effects of caffeine on RTs would become manifest when given the opportunity to prepare for the upcoming task. As for ERPs, the enhanced slow negativity amplitude in ERPs elicited on switch trials relative to repeat trials should be more pronounced after caffeine, reflecting strengthened anticipatory control. Furthermore, we expected all caffeine effects to be greater for the high dose than for the low dose. Finally, we studied whether caffeine influenced task-set maintenance processes as measured with mixing costs, and how these effects were reflected in the ERPs.

3.2 Methods

3.2.1 Participants

Eighteen healthy, nonsmoking undergraduate students (8 males, 10 females) participated in this study. Age ranged from 18 to 30 (mean = 20.9, SD = 3.1). Their self-reported daily coffee consumption was between 123 mg and 583 mg caffeine (mean = 406, SD = 135; i.e. 1.2 to 5.7 cups). Total caffeine consumption from coffee, tea, and chocolate ranged from 154 mg to 823 mg (mean = 406, SD = 170). Participants were right-handed, had normal or corrected-to-normal vision, did not use prescription medication except for birth control, had normal sleep patterns (Mulder-Hajonides van der Meulen, Wijnberg, Hollander, & van de Hoofdakker, 1980), and reported no history of brain damage or psychiatric illness. Course credits were obtained for participation.

3.2.2 Treatment manipulation

A double-blind, placebo-controlled, cross-over design was used. Each participant completed three experimental sessions, in which 3 mg/kg BW lactose (placebo), 3 mg/kg BW caffeine (low dose), and 5 mg/kg BW caffeine (high dose) dissolved in a cup of normally brewed decaffeinated coffee was administered. These substances could not be detected by taste or smell. Milk powder and sugar were added to suit the subjects' taste. The order of sessions was counterbalanced across participants. They abstained from caffeine-containing foods and beverages for 12 h prior to the experiment. Compliance was checked through analysis of saliva.

3.2.3 Stimuli and apparatus

Participants were seated in a dentist chair with response buttons attached to both armrests, facing a VGA color monitor at a distance of 90 cm. They completed a version of the alternating runs task (Lorist et al., 2000; Rogers & Monsell, 1995), in which they had to switch between two simple tasks in a predictable manner (AABB). After presentation of the task instructions, a grey square (16 cm^2), subdivided into four quadrants (4 cm^2 each), was displayed continuously at the center of a black screen. Stimuli consisted of red and blue letters, randomly chosen from the set A, E, O, U, G, K, M, and R (uppercase Arial font, 0.5 x 0.8 cm). They appeared, one by one, in the center of one of the quadrants in a clockwise manner. Participants had to judge whether the letter was a consonant or a vowel (letter identity task) or determine the color of the letter (color task). In single-task blocks, one task was performed throughout the whole block. In mixed-tasks blocks, participants alternated between the two tasks. Half of the participants was instructed to perform the color task if the letter appeared in either of the two upper squares, and the letter identity task if it appeared in the two lower squares, or vice versa. The other half of the participants was instructed to perform the color task if the letter appeared in either of the two left squares, and the letter identity task if it appeared in the two right squares, or vice versa. Thus, participants had to switch tasks every second trial. Responses were made with the left and right index finger, and stimulus-response mappings were counterbalanced across participants.

Stimuli remained on the screen until participants gave a response or until 2500 ms had elapsed. After an RSI of 150, 600, or 1500 ms (selected randomly but equiprobably) the next letter appeared on the screen. Repeat and switch trials were both presented within mixed-task blocks, while single-task blocks consisted of single-task trials only, yielding a total of 27 conditions (trial type (3) x RSI (3) x treatment (3)). In each experimental session, 4 single-task blocks and 8 mixed-tasks blocks were presented of 194 trials each (the first two trials of each block were instruction trials), which ensured an equal number of 256 trials in each condition. All letter (8) x color (2) x position (4) x RSI (3) combinations appeared once in each block. The single-task and mixed-tasks blocks were randomly presented with the restriction that within a sequence of three subsequent blocks, one of them was a single-task

block, and this sequence was repeated 4 times. The sequence of blocks was varied across experimental sessions. Speed and accuracy were equally emphasized.

3.2.4 Subjective measurements

Four questionnaires were used to measure subjective feelings before, during, and after the experimental blocks. The short version of the profile of mood states (POMS; Wald & Mellenbergh, 1990) measured changes in five mood states: Depression, anger, fatigue, vigor, and tension. Participants indicated how they felt at that moment for each of 32 adjectives on a 5-point scale ranging from 0 (not at all) to 4 (very much). The 20-item state part of the Dutch version of the State-Trait Anxiety Inventory (STAI; van der Ploeg, Defares, & Spielberger, 1980) assessed the current level of anxiety on a 4-point scale ranging from 1 (not at all) to 4 (almost always). The Activation-Deactivation Activation Checklist (AD-ACL; Thayer, 1967) measured four specific arousal states: General activation, deactivation/sleep, high activation, and general deactivation. Participants indicated how they felt at that moment for each of 20 adjectives on a 4-point scale ranging from 1 (very much) to 4 (not at all). The Rating Scale Mental Effort (RSME; Zijlstra, 1993) was employed to rate subjective fatigue. Participants indicated on 150-point rating scales how they felt for each of 7 items that addressed different aspects of fatigue. In addition, an inventory (Mulder-Hajonides van der Meulen et al., 1980) was used to measure participants' sleep duration and quality on the night before the experimental sessions.

3.2.5 EEG recording

The electroencephalogram (EEG) was recorded with a 64-channel tin-electrodes Quikcap (Neuroscan, Inc.) referenced to the left earlobe. Impedance was kept below 5 kΩ. Eye movements were recorded from bipolar tin electrode pairs placed above and below the left eye, and left and right of the outer canthi of both eyes. EEG signals were amplified by SynAmps amplifiers (Neuroscan, Inc) and online filtered with a time constant set to 5 seconds and a low pass cut off at 35 Hz. The data were digitized at 250 Hz.

3.2.6 Procedure

In an intake session the intention of the experiment was explained to the participants and they filled out an informed consent form. After verification that participants met all inclusion criteria, a training session followed in which they completed two single-task blocks followed by three mixed-tasks blocks of 194 trials each. Next participants completed three experimental sessions of three hours each, which were identical except for treatment. The interval between sessions was approximately one week.

All experimental sessions started at 9.30 a.m. Upon arrival a first saliva sample was taken. Subsequently, participants filled out the POMS, STAI, AD-ACL, and sleep quality

questionnaire. Then they were prepared for the EEG recordings after which they drank the coffee and completed three practice blocks. The experimental task started about 45 minutes after drinking the coffee at which point a second saliva sample was taken, to check the caffeine manipulation, and participants filled out the POMS and STAI for the second time. A total of twelve blocks were presented with a 10 minute break after the sixth block in which the AD-ACL and RSME were filled out. The task lasted about 90 minutes. After testing, participants completed the POMS, STAI, AD-ACL, and RSME for the last time, and a third saliva sample was taken. Participants were fully debriefed at the end of the last session.

Saliva samples were centrifuged for 3 minutes at 10,000 rpm and about 1 ml of the supernatant was stored at –20 C° for caffeine analysis (Medical Laboratories Dr Stein, Maastricht, Netherlands).

All experimental procedures were approved by the departmental ethical committee and conducted in compliance with relevant laws and institutional guidelines.

3.2.7 Data reduction

3.2.7.1 Behavioral data

The first two trials within each block were regarded as practice trials and were excluded from analysis. For the remaining trials, responses were defined as correct when made with the correct hand between 100 ms and 2500 ms after stimulus onset. Errors were defined as responses made with the wrong hand, regardless of speed. Mean RTs for correct responses and error rates were calculated for the factors treatment (placebo, low and high dose), trial type (single-task, repeat, and switch), RSI (150, 600, and 1500 ms), and task (color, letter identity).

3.2.7.2 ERP data

Single trial epochs of 4096 ms duration were extracted offline and subsequently scanned for A/D saturation and flat lines. Ocular artifacts were controlled according to the method of Woestenburg et al. (1983). Epochs containing artifacts (change in amplitude of more than 50 μV per 2 consecutive samples) or drifts (change in amplitude of more than 200 μV per epoch) in one or more channels were omitted for analysis. Then, epochs were filtered offline with a 25 Hz low-pass cutoff frequency. For each participant, condition, and electrode, two sets of epoched data were created. Response-locked ERPs were obtained aligned to a baseline of -50 to 50 ms around the preceding response, to evaluate ERP effects of preparation on brain activity. Thus, epochs were averaged separately according to whether the stimulus following the current response required a change in task (switch) or performance of the same task (repeat or single-task). In addition, stimulus-locked (i.e., poststimulus) waveforms were created by averaging EEG epochs synchronized to stimulus onset, aligned to a baseline from 100-0 ms preceding the stimulus.

For reasons of clarity, the same labels will be used for stimulus- and response-locked ERP waveforms. For stimulus-locked averages, a switch trial reflects stimulus processing associated with a change in task, whereas the same label for response-locked averages reflects processing associated with the anticipation of a change of task.

Isopotential contour maps were created with EEGLAB software (Delorme & Makeig, 2004).

3.2.8 Statistical analyses

Individual averages for subjective measurements, error rates, RTs, and ERP components were analyzed with repeated measures analyses of variance (ANOVA).

For the subjective measurements, baseline measurements were compared between experimental sessions in order to evaluate pre-existing differences within participants between the placebo and caffeine sessions. Significant differences in baseline levels were, if present, adjusted by including the concerning variable as a covariate in the statistical analyses. In addition, effects of treatment on subjective measures were assessed for the second and third measurement points.

Performance and ERP data were analyzed separately for mixing costs and switch costs with the factors treatment (placebo, low dose, and high dose), trial type (mixing costs: single-task and repeat trials; switch costs: repeat and switch trials), and task (color, letter identity).

To correct for violations of the sphericity assumption in the ANOVA, degrees of freedom were corrected using the Huynh-Feldt method when appropriate. Corrected p-values but uncorrected df-values are reported, the latter to facilitate interpretation of the data. Statistically significant effects of caffeine and RSI were followed by contrasts analyses, involving two orthogonal contrasts for the factor treatment (Helmert) and two for the factor RSI (repeated). For the factor treatment the first contrast evaluates placebo against the mean of the two caffeine conditions; the second contrast tests the low against the high dose condition. For the factor RSI the first contrast evaluates the 150 ms RSI against the 600 ms RSI; the second contrast tests the 600 ms RSI against the 1500 ms RSI.

To check whether saliva caffeine levels differed between treatment conditions, separate repeated measures ANOVAs were performed for each sample point, again using Helmert contrasts.

3.3 Results

3.3.1 Saliva caffeine levels

Saliva levels for caffeine and placebo conditions were not significantly different for pretreatment samples, which demonstrated compliance to the abstinence instructions

($F(2,34) = 2.33$, ns). For the first posttreatment sample, mean caffeine levels were 1.01, 6.21 and 11.31 mg/l for placebo, low dose, and high dose respectively ($F(2,34) = 66.15$, $p < .001$). Contrasts indicated differences between caffeine compared to placebo ($F(1,17) = 123.88$, $p < .001$), and between low and high dose ($F(1,17) = 33.27$, $p < .001$). For the second posttreatment sample, mean caffeine levels were 1.00, 3.03, and 6.41 mg/l for placebo, low dose, and high dose, respectively ($F(2,34) = 76.24$, $p < .001$). Contrasts again indicated differences between caffeine conditions compared to placebo ($F(1,14) = 85.5$, $p < .001$), and between low and high dose ($F(1,17) = 61.01$, $p < .001$).

3.3.2 Subjective measurements

Participants reported no differences in sleep quality on the night before the experimental sessions. In addition, their subjective state (as measured with the POMS, STAI, and AD-ACL) did not differ between treatment conditions as measured upon arrival. Averaged over treatment conditions, participants felt more fatigued after testing compared to before (Fatigue subscale of the POMS; $F(1,17) = 7.02$, $p < .05$). As for the AD-ACL, decreased feelings of high activation ($F(1,17) = 5.56$, $p < .05$) and general activation ($F(1,17) = 9.08$, $p < .01$) were observed after testing compared to before. An effect of treatment on feelings of deactivation/sleep was found ($F(2,34) = 3.57$, $p < .05$), with Helmert contrast showing reduced feelings of deactivation/sleep in both caffeine conditions compared to placebo ($F(1,17) = 8.85$, $p < .01$). RSME scores indicated differences in fatigue between treatment conditions ($F(2,34) = 3.38$, $p < .05$). Averaged over measurements, participants felt more fatigued in the placebo condition compared to both caffeine conditions ($F(1,17) = 10.93$, $p < .005$). Low and high dose conditions did not differ.

3.3.3 Behavioral data

3.3.3.1 Task type

A main effect of task type on RT was found ($F(1,17) = 23.47$, $p < .001$), indicating faster responses for the color task (mean = 529 ms, SD = 58) compared to the letter identity task (mean = 552 ms, SD = 63). Error rate was affected by task type as well ($F(1,17) = 10.34$, $p = .005$), with slightly more errors for the color task (mean = 5.1 %, SD = 3.2) than for the letter identity task (mean = 4.1 %, SD = 2.9). Since no interactions between treatment and task type took place, we pooled data across task type, both for behavioral and ERP measures.

3.3.3.2 Mixing costs

Overall analyses. Participants responded faster to single-task trials than to repeat trials, reflecting mixing costs ($F(1,17) = 35.50$, $p < .001$; see Table 1). Trial type interacted with RSI ($F(4,68) = 4.21$, $p < .05$) indicating higher mixing costs for the 1500 ms RSI compared

to the 600 ms RSI (54 vs 41 ms; $F(1,17) = 6.04$, $p < .05$). Post-hoc analyses showed that RSI affected responses on both single-task trials ($F(2,34) = 4.23$, $p < .05$) and repeat trials ($F(2,34) = 5.29$, $p < .05$). Repeated contrasts further demonstrated that single-task RTs slowed down as RSI was prolonged from 150 to 600 ms ($F(1,17) = 11.56$, $p < .005$), but no effect of further lengthening of the RSI occurred. For repeat trials, responses were slower after a 600 ms RSI compared to a 150 ms RSI ($F(1,17) = 5.23$, $p < .05$), and a trend towards a further reduction in speed after a 1500 ms RSI was observed ($F(1,17) = 4.04$, $p = .061$). Thus, the enhanced mixing costs after a 1500 ms preparation interval are mainly the result of slower responses on repeat trials, possibly reflecting increased task-set maintenance in mixed-task compared to single-task blocks. As for error rate, we found an effect of RSI ($F(2,34) = 4.71$, $p < .05$; see Table 2). Error rate became higher for the 600 ms RSI condition compared to 150 ms RSI ($F = (1,17) = 7.92$, $p < .05$), but dropped after a 1500 ms RSI ($F(1,17) = 7.11$, $p < .05$).

		placebo		low dose		high dose	
150 ms	single-task	459	(35)	435	(42)	435	(31)
	repeat	513	(57)	474	(46)	472	(47)
	switch	754	(127)	699	(135)	689	(97)
	mixing cost	*54*		*39*		*37*	
	switch cost	*241*		*225*		*217*	
600 ms	single-task	473	(38)	442	(44)	443	(40)
	repeat	527	(66)	478	(53)	476	(53)
	switch	687	(128)	630	(148)	619	(109)
	mixing cost	*54*		*36*		*33*	
	switch cost	*160*		*152*		*143*	
1500 ms	single-task	481	(54)	442	(53)	447	(47)
	repeat	537	(75)	494	(80)	500	(76)
	switch	656	(127)	579	(137)	574	(105)
	mixing cost	*56*		*52*		*53*	
	switch cost	*119*		*85*		*74*	

Table 1. Mean reaction times (RT) in milliseconds (standard deviations) as a function of treatment, trial type, and RSI condition. Mixing costs and switch costs reflect the difference in RT between repeat trials and single-task trials, and between switch trials and repeat trials, respectively.

Effects of caffeine. Caffeine dose shortened RT ($F(2,34) = 8.52$, $p < .002$). Helmert contrasts confirmed faster responding after caffeine compared to placebo ($F(1,17) = 13.74$, $p < .005$), although low and high dose conditions did not differ. A trend was found towards an interaction between treatment and trial type ($F(2,34) = 2.60$, $p = .089$), which indicated reduced mixing costs in caffeine conditions (42 ms and 41 ms for low and high dose, respectively) compared to placebo (55 ms; $F(1,17) = 4.81$, $p < .05$). As for errors, no main effect of treatment was found, but treatment interacted with trial type reflecting error mixing costs ($F(2,34) = 4.57$, $p < .05$). Participants made fewer errors on single-task trials compared to repeat trials in the placebo condition (.69 %), but this pattern was slightly reversed after caffeine (-.01 % and -.04 % for low and high dose, respectively; $F(1,17) = 6.00$, $p < .05$). No difference between low dose and high dose for RT or error rate was found.

Within single-task blocks, stimuli were presented in all four quadrants in a clockwise manner. One could argue that some additional attentional process in the single task blocks might take place when the task is presented in the quadrant that was contextually

		placebo		low dose		high dose	
150 ms	single-task	3.5	(2.7)	3.3	(2.4)	3.1	(2.6)
	repeat	3.7	(2.4)	2.8	(1.5)	2.9	(2.6)
	switch	6.3	(4.4)	5.6	(3.6)	5.5	(3.7)
	mixing cost	*0.2*		*-0.5*		*-0.2*	
	switch cost	*2.6*		*2.8*		*2.6*	
600 ms	single-task	3.8	(2.6)	3.7	(2.8)	1.2	(3.3)
	repeat	4.3	(2.5)	3.6	(2.6)	3.4	(2.3)
	switch	6.4	(4.4)	6.6	(4.3)	5.7	(3.5)
	mixing cost	*0.5*		*-0.1*		*2.2*	
	switch cost	*2.1*		*3.0*		*2.3*	
1500 ms	single-task	2.8	(2.4)	3.2	(2.4)	3.3	(2.6)
	repeat	4.2	(2.9)	3.5	(2.5)	3.2	(2.1)
	switch	6.2	(4.5)	5.1	(4.2)	4.7	(3.6)
	mixing cost	*1.4*		*0.3*		*-0.1*	
	switch cost	*2.0*		*1.6*		*1.5*	

Table 2. Mean error rates (standard deviations) as a function of treatment, trial type, and RSI conditions. Mixing costs and switch costs reflect the difference in error rate between repeat trials and single-task trials, and between switch trials and repeat trials, respectively.

associated with the alternative task. To test this assumption we conducted an additional ANOVA on the performance data, which involved a 3 (treatment) x 2 (quadrants contextually associated with the task versus quadrants associated with the other task) x 3 (RSI) design. Results indicated that performance did not differ between quadrants associated with the task versus quadrants associated with the alternative task, nor did this factor interact with any of the other factors. This was the case for both RTs ($F(1,17) = 2.03$, ns) and errors ($F(1,17) = .001$, ns). Thus, there appear to be no differences between these two types of single-task trials in the present study in performance measures.

3.3.3.3 Switch costs

Overall analyses. Participants slowed down on switch compared to repeat trials, reflecting switch costs ($F(1,17) = 66.93$, $p < .001$). An effect of RSI was observed ($F(2,34) = 14.05$, $p < .001$), indicating faster responses after a 600 ms RSI compared with a 150 ms RSI ($F(1,17) = 38.04$, $p < .001$). The interaction between trial type and RSI was also significant ($F(2,34) = 109.51$, $p < .001$), showing a reduction of switch costs after a 600 ms RSI (152 ms) compared to a 150 ms RSI (228 ms; $F(1,17) = 66.52$, $p < .001$), which was even further reduced as the RSI lengthened to 1500 ms (93 ms; $F(1,17) = 56.91$, $p < .001$). Error rates were higher for switch compared to repeat trials ($F(1,17) = 23.53$, $p < .001$).

Effects of caffeine. A main effect of treatment on RT was observed ($F(2,34) = 15.05$, $p < .001$), with faster responses in both caffeine conditions compared to placebo ($F(1,17) = 12.47$, $p < .005$). The interaction between treatment and trial type ($F(2,34) = 3.22$, $p = .052$) indicated reduced switch costs for low and high caffeine dose (154 ms and 144 ms, respectively) compared to placebo (173 ms; $F(1,17) = 5.85$, $p < .05$). Post-hoc analyses showed that caffeine, averaged over RSI conditions, speeded up responses on repeat trials ($F(2,34) = 7.55$, $p < .005$) but more so on switch trials ($F(2,34) = 54.73$, $p < .001$). The interaction between treatment, trial type, and RSI yielded a trend ($F(4,68) = 2.13$, $p = .087$). Helmert contrasts revealed a greater reduction in switch costs after caffeine relative to placebo in the 1500 ms RSI ($F(1,17) = 3.49$, $p = .079$) compared to the 600 ms RSI ($F(1,17) = 4.51$, $p < .05$). Thus, participants seemed to benefit mostly from caffeine if they were given sufficient time to prepare for the upcoming trial. This was confirmed through post-hoc analyses separately for each RSI, showing that caffeine reduced RT switch costs by about 8% in the 150 ms RSI ($F(4,68) = 3.02$, $p < .05$) and in the 600 ms RSI ($F(4,68) = 2.23$, $p = .092$), whereas a reduction of about 33% was observed for the 1500 ms RSI ($F(4,68) = 4.66$, $p < .005$). As for errors, a main effect of treatment was found ($F(2,34) = 4.67$, $p < .005$). Helmert contrasts revealed fewer errors in both caffeine conditions compared to placebo ($F(1,17) = 5.11$, $p < .05$). Again, no dose-dependent effects were found.

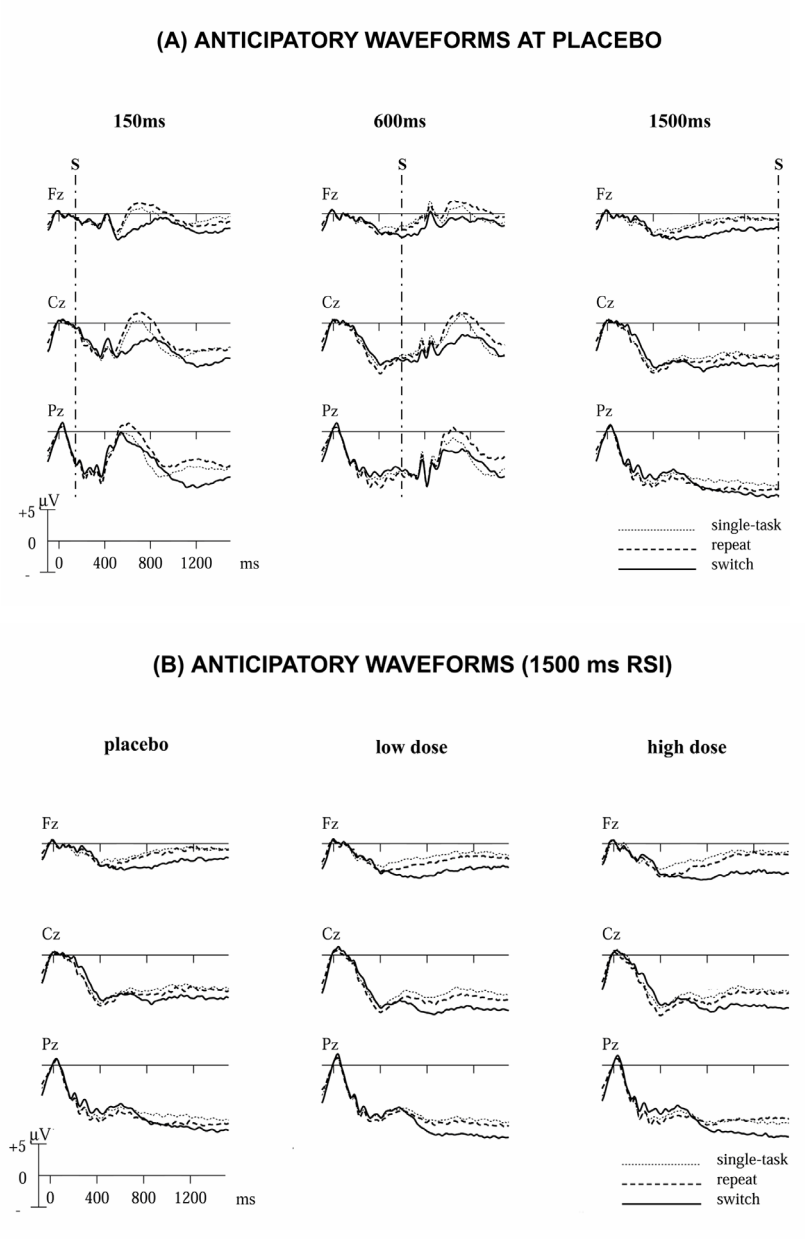

Figure 1. Average event-related potential (ERP) waveforms time-locked to the preceding response, elicited on single-task trials (dotted lines), repeat trials (dashed lines), and switch trials (solid lines). *A*: ERPs in the placebo condition, as recorded from Fz, Cz, and Pz, for 150, 600, and 1500 ms response-stimulus intervals (RSI). Vertical broken lines indicate subsequent stimulus onset. *B*: ERPs for the 1500 ms RSI, as recorded from Fz, Cz, and Pz, and for placebo, low dose, and high dose conditions.

3.3.4 Anticipatory ERPs

3.3.4.1 Early negativity

ERP waveforms time-locked to the preceding response, or anticipatory ERPs, are depicted for single-task, repeat, and switch trials, both at placebo for all RSI conditions (Figure 1A) and for all treatment conditions at the 1500 ms RSI (Figure 1B). These waveforms were characterized by a build-up of negativity in the interval between the emission of a response and the onset of the next stimulus. The negativity peaked around 400 ms after response onset (early component) and extended into a slow negativity (late component). These components occurred in all RSI conditions, but were most clearly observed in the 1500 ms RSI due to minimal overlap of the slow negative wave with poststimulus components, as can be clearly seen in Figure 1A. Therefore, we confined analyses of these ERP waveforms to the 1500 ms RSI condition.

The early negativity peaked roughly 400 ms after onset of the preceding response. In order to examine the early negativity in the preparatory ERPs, the area under the waveform was calculated within the time window 200-600 ms after response onset, which was determined by visual inspection, separately for all treatment and trial type conditions.

Effects of trial type. No differences in area measures of the early negativity were found between single-task and repeat trials. In the analysis of repeat and switch trials, trial type interacted with electrode ($F(2,34) = 5.58$, $p < .05$), showing a larger difference between repeat and switch ERPs at posterior sites than anteriorly, as confirmed by Helmert contrasts ($F(1,17) = 5.62$, $p < .05$).

Effects of caffeine. A main effect for caffeine occurred in the analysis of single-task and repeat trials ($F(2,34) = 3.51$, $p < .05$). Helmert contrasts showed a trend towards an enhanced negative amplitude in caffeine conditions compared to placebo ($F(1,17) = 4.11$, $p = .059$). A similar trend was also found in the analysis of repeat and switch trials ($F(2,34) = 2.7$, $p < .08$). Treatment did not interact with other factors.

3.3.4.2 Late slow negativity

In order to examine the slow negativity in the anticipatory ERPs, we calculated the area in the time window 800-1200 ms following the preceding response, since the negativity appeared to attain its maximum amplitude within this time window.

Effects of trial type. Although the late negative deflection seemed on average larger for repeat trials compared to single-task trials, this did not result in a main effect of trial type (Figure 1). For repeat and switch trials, the effect of trial type ($F(1,17) = 7.82$, $p < .05$)

indicated an enlarged slow negativity for switch compared to repeat trials. For comparison, scalp topographies depicting the mean potential distribution in the time window 800-1200 ms after response-onset (Figure 3) showed a widespread negativity which was larger for switch than for repeat trials as evidenced by a negative potential distribution of the difference waveform of switch minus repeat trials (Figure 2 and 3).

Effects of caffeine. For single-task and repeat trials, a three-way interaction was found between treatment, electrode, and trial type ($F(4,68) = 4.99$, $p < .01$). Anteriorly, the difference in slow negativity between repeat trials and single-task trials was enhanced in both caffeine conditions compared to placebo, while posteriorly the reverse pattern of a smaller difference between single-task and repeat trials after caffeine occurred, as revealed by Helmert contrasts ($F(1,17) = 6.76$, $p < .05$).

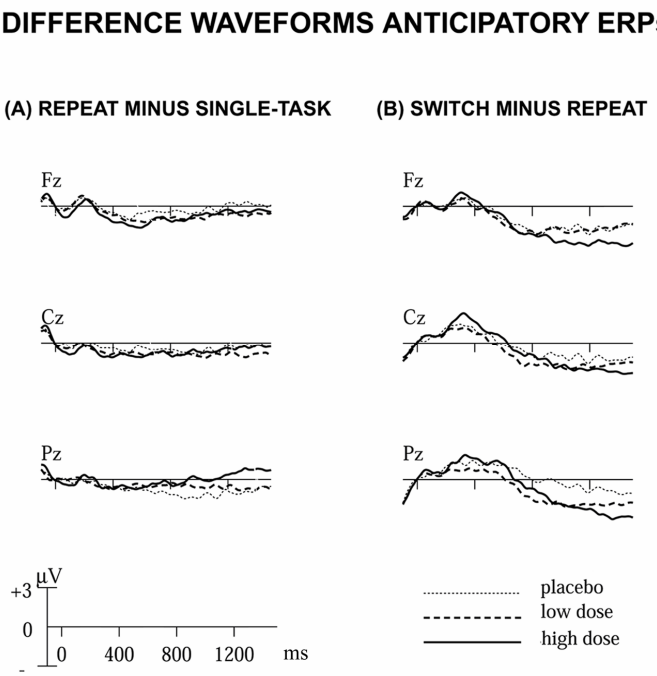

Figure 2. Average event-related potential (ERP) difference waveforms time-locked to the preceding response, as recorded from Fz, Cz, and Pz within the 1500 ms response-stimulus interval (RSI). Difference waves are shown for placebo (dotted lines), low dose (dashed lines), and high dose conditions (solid lines). *A*: Difference waves, as created by subtracting ERPs elicited on single-task trials from ERPs on repeat trials, reflect anticipatory processes associated with task-set maintenance. *B*: Difference waves, as created by subtracting ERPs elicited on repeat trials from ERPs on switch trials, reflect anticipatory processing associated with task-set updating.

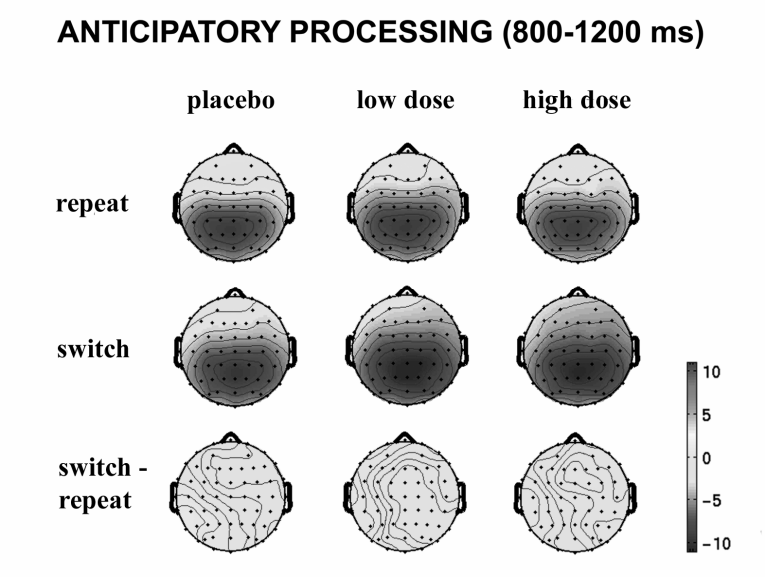

Figure 3. Grand-average spline-interpolated scalp potential maps for anticipatory processing involved in task-switching in placebo, low dose, and high dose conditions. The maps show the mean voltage distribution in the time window 800-1200 ms after the preceding response, for ERPs recorded in repeat and switch conditions and the difference waveforms (switch – repeat). In order to examine the slow negativity in the anticipatory ERPs, we calculated the area in the time window 800-1200 ms following the preceding response, since the negativity appeared to attain its maximum amplitude within this time window.
Note: For a color version of this figure, see Appendix.

For repeat and switch trials, an interaction between treatment, electrode, and trial type was found as well ($F(1,17) = 3.18$, $p < .05$). The larger negativity for switch than repeat trials was increased after caffeine compared to placebo, and more so on posterior sites than anterior sites as confirmed by Helmert contrasts ($F(1,17) = 12.68$, $p < .005$; see bottom panel Figure 3). Separate post-hoc analyses for repeat and switch trials indicated that the slow negativity elicited on switch trials, but not on repeat trials, was affected by caffeine ($F(1,17) = 7.62$, $p < .05$). No dose-specific effects were found.

3.3.5 Poststimulus ERPs

ERP waveforms time-locked to stimulus onset, or poststimulus ERPs, are depicted for single-task, repeat, and switch trials, both at placebo for electrodes Fz, Cz, and Pz (Figure 4A) and for all treatment conditions at Pz (Figure 4B). Poststimulus ERPs were composed mainly of a pattern of P2, N2, and P3 deflections. These components were largest at parietal scalp sites, which is in line with previous task-switching studies (Karayanidis et al., 2003;

Lorist et al., 2000; Moulden et al., 1998; Rushworth et al., 2002; Wylie et al., 2003). For reasons of clarity, we restricted our analyses therefore to the Pz electrode.

P2 and P3 components were defined as the positive peaks in the segments 100-200 ms (P2) and 300-600 ms (P3) poststimulus, while N2 was defined as the negative peak in the segment 150-300 ms poststimulus. To facilitate detection of the P3, ERP waveforms were filtered with 10Hz cutoff frequency prior to P3 peak picking. A negative shift was superimposed on poststimulus components in the 150 and 600 ms RSI condition. This negative shift might result from overlap between stimulus-related brain activity and the response-locked slow negativity that continues in the shorter RSI conditions beyond stimulus presentation.

3.3.5.1 Effects of trial type and RSI

For single-task and repeat trials, the only effect of trial type was a reduced P3 amplitude for single-task trials relative to repeat trials ($F(1,17) = 27.03$, $p < .001$). In addition, all poststimulus components were lowered in the short RSIs compared to longer RSIs, reflecting the influence of the late negativity extending into the period after stimulus presentation. This resulted in a smaller, or more negative, P2 ($F(2,34) = 23.36$, $p < .001$) and P3 ($F(2,34) = 19.51$, $p < .001$) in short compared to longer RSIs, as well as a more negative N2 ($F(2,34) = 15.95$, $p < .001$).

With respect to repeat and switch trials, P2 and P3 amplitudes were smaller for switch compared to repeat trials (P2: $F(1,17) = 33.62$, $p < .01$; P3: $F(1,17) = 68.05$, $p < .001$) whereas N2 was unaffected by trial type. Again, all components were more negative in the short compared to longer RSIs, resulting in a more negative P2 ($F(2,34) = 52.67$, $p < .001$) and P3 ($F(2,34) = 32.67$, $p < .001$) and a more negative N2 ($F(2,34) = 18.85$, $p < .001$). In addition, trial type interacted with RSI, such that all components showed maximal differentiation between switch and repeat trials at the 600 ms RSI (P2: $F(2,34) = 79.77$, $p < .001$; N2: $F(2,34) = 18.98$, $p < .001$; P3: $F(2,34) = 9.52$, $p = .001$).

3.3.5.2 Effects of caffeine

For single-task and repeat trials, caffeine increased N2 amplitude ($F(2,34) = 3.47$, $p < .05$) but had no effect on latency. Helmert contrasts revealed an enlarged N2 in caffeine conditions compared to placebo ($F(1,17) = 5.67$, $p < .05$). P2 and P3 amplitudes were not affected by caffeine, although their latencies were shortened (P2: $F(2,34) = 7.82$, $p < .005$; P3: $F(2,34) = 3.36$, $p < .05$). Helmert contrasts showed shorter peak latencies in caffeine conditions compared to placebo (P2: $F(1,17) = 25.41$, $p < .001$; P3: $F(1,17) = 5.44$, $p < .05$).

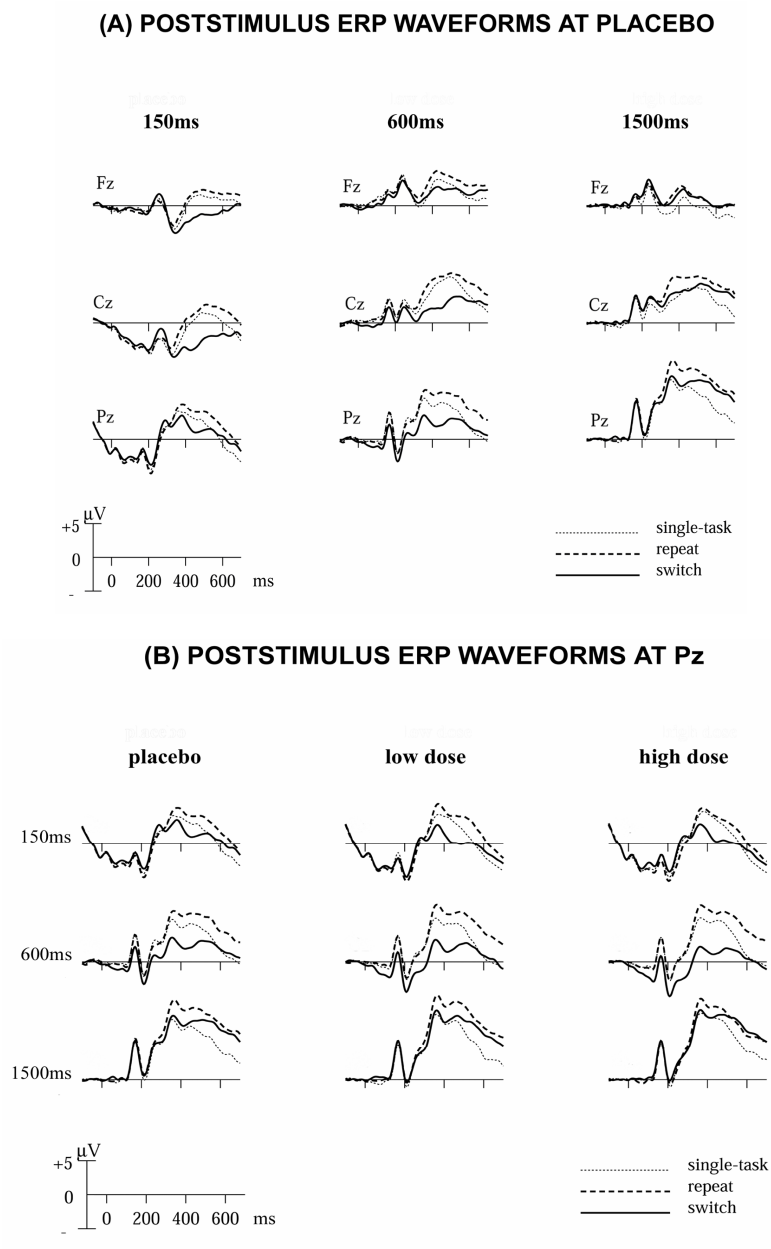

Figure 4. Average event-related potential (ERP) waveforms time-locked to stimulus onset, elicited on single-task trials (dotted lines), repeat trials (dashed lines), and switch trials (solid lines). *A*: ERPs in the placebo condition, as recorded from Fz, Cz, and Pz, for 150, 600, and 1500 ms response-stimulus intervals (RSI). *B*: ERPs at Pz, for 150, 600, and 1500 ms RSIs, and for placebo, low dose, and high dose conditions.

For repeat and switch trials, again N2 amplitude ($F(2,34) = 3.61$, $p < .05$) but not latency was increased by caffeine. Helmert contrasts revealed an enlarged N2 in caffeine conditions compared to placebo ($F(1,17) = 5.84$, $p < .05$). Caffeine affected P2 and P3 latencies (P2: $F(2,34) = 3.79$, $p < .05$; P3: $F(2,34) = 4.41$, $p < .05$) but not amplitudes. Helmert contrasts revealed shorter peak latencies in caffeine conditions compared to placebo (P2: $F(1,17) = 5.52$, $p < .05$; P3: $F(1,17) = 6.36$, $p < .05$). The absence of caffeine effects on P2 and P3 amplitudes suggests that the caffeine-induced changes in prestimulus slow negativity reflect effects specific to task switching, rather than general changes in arousal or in perceptual or cognitive processes.

3.4 Discussion

The present study examined effects of caffeine on cognitive control functions involved in task switching and maintenance of task set. We predicted that caffeine would improve task-switching performance, specifically by enhancing anticipatory control processes. The results support this prediction. The ability to reconfigure or update the cognitive system when switching from one task to another was improved by caffeine, as evidenced by reduced RT switch costs after caffeine, and this reduction was largest when participants were given sufficient preparation time. In the ERPs, an early negativity transforming into a slow negativity developed within the preparation interval. The early negativity was smaller for switch compared to repeat conditions, and more so posteriorly. Caffeine did not influence this effect of switching. The late slow negativity was larger on switch compared to repeat trials, presumably reflecting the greater need for anticipatory control required for an upcoming switch of task. Importantly, this switch-specific modulation of the slow negativity was enhanced after caffeine reflecting intensified anticipatory control. These caffeine-induced changes in slow negativity are not merely the result of general caffeine-induced enhancements in ERP components, since the early negativity as well as P2 and P3 amplitudes were not affected by caffeine. Rather, this effect of caffeine seems to be specific to preparatory processes involved in task switching.

In addition, we explored whether caffeine improves the ability to flexibly maintain and co-ordinate two task sets during task switching. Reduced mixing costs after caffeine, which was mainly seen for errors, provides some support for this notion. In the ERPs, the slow negativity appeared somewhat larger for repeat compared to single-task trials, and this difference between repeat and single-task ERPs was enhanced after caffeine at frontal sites (but reduced at parietal sites).

In sum, caffeine seems to strengthen anticipatory processes such as task-set updating, yielding reduced switch costs, while processes related to task-set maintenance are affected to a lesser degree, resulting in a (marginally significant) reduction in mixing costs by caffeine.

3.4.1 ERP indices of task switching

The ERP findings in the present study resemble data from previous task-switching investigations. For instance, Karayanidis et al. (2003) found a comparable switch-related reduction in amplitude of the early negativity, which was followed by a slow negativity that showed a similar (but not statistically significant) switch-specific enhancement in amplitude. Lorist et al. (2000), Rushworth et al. (2002), and Wylie et al. (2003) reported a similar negative-going component and the concurrent negative modulation of this component on switch compared to repeat conditions, but with a more frontal distribution.

Interpreting the effect of switching on the early negativity in the present study as a true reflection of anticipatory processes of task switching seems premature, since this component peaks within 400 ms after the previous response and might therefore be confounded with response-related processes (such as the response-set adjustment process proposed by Meiran, 2000).

The late negativity might be similar to the contingent negative variation (CNV) wave, a slow negative brain potential that is typically recorded in the interval between two successive stimuli (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The CNV is assumed to reflect processing related to response preparation and stimulus anticipation (van Boxtel & Brunia, 1994a; 1994b), which is comparable to our interpretation of the late negativity in the present study. Interestingly, it has been shown that negative slow waves are sensitive to working memory demands, thus ruling out general response preparation only as an explanation (Ruchkin et al., 1988; 1995).

Some authors (e.g., Rogers & Monsell, 1995) have proposed that it takes about half a second to prepare an upcoming task. One might argue therefore that the late negativity, which begins around 600 ms within the preparation interval, reflects task-set maintenance instead of updating. Yet, while repeat trials are associated with increased active maintenance demands (associated with keeping multiple task sets at a relatively high level of activation) compared to single-task conditions, no differences were found between ERPs elicited on single-task and repeat trials. This argues against an interpretation of the late negativity exclusively in terms of task-set maintenance.

Furthermore, we found a significant decrease in switch costs as the preparation interval is prolonged from 600 to 1500 ms, suggesting that an active preparation process, such as updating of task set, takes place within this time window. This supports the notion that the switch-specific increase in amplitude of the late negativity reflects the greater need for task-set updating prior to a switch of task. Alternatively, the late negativity might represent a combination of task-set updating and maintenance. Whereas task-set updating mainly involves refreshing the task rules and the concurrent stimulus-response mappings (Bunge, Wendelken, Badre, & Wagner, 2005), active task-set maintenance (i.e. keeping the task set active in working memory and protecting it against interference) might strengthen the representation of the task sets in working memory, which could also account for the reduced switch costs after a long preparation interval.

In the present study, we found no evidence of a distinct component within the ERPs that was uniquely associated with switching. Rather, the effect of switching was evident as modulations in amplitudes of the various ERP components (as supported by scalp topographies). Our data are therefore in line with the view that the neural circuitry involved in task switching is more strongly activated on switch trials compared to repeat trials, instead of the activation of additional areas specifically involved in task switching.

The present findings of enhanced switch-specific preparatory activation are opposed to the absence of such effects in some fMRI studies (Brass & von Cramon, 2002, 2004). This apparent discrepancy might be related to the fact that ERP and fMRI techniques each emphasize different aspects of information processing in the nervous system. ERP measures provide a direct, high temporal-resolution reflection of neural activity, while functional neuro-imaging yields high anatomical-resolution measures of the blood flow that is coupled to neuronal activity (Mangun, Buonocore, Girelli, & Jha, 1998).

The imperative stimulus evoked a series of P2, N2, and P3 components. Reduced P3 amplitudes were observed in single-task compared to repeat trials. This effect could simply reflect heightened arousal in mixed-task compared to single-task blocks. In addition, P3 amplitudes were smaller for switch than for repeat trials, perhaps reflecting the higher task difficulty of switch trials (Kok, 2001; Polich, 1987). Similar effects of switching in P3-like components were reported by others (Karayanidis et al., 2003; Lorist et al., 2000; Rushworth et al., 2002). It should be noted, however, that the present study does not permit differentiation of carry-over anticipatory versus stimulus-elicited effects on poststimulus components.

3.4.2 Caffeine effects on task switching

The caffeine-induced improvements in task-switching performance, as seen in the present study, may result from boosting DA activity (Garrett & Griffiths, 1997), which is in accord with the reported DA involvement in task switching (Mehta et al., 2004). Nevertheless, we can only speculate about the brain areas that are affected by caffeine in the present study. Neuro-imaging studies have shown a fronto-parietal network to be involved in task switching (Brass & von Cramon, 2002, 2004; Braver et al., 2003; Dove et al., 2000; Dreher & Berman, 2002; Kimberg et al., 2000; Konishi et al., 1998; Luks et al., 2002). One possibility is that caffeine directly targets the frontal cortex, which is supported by the finding that caffeine selectively stimulates DA transmission in the prefrontal cortex, but not the nucleus accumbens of rats (Acquas et al., 2002). Alternatively, the beneficial effects on task switching may be attributable to caffeine-mediated DA changes in the striatum, which is highly sensitive to caffeine (Fredholm et al., 1999; Nehlig, 1999). Evidence for striatal involvement in task switching comes from studies with Parkinson patients, who suffer from DA depletion in the striatum, disrupting the striato-cortical circuits that are believed to subserve task switching (Monchi et al., 2004; Owen, Doyon, Dagher, Sadikot, & Evans, 1998). These patients exhibit task-switching deficits (Cools et al., 2001; Marie et al., 1999;

Monchi et al., 2004), which is remediated by DA medication (Cools et al., 2001). Moreover, impaired task switching in Parkinson patients was associated with less neural activation of the striato-frontal circuit compared to matched controls (Monchi et al., 2004).

An alternative account for beneficial effects of caffeine in general is the relief from caffeine withdrawal (Juliano & Griffiths, 2004). However, this opinion is controversial and has not been reliably supported (Rogers, Richardson, & Dernoncourt, 1995; Smith, 2002). In fact, one study (Richardson, Rogers, Elliman, & O'Dell, 1995) reported improved performance in deprived consumers as well as nonconsumers, whereas the withdrawal hypothesis would predict that beneficial effects of caffeine are limited to the former.

Low and high caffeine dose conditions did not differ on any of the behavioral or ERP measurements, which is consistent with previous studies showing a flat dose-response relationship in mood and psychomotor performance (Lieberman et al., 1987; Robelin & Rogers, 1998). Two explanations can be given for the absence of dose-specific effects. First, while caffeine effects are especially found in suboptimal conditions, such as boredom and fatigue, arousal levels of our participants were close to optimal during testing, due to the demanding nature of the switch task. Secondly, the between-subjects variability in reported caffeine intake from coffee, ranging from 123 mg to 583 mg per day, could have resulted in performance deterioration in low users after a high dose because of induced arousal levels beyond the optimum, while high users benefited from the high dose. However, the ERP and behavioral data did not show such a pattern (sample sizes of a low and high users group, based on a median split, were too small to reliably corroborate this observation with statistical analyses).

4

Effects of caffeine on anticipatory control processes: Evidence from a cued task-switch paradigm

Effects of caffeine on task switching were studied using ERPs in a cued task-switch paradigm. The need for advance preparation was manipulated by varying the number of task-set aspects that required switching. In a double-blind, within-subjects experiment, caffeine reduced shift costs compared to placebo. ERPs revealed a negative deflection developing within the preparatory interval, which was larger for shift than for repeat trials. Caffeine increased this shift-induced difference. Furthermore, shift costs increased as a function of the number of task-set features to be switched, but this pattern was not modulated by caffeine. The results suggest that caffeine improves task-switching performance by increasing general effects on task switching, related to task-nonspecific (rather than task-specific) anticipatory processes. Caffeine's actions may be mediated by dopaminergic changes in the striatum or anterior cingulate cortex.

Chapter 4 has led to the following publication:

Tieges, Z, Snel, J., Kok, A., Plat, N., & Ridderinkhof, K.R. (2007). Effects of caffeine on anticipatory control processes: Evidence from a cued task-switch paradigm. Psychophysiology, 44(4), 561-578.

4.1 Introduction

The ability to rapidly and flexibly adjust behavior to continually changing environmental demands is a key aspect of cognitive control. These dynamic control processes have been extensively studied using the task-switching paradigm, in which participants rapidly shift back and forth between two or more choice reaction time (RT) tasks afforded by the same class of stimuli. Performance is usually slower and less accurate after a change of task than when the same task is repeated, which is termed the "shift cost." The task to be performed on a given trial may be determined by a fixed order (e.g., the alternating-runs paradigm in which participants shift tasks every second trial; Rogers & Monsell, 1995) or by an explicit cue presented prior to the stimulus (e.g., Meiran, 1996).

The shift cost can be reduced when participants are given sufficient time to prepare for the impending task (Rogers & Monsell, 1995). This diminution is said to result from an active process of advance reconfiguration or updating of the task set (Meiran, 1996, 2000; Rogers & Monsell, 1995; Rubinstein et al., 2001), from slowly decaying interference from the previously relevant task set (Allport et al., 1994; Allport & Wylie, 1999;), or from long-term priming due to associative retrieval of conflicting task sets (Allport & Wylie, 1999, 2000; Rogers & Monsell, 1995). This priming can be quite stimulus specific (Waszak et al., 2003), such that stimuli acquire associations (i.e., "bindings") with the tasks in which they occur. When the current task activation is weak, as is the case on shift trials, the target stimuli can trigger retrieval of the residually associated, competing task, provoking larger time costs. Although most researchers agree that both bottom-up, stimulus-driven processes and top-down control processes contribute to task switching (e.g., Ruthruff et al., 2001), there is still disagreement about the exact blend.

Neuro-imaging studies have revealed that task switching involves an extensive neural network, including regions of lateral prefrontal cortex (PFC) and parietal cortical areas, the presupplementary motor area, and the anterior cingulate cortex (ACC; Braver et al., 2003; Dove, et al., 2000; Dreher & Berman, 2002; Kimberg et al., 2000; Konishi, et al., 1998; Luks, et al., 2002). Furthermore, fMRI studies that have attempted to isolate brain activity associated with preparing for a shift of task report heterogeneous preparation-related activation in PFC and parietal cortex (Luks, et al., 2002; MacDonald, et al., 2000; Sohn, et al., 2000). Specifically, the lateral PFC has been implicated in processes such as rule retrieval, online maintenance during task preparation, and rule-based response selection (Bunge, 2004). Moreover, Yeung, Nystrom, Aronson, and Cohen (2006) argued that, during task preparation, anterior PFC regions regulate the operation of task-specific representations in more posterior regions, supporting the notion that task switching involves an active process of task preparation.

4.1.1 Neurocognitive effects of caffeine on task switching

Recently, we have found effects of caffeine on task switching using a modified version of the alternating-runs paradigm (Tieges et al., 2006). Compared to placebo, a dose of 3 and 5 mg/kg body weight (BW) caffeine reduced RT shift costs. These results coincide with previous studies showing that caffeine caused subtle improvements in cognitive operations, the most consistently reported of which are shorter RTs, often accompanied by fewer errors. These improvements have been ascribed to both general caffeine effects on arousal, such as enhanced alertness and wakefulness, and to more specific effects on perceptual, attentional, and motor processes (Barthel, et al., 2001; Lorist & Snel, 1997; Snel et al., 2004; Warburton et al., 2001), as well as improvements in the ability to monitor ongoing actions for signs of conflict or erroneous outcome (Tieges, et al., 2004).

The beneficial effects of caffeine presumably arise from its neurochemical effects on the dopamine (DA) system. That is, low doses of caffeine (1,3,7-trimethylxanthine) block inhibitory adenosine A_1 and A_{2A} receptors. A_{2A} receptors are found mainly in the DA-rich regions of the brain (e.g., striatum) where they are co-localized with DA receptors, whereas adenosine A_1 receptors are present in almost all brain areas (Acquas et al., 2002; Ferré, et al., 1997). Consequently the DA-system is stimulated through antagonistic A_{2A}-DA receptor-receptor interactions (Garrett & Griffiths, 1997). This boosting of DA-activity appears to underlie most behavioral effects of caffeine.

Our finding of more efficient task-shift performance induced by the DA-agonist caffeine is in line with the observation that task switching is impaired by the DA antagonist sulpiride (Mehta et al., 2004). Moreover, our results agree with those obtained by Lorist et al. (2000), who found expressions of shift-specific processing to be reduced with mental fatigue using the same alternating-runs paradigm and who showed further that caffeine compensates the detrimental effects of fatigue (Lorist et al., 1994; Lorist & Tops, 2003). Specifically, Lorist et al. (1994) compared effects of caffeine between groups of well-rested and fatigued participants and concluded that caffeine interacts with fatigue, pointing to a possible modulation by caffeine of mechanisms involved in the regulation of behavioral energy expenditure.

4.1.2 ERP indices of task switching

In our initial investigation, we employed ERP measurements in addition to studying task switching behavior (Tieges et al., 2006). Within the preparation interval, an early negativity (peaking around 400 ms relative to the onset of the trial, which started right after response execution on the previous trial) transformed into a slow negativity (from ~800 ms until the end of the preparatory interval) at posterior sites. Although the former component was larger (i.e., more negative) for repeat compared to shift trials, the latter component showed the opposite pattern of larger amplitudes for shift relative to repeat trials. Importantly, this shift-induced modulation of the late slow negativity, which possibly reflects the greater need for

anticipatory control on shift trials, was increased after caffeine relative to placebo. Thus, caffeine appeared to improve task-switching performance by intensifying processes related to preparation for the upcoming task. This notion is supported by the fact that effects of caffeine were largest when participants had sufficient preparation time (i.e. 1500 ms). Importantly, caffeine did not influence switch-specific reductions in poststimulus components, which points to the specificity of caffeine's actions on anticipatory processing.

It is difficult to relate these findings to results of other task-switching studies, due to the large variety of paradigms that have been used and the variability of results in terms of the number, distribution, and range of differential shift versus repeat effects. Nevertheless, some researchers have identified one or more ERP components that developed within the preparatory interval and differentiated between shift and repeat conditions (Goffaux, Phillips, Sinai, & Pushkar, 2006; Karayanidis et al., 2003; Lorist et al., 2000; Moulden et al., 1998; Rushworth et al., 2002; Swainson, Jackson, & Jackson, 2006; Wylie et al., 2003). First, a differentiation between shift and repeat trials during the preparation period over posterior scalp regions has been repeatedly found, such that amplitudes became more positive (or less negative) in shift compared to repeat conditions. Specifically, this effect was seen as an amplitude reduction in the early negativity (or a superimposed positivity) in shift compared to repeat conditions (Karayanidis, et al., 2003; Nicholson, et al., 2005, 2006; Rushworth et al., 2002, 2005; Hsieh & Cheng., 2006; Swainson et al., 2006) or as an enhanced P3-like positive waveform (e.g., Rushworth et al., 2002; Nicholson et al., 2006).

In addition, some studies report a late slow negativity that appears to differentiate between shift and repeat trials (Goffaux, et al., 2006; Karayanidis, et al., 2003; Kieffaber & Hetrick, 2005; Lorist, et al., 2000; Rushworth, et al., 2002; Wylie, et al., 2003), although the direction (and distribution) of this effect is inconsistent among studies. These anticipatory negativities have been commonly interpreted as reflecting control processes such as task set reconfiguration (or competition between task rules; Wylie et al., 2003), triggered when preparing for the upcoming task.

4.1.2.1 The slow negativity

The sustained slow negativity in our previous study (Tieges et al., 2006) appears to be similar to the contingent negative variation (CNV), a slow negative brain potential that precedes the target stimulus (Walter et al., 1964). Specifically, the slow negativity shares characteristics with the early portion of the CNV, which usually peaks around 1 s after onset of the warning stimulus (although its distribution is usually fronto-central, whereas the slow negativity in our study was more posteriorly distributed). The CNV is assumed to reflect processing related to response preparation and stimulus anticipation (van Boxtel & Brunia, 1994a). To be precise, it appears to reflect a mixture of sensory, cognitive, and motor preparation, with their shares depending on the type of task. Whereas some authors have suggested that (especially frontal) CNV-like negativities in studies of task switching index processes related to task-set maintenance (e.g., Barcelo, Escera, Corral, & Perianez, 2006;

Kray, Eppinger, & Mecklinger, 2005), we have proposed instead that they represent a combination of task-set updating and active maintenance (the exact interpretation being dependent on the specific task). This is concluded from our previous study, in which we showed that the slow negativity was enhanced in shift conditions relative to repeat conditions, but also on repeat conditions relative to single-task trials. However, caffeine's effects were most pronounced for the former rather than for the latter effect, which was paralleled by findings of a greater RT shift cost reduction as compared to a reduction in mixing cost (i.e., the RT difference between performance on repeat conditions within mixed-task blocks and single-task blocks) after caffeine.

It should be emphasized that, although task-set updating mainly involves refreshing the task rules and the concurrent stimulus-response (S-R) mappings (Bunge et al., 2005), active task-set maintenance (i.e., keeping the task set active in working memory and protecting it against interference) might strengthen the representation of the task sets in working memory, resulting in stable S-R associations, such that both processes could account for reduced shift costs after a long preparation interval. Whatever the exact nature of these processes, it seems reasonable to assume that the slow negativity (and other CNV-like components) generated in switching tasks represent an active form of anticipatory processing, although clearly more research is needed to attain a functional understanding of the negativities elicited during task preparation.

The neural substrates that give rise to CNV-like activation include the supplementary motor area (SMA), ACC, and the basal ganglia (e.g., Brunia & van Boxtel, 2001). In a combined EEG and fMRI study (Nagai et al., 2004), ACC activation was shown to be correlated with negative amplitude of the CNV, which led the authors to suggest that the ACC might be the critical generator of the early phase of the CNV. This appears to be a conceivable notion in light of the presumed role of the ACC in preparatory processes of task switching (e.g., Luks et al., 2002).

4.1.2.2 Cue-related ERP components

Whereas early studies of task switching employed a paradigm in which switches were completely predictable and were cued by the position of the target stimulus on any given trial, more recent studies have turned to investigating unpredictable switches as indicated by a specific task cue. The latter approach has the advantage of being able to precisely measure in time the onset of anticipatory processing (as elicited by the *task cue*) without being confounded by processing of the previous response. Such cued task-switching paradigms typically generate a cue-related P3 that is larger for shift compared to repeat trials (e.g., Kieffaber & Hetrick, 2005; Kray et al., 2005).

This shift-sensitive cue-P3 effect has been interpreted in terms of, for example, updating the currently relevant task set (Kray et al., 2005) or the extent to which attentional resources are configured (Kieffaber & Hetrick, 2005). Furthermore, it has been shown that the size of the switching effect in the cue-related P3 was positively correlated with the

decrease in shift costs (Kieffaber & Hetrick, 2005), which the authors interpreted as supporting the notion that anticipatory activity evoked by cue presentation indexes cognitive control mechanisms responsible for optimizing task performance. One must keep in mind, though, that the shift-effect in P3 amplitude may, in fact, have been caused by a superimposed shift-sensitive sustained positivity that was evident in some studies and had a distribution and time course consistent with the P3 (e.g., Karayanidis et al., 2003; Nicholson et al., 2006; Rushworth et al., 2002).

Anyhow, the P3-like effects generated by cues in task-switching studies support an interpretation in terms of shift and repeat differences in the demands placed on processes involved in encoding and updating the currently relevant task context (Donchin & Coles, 1988; Kok, 2001). Alternatively, the shift effect on P3 amplitude may be related to the cue manipulation, which is essentially a manipulation of processing difficulty, such that the effect of shifting on P3 amplitude may reflect the greater demands placed on cue processing when a shift of task is required than when the task has to be repeated (Johnson, 1986).

In addition to the P3, task-switching studies have sometimes mentioned shift-sensitive effects in other cue-evoked ERP components, in particular the P2 and N2. The P2 has been classically related to selective attention and basic perceptual processing *(*e.g., Luck & Hillyard, 1994). Within the context of task switching, Kieffaber and Hetrick (2005) showed that the P2 was not sensitive to the information carried by the cue, as manipulated by presenting noninformative cues as well as cues indicating an upcoming shift or repetition of task. However, in conditions in which the cue was instructive, cue-P2 amplitude appeared to be sensitive to modality of the impending task, being larger for shift compared to repeat trials in anticipation of a visual-target task, whereas the opposite pattern was found in an auditory-target task. The authors tentatively concluded that the P2 seems to be sensitive to the perceptual complexity of the anticipated task. With respect to the N2, sensitivity to the informative value of the cue was shown by Nicholson et al. (2006). They separately manipulated cue switching and rule switching and found that N2 amplitude was sensitive to cue switching, because enhanced N2 amplitudes were observed in cue-repeat conditions compared to cue-shift conditions.

In sum, task switching studies have shown a series of cue-evoked P2, N2, and P3-like components, followed by a late slow negativity. A shift-induced increase in P3 magnitude may index the encoding and updating of the currently relevant task context, or it may be related to the increased processing difficulty related to shift cues. N2 amplitude appears to be mainly sensitive to cue switching (but not rule switching). Interpretation of P2 effects is not straightforward, but may be related to early processing of the cue or, alternatively, to the complexity of the anticipated task. The late slow negativity has been related to task-set updating and maintenance. Caffeine has been previously found to increase the shift-induced enhancement in the slow negativity while having no effect on similar increases occurring in the time domain of the P3.

4.1.2.3 Target-related ERP components

The most consistent finding regarding ERPs elicited by the *imperative stimulus* is a poststimulus P3-like component, that is reduced on shift compared to repeat trials (Karayanidis et al., 2003; Kieffaber & Hetrick, 2005; Lorist et al., 2000; Nicholson et al., 2005, 2006; Rushworth et al., 2005; Swainson et al., 2003, 2006; Tieges et al., 2006; Wylie et al., 2003). The P3 attenuation on shift trials may be related to a weaker or unstable task-set on shift compared to repeat trials (Barcelo, Munoz-Cespedes, Pozo, & Rubia, 2000), also referred to as a "task-repetition benefit" (Swainson et al., 2006). However, the shift-induced attenuation in stimulus-P3 has also been ascribed to sustained amplitude reductions (e.g., Karayanidis et al., 2003; Kieffaber & Hetrick, 2005), indexing preparation-related activity that continues beyond stimulus presentation and overlaps with stimulus-related brain activity (see Tieges et al., 2006). Accordingly, Swainson et al. (2006) suggested that such a sustained negative shift may reflect a nonobligatory switch-related process, such as a shift from controlled to relatively automatic task processing rather than an obligatory reconfiguration allowing performance of the appropriate task.

Thus, in contrast with the cue-related P3 effects which showed increased magnitudes on shift trials, the stimulus-related P3 has been consistently shown to be attenuated in shift conditions. As Kieffaber and Hetrick (2005) have pointed out, the structural and temporal similarity of the cue-P3 and stimulus-P3, combined with their differential shift-induced effects, appears consistent with the notion that multiple neural generators give rise to the P3 (Johnson, 1993) and suggests that these different P3 generators may be related to unique anticipatory and stimulus-dependent components of task processing during the cue-target interval and posttarget period, respectively.

In addition to the P3, a shift-induced attenuation in the posterior P2 has been reported (e.g., Kieffaber & Hetrick, 2005; Tieges et al., 2006; Wylie et al., 2003). Kieffaber and Hetrick (2005) suggested that the P2 may be an index of stimulus-dependent associative strengthening, as evidenced by a positive correlation between the P2 shift effect and RT shift costs.

Whereas we previously found N2 amplitude to be unaffected by switching, other studies did observe such a shift-specific N2 modulation (Rushworth et al., 2002; Swainson et al., 2006). For example, Rushworth et al. reported an increased N2-like component over the central posterior scalp in the first trials following a shift that disappeared thereafter (as compared with the first trials following a task repetition). Furthermore, Swainson et al. (2003) found an enhanced frontal N2 on shift compared to repeat trials (but only in a delayed-response condition), which was associated with right ventrolateral PFC activation. In both studies, this shift-sensitive increase in N2 amplitude was interpreted as reflecting increased response suppression associated with a shift of task. This is in line with the notion that the N2 is elicited on correct conflict trials and is generated by the ACC (e.g., van Veen & Carter, 2002). As such, the fact that the N2 effect was associated with switching into a

response-suppression mode (Swainson et al., 2003) implies that switching may involve a process of active inhibition of the currently relevant task set as indexed by N2 amplitude.

In sum, task-switching studies have shown a number of ERP components, including the P2, N2, and P3, to be evoked by target stimuli. The main finding concerns a P3 attenuation on shift trials, possibly related to the weaker task set on shift compared to repeat trials. The P2 shift effect may reflect processes related to stimulus-dependent associative strengthening. The shift-sensitive increase in N2 amplitude has been taken to index a process of inhibition of the currently relevant task set. Importantly, we previously showed that caffeine did not modulate these shift effects in poststimulus components (Tieges et al., 2006).

Overall, our previous results appear to be in line with the above-mentioned ERP reflections of task switching. In particular, we found a slow negative ERP component differentiating between shift and repeat conditions, indicating that the neural circuitry involved in task-set preparation is differentially activated on shift compared to repeat trials. These ERP components might be generated in prefrontal and/or parietal cortical areas involved in the internal updating of goals (Brass & von Cramon, 2004; Braver et al., 2003).

4.1.3 The present study

We further examine the effects of caffeine on anticipatory processes associated with task switching, but now on unpredictable (cued) rather than predictable switches. We reasoned that this would enable us to explore the exact timing of anticipatory task-switching processes, without being confounded by response-related processing. Moreover, it was made sure that participants always had ample time to prepare for the upcoming task, because previous caffeine effects on task switching were shown to be largest with sufficient preparation time.

We have proposed that effects of caffeine on anticipatory processing, as found in our previous investigation (Tieges et al., 2006), may have resulted from differential task-set updating and/or active task-set maintenance under caffeine. The goal of the present study is to further explore whether effects of caffeine on task switching result from caffeine-induced improvements in task-nonspecific anticipatory processes (e.g., goal setting; Rubinstein et al., 2001; actively maintaining the task set in working memory and protecting it against interference; Bunge et al., 2005) or in task-specific processes (e.g., rule retrieval and rule-based response selection; Bunge, 2004). We predicted the latter; that is, effects of caffeine on task switching are task-specific, and hence should be related to the characteristics of the tasks that have to be switched. Our prediction was that a manipulation of "task shift load" would lead to greater demands on processes such as the retrieval and updating (or consolidating) of task sets and their associated S-R assignments. If caffeine's effects are not modulated by shift load, then caffeine apparently has a more general effect on task switching, related to task-nonspecific processes.

To this end, task shift load was manipulated in the following manner. Participants alternated between two tasks that differed from each other in terms of the set of S-R hand mapping rules, the set of response effectors (i.e., the fingers with which the response buttons had to be pressed: index vs. middle fingers), or both. Thus, a switch could occur between only one aspect of the task set (either mapping rule or response effectors) or both aspects of the task, which we will refer to as single versus dual shifts. We expected effects of caffeine on shift costs and shift-sensitive increases in ERP components to increase parametrically with shift load (i.e. single vs. dual shift conditions). In other words, shifting two elements of the task set would be affected more by caffeine than shifting only one task-set element, as evidenced by a greater reduction in shift costs after caffeine for dual shifts than single shifts. Within the ERPs, the shift-induced enhancement in slow negativity under caffeine should be increased in dual versus single shift conditions. If, on the other hand, caffeine effects on the shift-sensitive slow negativity do not differentiate between low and high task shift load, this finding would support a role for caffeine in modulating more general, task-nonspecific processes.

A few studies have provided some insight into the processes involved in switching between multiple task dimensions (Allport et al., 1994; Hahn, Andersen, & Kramer, 2003; Kleinsorge, 1999). These dual shift conditions consisted of switching between both task rule (i.e., even/odd or >/< 5) and stimulus set (i.e., numerical value or group size; Allport et al., 1994), switching between both task and response mapping (Kleinsorge, 1999), or switching between both perceptual task and response set (Hahn et al., 2003). Yet, Kleinsorge, Heuer, and Schmidtke (2002) showed that changing only the type of judgment (numerical vs. spatial) took longer than when both judgment type and S-R mapping had to be changed. However, by itself, shifting the S-R mapping was actually associated with *smaller* shift costs compared to when also the judgment type required shifting simultaneously. With respect to such seemingly contradictory results, it should be noted that the nature of shifts between multiple task-set dimensions likely depends to a large extent on the specific properties of the task that has to be switched (e.g., Meiran & Marsiano, 2000).

In all, under-additive interactions between switching of two task aspects, at least in the case of unpredictable switching, has been reported quite consistently. This suggests to us that multiple preparatory operations are performed in parallel. Specifically, the pattern of results from the Hahn et al. study suggests overlapping task- and response-set preparation (at least when a short preparation interval was used). Extending these findings to the present investigation, we predicted that, rather than finding some additional ERP component (i.e., when multiple task items would be reconfigured in a serial manner), dual shift conditions would yield an enhanced shift-specific modulation of the slow negativity compared to single shifts. Thus, we expected the present data to be in line with previous studies, yielding under-additive effects of switching between two task set aspects (instead of just one).

In addition to the slow negativity, we put forward specific hypotheses regarding the other ERP components associated with task switching. First, with respect to cue-generated components, we predicted a shift-induced increase in cue-P3 amplitude, which would be

suggestive of stronger encoding and updating of the task set on shift trials, and consecutively such a finding should be stronger in dual compared to single shift conditions. If this effect is further enhanced by caffeine, it would support the fact that caffeine's effects on anticipatory processing are fairly specific. However, cautiousness with respect to such a conclusion is needed, because other accounts of the P3 can also explain these effects (such as cue-processing difficulty; Johnson, 1986). Also, it cannot be ruled out that a shift-induced increase in P3 amplitude may, in fact, reflect an effect of shifting on a superimposed shift-sensitive component, as previously found (e.g., Karayanidis et al., 2003).

Furthermore, we expected to find shift-induced effects in cue-related P2 and N2 components, but we had no particular reason for assuming caffeine-induced modulations of these effects. Finally, in line with previous studies, we predicted shift-induced attenuations of poststimulus P2, N2, and P3 components, but caffeine was not expected to influence these effects of shifting.

Previously, we did not find dose-dependent effects of caffeine; a dose of 3 and 5 mg/kg BW caffeine produced similar effects on task switching, although the pattern of data was in the direction of improved switching in the high (5 mg/kg BW) compared to the low dose condition, as evidenced by reduced shift costs (Tieges et al., 2006). The notion of improved task performance after a relatively high dose of caffeine is in line with a study by Ruijter et al. (1999), who investigated multiple doses of caffeine in a complex dual task study, and found reduced RTs on both tasks with increasing caffeine dose up to 7.5 mg/kg BW. Thus, in a further attempt to check for dose-dependent effects, the high dose was enhanced to 6 mg/kg BW caffeine.

4.2 Methods

4.2.1 Participants

Eighteen healthy, right-handed undergraduate students (9 men, 9 women) participated in the present study. Age ranged from 18 to 31 (mean = 21.6, SD = 3.6). Their self-reported daily coffee consumption was between 233 mg and 729 mg caffeine (mean = 448, SD = 136; i.e., 2.7 to 8.6 cups). Total caffeine consumption from coffee, tea, soft drinks, and chocolate ranged from 261 mg to 760 mg (mean = 510, SD = 142). All participants were nonsmokers, had normal or corrected-to-normal vision, did not use prescription medication except for birth control, had normal sleep patterns (Mulder-Hajonides van der Meulen et al., 1980), and reported no history of brain damage or mental illness. Written informed consent was obtained from all participants, and they received course credits for participation.

4.2.2 Treatment manipulation

In a double-blind, placebo-controlled, cross-over design, each participant completed three experimental sessions in which 3 mg/kg BW lactose (placebo), 3 mg/kg BW caffeine (low dose), and 6 mg/kg BW caffeine (high dose) dissolved in a cup of normally brewed decaffeinated coffee were administered. These substances could not be detected by taste or smell. Milk powder and sugar were added to suit their own taste. The order of sessions was counterbalanced across participants. They abstained from caffeine-containing foods and beverages for 12 h prior to the experiment. Saliva samples were taken at the beginning of the experimental sessions in order to encourage compliance to the abstinence instructions.

4.2.3 Stimuli and apparatus

Participants were tested individually in a dimly lit, sound-attenuated room. They were seated in a dentist chair with response buttons attached to both armrests, facing a VGA color monitor at a viewing distance of 90 cm. They completed three variants of a shifting task in which they had to shift between two simple tasks designated by a cue.
All stimuli were presented within a grid of grey color, which was continuously projected against a black background (Figure 1A). The grid consisted of a square (10 x 10 cm) that was divided in four quadrants of 5 x 5 cm each. The center of the larger square contained a smaller square (5 x 5 cm), in which the target stimuli were presented. These stimuli consisted of red and blue letters, randomly chosen from the set A, E, O, U, G, K, M, and R (uppercase Arial font, 0.5 x 0.8 cm). Associated with each of the four quadrants was a unique task that consistently belonged to that quadrant. The two left quadrants indicated that participants had to judge whether the letter was a consonant or a vowel (letter identity task), whereas the two right quadrants indicated that they had to determine whether the letter was printed in red or blue (color task). In addition, the two upper quadrants indicated that responses should be made with middle fingers, whereas the two lower quadrants instructed participants to respond with index fingers. Thus, four unique task cues were formed by combination of task type (color or letter identity task) and effector type (index finger or middle finger). Participants learned the association of a specific quadrant with a particular task in a series of practice blocks. Responses were made by pressing the two inner buttons with the left and right index fingers, and the outer buttons with the left and right middle fingers. S-R mappings were counterbalanced across participants.

At the onset of a block of trials, a task instruction on the screen informed the participant which task cues would appear in the following block of trials. A fixation cross was then presented in the inner square for 1000 ms, indicating the onset of each trial (Figure 1B). Next, one task cue was highlighted (the associated quadrant was colored grey). After a cue-stimulus interval of 1000 ms, the target stimulus appeared in the center of the inner square and remained on the screen until participants gave a response or until 5000 ms had elapsed, at which time the task cue was removed. After a random intertrial interval between

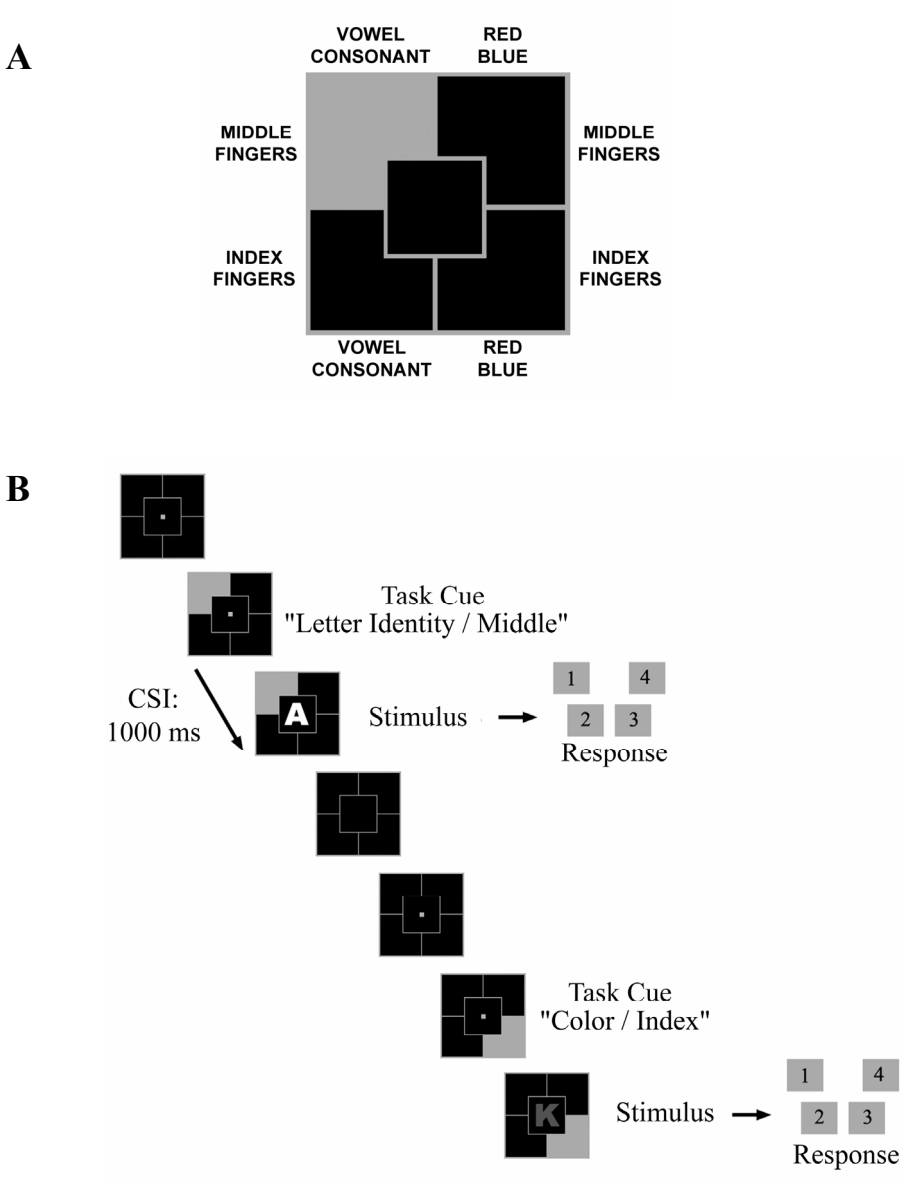

Figure 1. Stimulus display grid (A). An example of a sequence of two trials is displayed (B). In this particular example, participants were required to shift from the letter identity/middle finger task to the color/index finger task (dual shift condition). Responses were made by pressing one of four response buttons.

1000 and 2000 ms (in 20 steps of 50 ms each), the presentation of the fixation cross announced the beginning of the next trial.

In single-task blocks (which were used only in the practice session) the task cue was always the same on each trial throughout a block of trials. That is, participants performed only task repetitions. In mixed-task blocks, on each trial the task cue was selected randomly (but equiprobably) from a subset of two possible task cues. In the "effector shift" condition, either the two quadrants on the left or the two quadrants on the right signified the two possible task cues. Thus, participants alternated between responding with middle fingers and index fingers, while using the same S-R mapping rule throughout a block. Similarly, in the "rule shift" condition, either the two upper quadrants or the two lower quadrants reflected the two possible task cues. Thus, participants alternated between two S-R mapping rules (color or letter identity task) while responding with one set of effectors (middle or index fingers) throughout a block. Finally, in the "dual shift" condition, the two task cues were represented either by the left/upper and right/lower quadrants or by the two quadrants on the other diagonal. Thus, the set of S-R mapping rules and the set of effectors to be used with the S-R rule could be alternated, but only simultaneously.

In sum, the three shift conditions each comprised two different mixed-task blocks in which 50% of the trials were task repetitions and 50% were task alternations, requiring the participants to shift between two tasks. This yielded a total of 18 experimental conditions (treatment (3) x shift type (3) x trial type (2)). Each mixed-task block consisted of 96 trials preceded by presentation of an instruction on the screen. In each experimental session, the six different mixed-task blocks (two of each shift condition) were presented twice, yielding a total of 12 blocks. All letter (8) x color (2) x task cue (2) combinations appeared three times within a block. Speed and accuracy were equally emphasized.

4.2.4 Subjective measurements

Four questionnaires were used to measure subjective feelings before, during, and after the experimental blocks. A sleep quality inventory (Mulder-Hajonides van der Meulen et al., 1980) was employed to measure participants' self-reported sleep duration and quality on the nights before the experimental sessions. The short version of the profile of mood states (POMS; Wald & Mellenbergh, 1990) measured changes in five mood states: Depression, anger, fatigue, vigor, and tension. Participants indicated how they felt at that moment for each of 32 adjectives on a 5-point scale ranging from 0 (not at all) to 4 (very much). The 20-item state part of the Dutch version of the state-trait anxiety inventory (STAI; van der Ploeg et al., 1980) assessed the current level of anxiety on a 4-point scale ranging from 1 (not at all) to 4 (almost always). To rate subjective fatigue, the rating scale mental effort (RSME; Zijlstra, 1993) was used. Participants indicated on 150-point rating scales how they felt for each of 7 items that addressed different aspects of fatigue.

4.2.5 EEG recording

The electroencephalogram (EEG) was continuously recorded from a 64-channel Ag-AgCl Easy-Cap (Falk Minow Services, Munich) referenced to the left earlobe. Impedance was kept below 5 kΩ. Eye movements were recorded from bipolar Ag-AgCl electrode pairs placed above and below the left eye (vertical eye movements and eye blinks) and left and right of the outer canthi of both eyes (horizontal eye movements). EEG signals were amplified by two 32-channel SynAmps amplifiers (Neuroscan Inc.) in AC mode, and online filtered with a time constant set to 5 s and a low-pass cutoff at 35 Hz. Signals were digitized online at 250 Hz.

4.2.6 Procedure

In an intake session, the intention of the experiment was explained to the participants and they filled out an informed consent form. After verification that participants met all inclusion criteria, a training session followed in which they completed four single-task blocks of 50 trials, one for each task cue. Subsequently, six mixed-task blocks of 96 trials each were presented. Next, participants completed three experimental sessions of about 3 h each, which were identical except for treatment. The interval between sessions was approximately 1 week.

Experimental sessions started either at 9:30 a.m. or at 1:00 p.m., but time of measurement was kept constant across sessions for each participant. Upon arrival a saliva sample was taken in order to reinforce compliance to the caffeine abstinence instructions. Next, participants filled out the POMS, STAI, and sleep quality questionnaire. Then they were prepared for the EEG recordings after which they drank the coffee. Subsequently, participants completed six mixed-task blocks (but only for about 50 trials per block) to familiarize themselves again with the tasks at hand. About 40 min after drinking the coffee, participants filled out the POMS and STAI for the second time, and thereafter the experimental task started. Twelve mixed-task blocks were presented with a short break after the sixth block in which the RSME was filled out. The order of shift blocks was semi-random, such that within a sequence of three subsequent blocks, one block of each shift condition appeared. The task lasted about 90 min and afterward participants completed the POMS, STAI, and RSME for the last time. They were fully debriefed at the end of the last session.

All experimental procedures were conducted in compliance with relevant laws and institutional guidelines and were approved by the departmental ethical committee.

4.2.7 Data reduction

The first two trials within each block were regarded as practice trials and were excluded from analysis. For the remaining trials, responses were defined as correct when made with the correct hand between 100 ms and 2500 ms after stimulus onset. Responses were considered incorrect if they were committed with the wrong hand or finger, regardless of speed. Mean RT for correct responses and error rates were calculated for the factors treatment (placebo, low dose, and high dose), shift type (effector shift, rule shift, and dual shift) and trial type (repeat and shift).

EEG data ware segmented offline into single-trial epochs of 4096 ms and subsequently scanned for A/D saturation and flat lines. Ocular artifacts were controlled according to the method of Woestenburg and colleagues (1983). Epochs containing artifacts (change in amplitude of more than 50 μV per two consecutive samples) or drifts (change in amplitude of more than 200 μV per epoch) in one or more channels were omitted from analysis. Then, epochs were filtered offline with a 25-Hz low-pass cutoff frequency. For each participant, condition, and electrode, two sets of epoched data were created. Cue-locked ERPs were obtained aligned to a baseline of 100 to 0 ms preceding the cue, to evaluate ERP effects within the cue-stimulus interval. Thus, epochs were averaged separately according to whether the cue indicated an upcoming change in task or a repetition of the same task. In addition, stimulus-locked (i.e., poststimulus) waveforms were created by averaging EEG epochs synchronized to stimulus onset, aligned to a baseline from 100 to 0 ms preceding the stimulus. Finally, ERP data were re-referenced offline to linked earlobes.

Isopotential contour maps were created with EEGLAB software (Delorme & Makeig, 2004).

4.2.8 Statistical analyses

Individual averages for subjective measurements, RTs, error rates, and ERP components were analyzed with repeated-measures analyses of variance (ANOVA).

For the subjective measurements, baseline measurements were compared between experimental sessions in order to evaluate pre-existing differences within participants between sessions. Significant differences in baseline levels were, if present, adjusted by including the concerning variable as a covariate in the statistical analyses. In addition, effects of treatment and effects of testing on subjective measurements were assessed.

Performance and ERP data were analyzed with the factors treatment (placebo, low dose, and high dose), shift type (effector shift, rule shift, and dual shift), and trial type (repeat and shift). The data are reported using $p < .025$. We adopted this criterion in an attempt to correct for type I error while still being able to notice relevant effects (because a suitable procedure for correction of type I error seems to be lacking for this type of research).

To correct for violations of the sphericity assumption in the ANOVA, degrees of freedom were corrected using the Huynh-Feldt method when appropriate. Corrected *p* values but uncorrected df values are reported to facilitate interpretation of the data. Statistically significant effects of treatment and shift condition were followed up by contrast analyses, involving two orthogonal contrasts for the factor treatment (Helmert) and two for the factor shift type (simple). For the factor treatment, the first contrast evaluates placebo against the mean of the two caffeine conditions; the second contrast tests the low against the high dose condition. For the factor shift type, the contrasts evaluate the mean of the dual shift condition against the effector shift condition (first contrast) and against the rule shift condition (second contrast).

			placebo		low dose (3 mg/kg BW)		high dose (6 mg/kg BW)	
effector shift	RT	repeat	431	(63)	415	(69)	403	(59)
		shift	469	(89)	445	(92)	431	(86)
		shift cost	*38*		*30*		*27*	
	%	repeat	3.2	(2.8)	3.4	(2.9)	3.7	(3.2)
		shift	3.1	(3.2)	2.6	(2.6)	3.1	(3.1)
		shift cost	*0.0*		*-0.8*		*-0.6*	
rule shift	RT	repeat	470	(68)	447	(89)	434	(78)
		shift	565	(113)	518	(128)	507	(108)
		shift cost	*95*		*72*		*73*	
	%	repeat	3.8	(3.8)	2.7	(2.3)	3.1	(2.7)
		shift	6.0	(4.2)	4.2	(2.5)	4.9	(3.5)
		shift cost	*2.2*		*1.5*		*1.8*	
effector+rule shift	RT	repeat	458	(60)	443	(80)	437	(75)
		shift	578	(114)	530	(129)	515	(110)
		shift cost	*120*		*87*		*78*	
	%	repeat	4.4	(3.1)	3.2	(2.5)	3.6	(2.8)
		shift	6.2	(4.7)	4.5	(3.9)	5.4	(3.7)
		shift cost	*1.8*		*1.3*		*1.8*	

Table 1. Mean reaction times (RT) in milliseconds and error rates (standard deviations in parentheses) as a function of treatment, shift condition, and trial type. Shift costs reflect the difference in RT and error rate between shift and repeat trials.

4.3 Results

4.3.1 Subjective measurements

Participants reported no differences in sleep quality on the night before the experimental sessions, or in their subjective state (as measured with the POMS and STAI) upon arrival. They felt more fatigued after testing compared to before (Fatigue subscale of the POMS; $F(1,17) = 6.49$, $p < .05$). Treatment affected reported feelings of fatigue ($F(2,34) = 4.12$, $p < .05$), with Helmert contrasts showing less fatigue in both caffeine conditions compared to placebo ($F(1,17) = 6.96$, $p < .05$). In addition, a trend was found towards more subjective vigor in caffeine conditions compared to placebo (vigor subscale of the POMS; $F(2,34) = 2.82$, $p = .077$). No effects of treatment or testing on subjective fatigue or anxiety (as measured with the RSME and STAI, respectively) were found.

4.3.2 Behavioral data

4.3.2.1 Effects of task switching

RT and error rate across the different conditions are shown in Table 1. Participants responded slower on shift compared to repeat trials, reflecting RT shift costs ($F(1,17) = 43.75$, $p < .001$). In addition, they made more errors on shift compared to repeat trials, reflecting error shift costs ($F(1,17) = 8.11$, $p < .025$).

4.3.2.2 Effects of shift type: Single vs. dual shifts[1]

Shift type affected overall RT ($F(2,34) = 34.75$, $p < .001$). Simple contrasts showed that participants slowed down in dual shift conditions (mean = 493 ms, SD = 85) compared to effector shift conditions (mean = 432 ms, SD = 71; $F(1,17) = 56.44$, $p < .001$), but not compared to rule shift conditions (mean = 490 ms, SD = 88). Shift type affected error rate as

1 The factors 'task type' (color and letter identity task) and 'effector type' (index and middle finger) were not included in the analyses. Since we are not primarily interested in these factors, we reasoned that they might contribute to the error variance and might therefore weaken or obscure other effects. For this reason, we inspected the analyses separately for data that were pooled over both task types (adding the factor "effector type" to the analyses), and data pooled over both effector types (adding the factor "task type"). Note that we included only effector shift and effector+rule-shift conditions in the data set pooled over effector types, since these conditions required participants to alternate between index and middle finger responses. By the same logic, we included only the rule shift and effector+rule-shift conditions in the data that were pooled over task types. These separate analyses largely replicated the findings obtained in the main analyses, both for behavioral and ERP data. For reasons of clarity, we did not include these additional analyses in the text.

well ($F(2,34) = 8.59$, $p < .005$; see Table 1). Post hoc tests indicated higher error rates in dual compared to rule shift conditions (mean = 490 ms, SD = 88). Shift type affected error rate as shift conditions (mean = 4.6, SD = 2.9) than in effector shift conditions (mean = 3.2, SD = 2.4; $F(1,17) = 12.77$, $p < .005$).

The Shift Type x Trial Type interaction was significant both for RT ($F(2,34) = 28.12$, $p < .001$) and error rate ($F(2,34) = 10.73$, $p < .001$). RT shift costs were enhanced in dual shift compared to effector shift conditions ($F(1,17) = 50.75$, $p < .001$) and rule shift conditions ($F(1,17) = 6.41$, $p < .025$). In addition, larger error shift costs were found in dual shift (compared to effector shift) conditions ($F(1,17) = 14.87$, $p < .005$). In fact, error rates in effector shift conditions were slightly smaller for shift compared to repeat trials, yielding negative shift costs.

In summary, the present investigation yielded substantial RT and error shift costs, which were increased in dual shift compared to single shift conditions. Hence, the manipulation of task shift load was successful in the present study, yielding larger costs when reconfiguring two task-set elements instead of only one element (although for error rate, this was only seen relative to effector shifts).

4.3.2.3 Effects of caffeine

A main effect of treatment on RT was observed ($F(2,34) = 5.84$, $p < .01$), with faster responses in both low dose and high dose caffeine conditions compared to placebo ($F(1,17) = 14.69$, $p < .005$). Moreover, a significant Treatment x Trial Type interaction was found for RT ($F(2,34) = 7.90$, $p < .005$), which revealed reduced shift costs for low and high caffeine dose (63 ms and 60 ms, respectively) compared to placebo (84 ms; $F(1,17) = 12.05$, $p < .004$). Treatment affected error rate as well ($F(2,34) = 4.68$, $p < .017$), resulting in fewer errors after a low and high dose compared to placebo ($F(1,17) = 5.68$, $p < .03$). Yet, error shift costs were not affected by caffeine.

The expected three-way Treatment x Shift Type x Trial Type interaction, testing the differential effects of caffeine on single shift and dual shift conditions, was not significant for RT ($F(4,48) = 1.94$, ns) or error rate ($F(4,68) = .096$, ns). Thus, the hypothesis that caffeine would have greater shift-related effects on dual shift conditions was not confirmed. It should be noted, though, that the pattern of RT data was in the expected direction, as revealed by post hoc analyses showing a trend toward a Treatment (placebo vs. caffeine) x Shift Type (effector vs. dual shift) x Trial Type (repeat vs. shift) interaction, such that caffeine conditions yielded somewhat reduced shift costs in dual shift compared to effector shift conditions, relative to placebo ($F(1,17) = 4.79$, $p < .044$). With respect to dose-dependent effects, none of the behavioral analyses showed differences between low dose and high dose conditions.

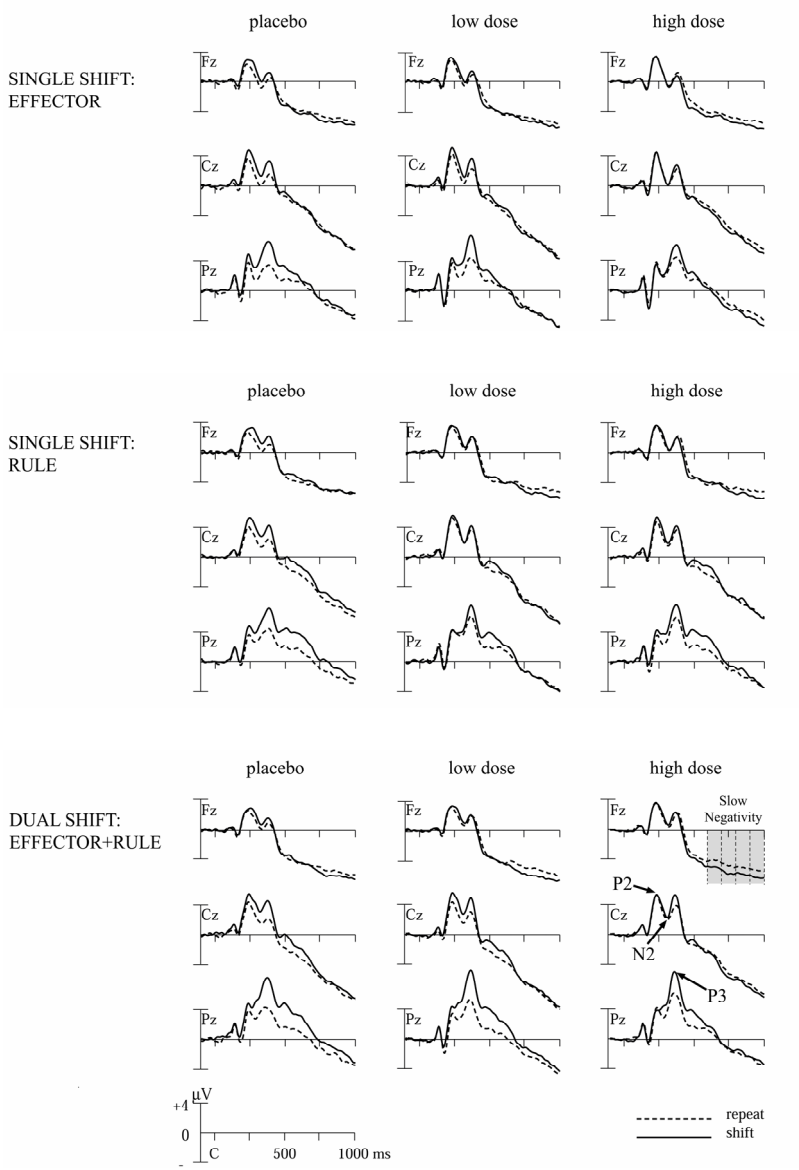

Figure 2. Average event-related potential (ERP) waveforms time-locked to onset of the cue, as recorded from Fz, Cz, and Pz. ERPs are shown for effector shift (upper panel), rule shift (middle panel), and dual shift (bottom panel) conditions, elicited on repeat trials (dashed lines) and shift trials (solid lines). P2 and P3 components were defined as the most positive peaks in the segments 150-300 ms (P2) and 300-600 ms (P3) postcue; N2 was defined as the negative peak in the segment 200-350 ms. Cumulative amplitudes for the slow negativity were calculated for the time segments 600-700 ms, 700-800 ms, 800-900 ms, and 900-1000 ms.

	time window			
	600-700 ms	700-800 ms	800-900 ms	900-1000 ms
treatment	—	—	—	—
shift type	—	—	.041	.022*
effector shift - effector+rule shift			*.090*	*.071*
rule shift - effector+rule shift			*.001***	*.001***
trial type	.061	.007*	.004**	.003**
treatment x shift type	—	—	—	—
treatment x trial type	—	—	—	.016*
placebo - caffeine				*.013**
low dose - high dose				—
shift type x trial type	0.052	.022*	—	—
effector shift - effector+rule shift	*.043*	*.032*		
rule shift - effector+rule shift	*.043*	*.020**		
treatment x shift type x trial type	—	—	—	—

* $p < .025$
** $p < .005$

Table 2. P-values obtained in analyses of the slow negativity within anticipatory ERP waveforms. Areas were calculated within the time windows 600-700 ms, 700-800 ms, 800-900 ms, and 900-1000 ms post-cue.

To summarize, the shift cost reduction induced by caffeine did not differ significantly between dual and single shift conditions (although additional analyses showed the predicted pattern for dual compared to effector shifts).

4.3.3 Anticipatory ERPs

ERP waveforms time-locked to the preceding cue, or anticipatory ERPs, are shown in Figure 2, for each trial type, shift type, and treatment condition and for electrodes Fz, Cz, and Pz. These waveforms were mainly composed of a pattern of P2, N2, and P3 deflections, followed by a build-up of slow negativity continuing until stimulus onset. The N2 and P2 components appeared to attain maximal amplitudes at central sites, whereas the P3 was

observed most clearly at parietal sites. The slow negativity, which followed the P3 component, evolved gradually within the cue-stimulus interval and was most pronounced at the end of this interval.

P2 and P3 components were defined as the positive peak amplitudes in the segments 150-300 ms (P2) and 300-600 ms (P3) postcue, whereas N2 was defined as the negative peak amplitude in the segment 200-350 ms postcue. Because the N2 appeared to be closely linked to the magnitude of the preceding P2, we also determined, and analyzed, N2 amplitude relative to the preceding P2 peak (i.e., peak-to-peak). For reasons of clarity, we restricted our analyses to electrodes where the components attained maximal amplitudes, that is Cz and Pz. The slow negativity within anticipatory ERPs appeared to evolve within the time window 600-1000 ms following the preceding cue and was maximal at frontal sites. We examined the slow negativity by calculating areas (i.e., the cumulative amplitude) for each of four consecutive 100-ms segments starting at 600 ms until presentation of the target stimulus (1000 ms), at Fz (see Table 2 for an overview of the findings).

Latency effects were not statistically significant, unless otherwise reported.

4.3.3.1 Effects of task switching

Compared with repeat trials, shift trials were associated with enhanced amplitudes for the P3 ($F(1,17) = 25.24$, $p < .001$), which can be clearly seen in Figure 3, showing P3 amplitudes in the different experimental conditions. A nonsignificant trend was seen for P2 amplitudes ($F(1,17) = 5.27$, $p < .036$). N2 amplitude was not affected by task switching. As for the following slow negativity, a significant effect of trial type was found for the subsequent segments 700-800 ms ($F(1,17) = 10.08$, $p < .01$), 800-900 ms ($F(1,17) = 11.71$, $p < .005$), and 900-1000 ms ($F(1,17) = 13.43$, $p < .005$), indicating enlarged slow negativities when participants anticipated a shift of task as compared with a task repetition. This is evident from the ERPs as presented in Figure 2, and from Figure 5 which depicts mean amplitudes of the slow negativity for the 900-1000 ms segment.

For comparison, scalp topographies depicting the mean potential distribution in the time window 900-1000 ms after cue-onset (Figure 5) show a widespread mediofrontal negativity that was larger for shift than repeat trials, as evidenced by a negative potential distribution of the difference waveform of shift minus repeat trials.

4.3.3.2 Effects of shift type: Single versus dual shifts

With respect to the P3, a Shift Type x Trial Type interaction was found ($F(2,34) = 4.75$, $p < .025$), showing that the increased P3 on shift (compared to repeat) trials was further enhanced in dual compared to rule shift conditions ($F(1,17) = 12.56$, $p < .005$). To better understand this effect, two more analyses were run separately for each trial type, showing that it was the result of enhanced P3 amplitudes in shift conditions ($F(1,17) = 8.64$, $p < .01$), but not repeat conditions ($F(1,17) = .31$). This supports our prediction of enhanced shift-

sensitive P3 components in dual shift compared to single shift conditions, and may reflect the greater demands related to updating the relevant task set (or, alternatively, cue processing) on shift trials, and more so for dual shifts. No such effects were observed for the P2 and N2.

Regarding the slow negativity, we observed a nonsignificant trend for the main effect of shift type in the 800-900 ms time segment ($F(2,34) = 4.08$, $p < .041$) that reached statistical significance within the 900-1000 ms segment ($F(2,34) = 4.98$, $p < .025$; see Table 2 and Figure 4). Simple contrasts revealed an enhanced negativity for dual compared to rule shift conditions ($F(1,17) = 24.29$, $p < .001$). More important, a Shift Type x Trial Type interaction was found, but only in the 700-800 ms interval ($F(2,34) = 4.33$, $p < .025$; see Table 2), showing that the enhanced slow negativity on shift (relative to repeat) trials was further increased in dual shift compared to rule shift conditions ($F(1,17) = 6.56$, $p < .025$; for dual shift and effector shift conditions, a nonsignificant trend was found, $F(1,17) = 5.54$, $p < .032$). The implication of this finding is that the slow negativity was sensitive to task switching and also (to some extent) to the task-set load that had to be shifted (one vs. two task-set elements).

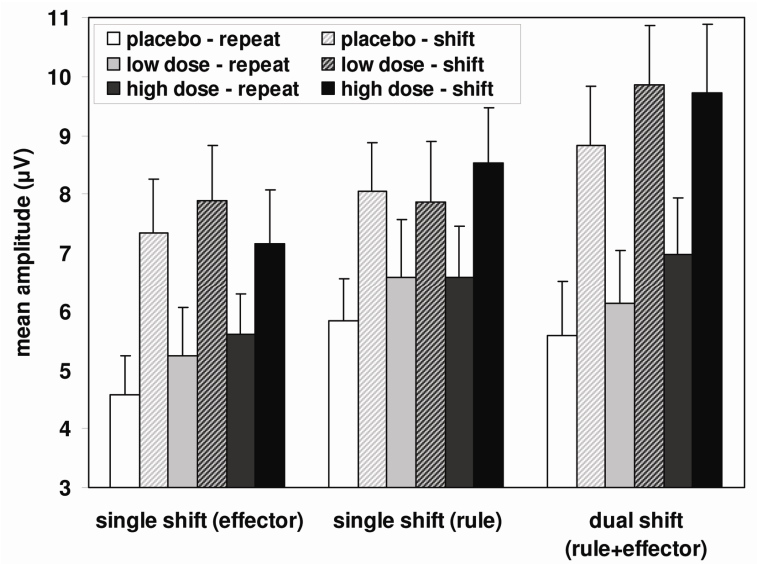

Figure 3. Peak amplitude of the cue-related P3 at lead Pz as a function of treatment condition (placebo, 3 mg/kg BW caffeine, 6 mg/kg BW caffeine), shift condition (effector shift, rule shift, dual shift), and trial type (repeat, shift). Error bars reflect standard errors.

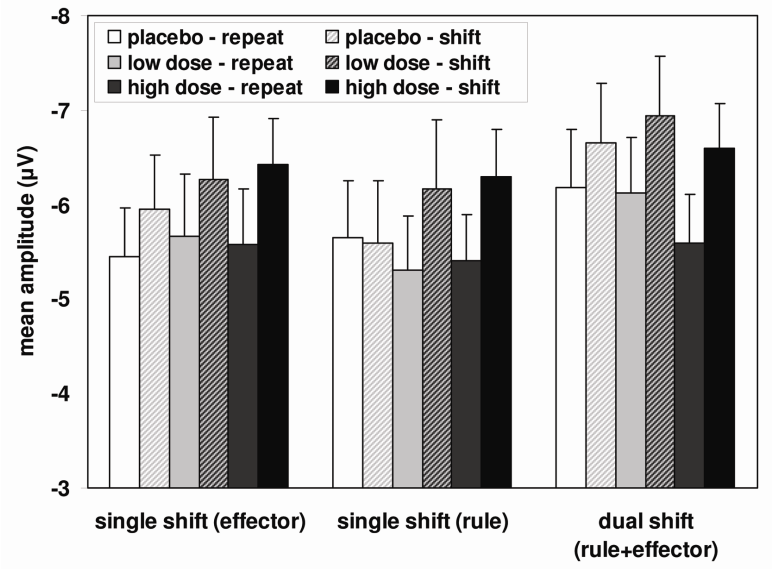

Figure 4. Peak amplitude of the slow negativity in the final segment (900-1000) before stimulus presentation at lead Fz, as a function of treatment condition (placebo, 3 mg/kg BW caffeine, 6 mg/kg BW caffeine), shift condition (effector shift, rule shift, dual shift), and trial type (repeat, shift). Error bars reflect standard errors. Note that the mean amplitude of the slow negativity is shown to facilitate interpretation of the data.

In sum, the presently used cued switching task yielded a number of ERP effects in the preparation interval: Switching between tasks was associated with enhanced P2 and P3 amplitudes and an enhanced slow negativity (700-1000 ms postcue), compared to task repetitions. For P3 amplitude and the slow negativity, these effects of switching were further increased on dual compared to single shift conditions.

4.3.3.3 Effects of caffeine

A Treatment x Trial Type interaction was found for the P2 component ($F(2,34) = 7.05$, $p < .005$). Helmert contrasts revealed that caffeine reduced the shift-repeat difference in P2 amplitude compared to placebo ($F(1,17) = 9.62$, $p < .01$), and a trend towards a reduced shift-repeat difference in the P2 after a high compared to low dose was found as well ($F(1,17) = 5.50$, $p < .032$). A similar effect of caffeine was observed for the N2 ($F(2,34) = 11.75$, $p < .001$), showing a reduction of the shift-repeat difference in N2 amplitude for caffeine conditions relative to placebo $F(1,17) = 19.34$, $p < .001$). However, this effect failed to reach significance when the N2 amplitude relative to the preceding P2 peak was analyzed ($F(2,34) = 2.72$). N2 latency was affected by caffeine as well ($F(2,34) = 4.14$, $p < .036$), with the N2 peaking slightly earlier after caffeine relative to placebo ($F(1,17) = 5.16$, $p < .036$).

These effects seemed rather puzzling, and consequently we performed additional analyses for these components, separately for each trial type. The caffeine effect on the shift-repeat difference in P2 amplitude appeared to result from a caffeine-induced enhancement on repeat trials ($F(4,68) = 3.07$, $p < .025$), whereas no modulation on shift trials was seen. For the N2, these analyses did not produce statistically significant effects.

A significant three-way Treatment x Shift Type x Trial Type interaction was obtained for P3 amplitude ($F(4,68) = 3.69$, $p < .01$; see Figure 3). That is, the shift-induced increase in P3 amplitude was enhanced in dual compared to rule shift conditions, and more so for low than high dose conditions ($F(1,17) = 10.41$, $p < .01$) but not compared with the placebo condition. This finding suggest that processing of the cue and/or updating of the relevant task set was intensified after a low dose compared to a high dose.

With respect to the slow negativity, a significant Treatment x Trial Type interaction was found within the 900-1000 ms segment ($F(2,34) = 4.77$, $p < .025$), such that the shift-induced modulation in the slow negativity was enhanced in both caffeine conditions compared to placebo ($F(1,17) = 7.83$, $p < .025$, see Figure 4). Low and high conditions did not differ. Importantly, contrary to our prediction the Treatment x Shift Type x Trial Type interaction for the slow negativity was not found.

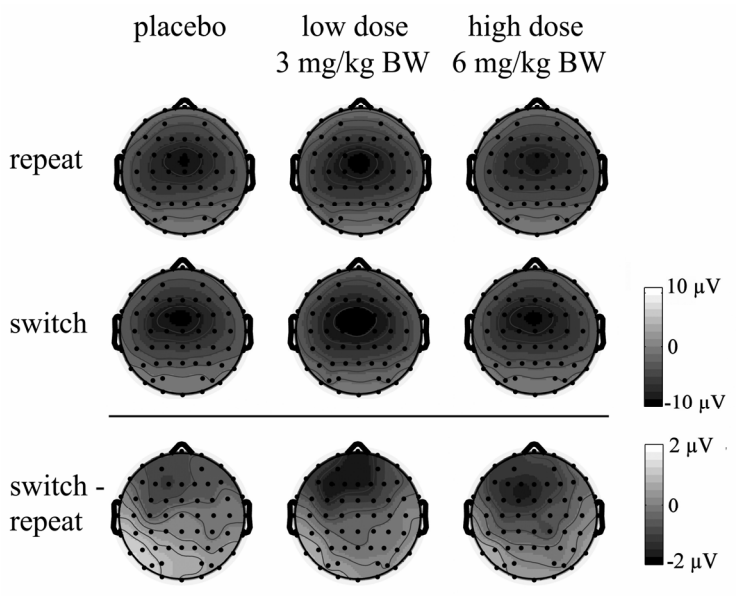

Figure 5. Grand-average spline-interpolated scalp potential maps for anticipatory processing involved in task switching in placebo, low dose, and high dose conditions. The maps show the mean voltage distribution in the time window 900-1000 ms after cue presentation, for ERPs recorded in repeat and shift conditions and the difference waveforms (shift – repeat).
Note: For a color version of this figure, see Appendix.

As can be seen in Figure 5, the scalp topographies for the difference waves (shift – repeat) in the treatment conditions show that the effects of caffeine are evident as a shift-induced increase in slow negativity, whereas the distribution of these effects is comparable across treatment conditions. It appears, therefore, that caffeine boosts activation in the neural circuits that are involved in anticipatory shift-related processing, rather than, for example, call upon different neural circuits.

To conclude, the shift-repeat difference in P2 (and to a lesser extent N2) amplitude was reduced by caffeine compared to placebo, by enhancing its magnitude on repeat trials. In addition, the shift-repeat difference in P3 amplitude was enhanced on dual compared to single shift trials, and more so in low (compared to high) dose conditions. Moreover, caffeine enhanced the shift-induced enhancement on shift compared to repeat trials in the final segment of the slow negativity, but this effect was not different for dual shift and single shift conditions. Thus, with respect to cue-related ERP components, the three-way interaction was evident only for P3 amplitude.

4.3.4 Poststimulus ERPs

ERP waveforms time-locked to stimulus onset, or poststimulus ERPs, are depicted in Figure 6, for each trial type, shift type, and treatment condition and for electrodes Fz, Cz, and Pz. These waveforms were characterized by a sequence of stimulus-elicited P2, N2, and P3 components that were largest at parietal scalp sites, which is in line with previous studies of task switching (Karayanidis et al., 2003; Rushworth et al., 2002; Tieges et al., 2006; Wylie et al., 2003). P2 and P3 were defined as the positive peak amplitudes in the segments 100-200 ms (P2) and 300-600 ms (P3), whereas N2 was defined as the most negative peak amplitude in the segment 200-350 ms poststimulus. Again, we also determined, and analyzed, N2 amplitude relative to the preceding P2 peak.

4.3.4.1 Effects of task switching

As can be seen in Figure 6, as predicted all stimulus-related components were smaller (or more negative) in shift compared to repeat conditions (P2: $F(1,17) = 16.33$, $p < .005$; N2: $F(1,17) = 23.30$, $p < .001$; P3 $F(1,17) = 59.31$, $p < .001$). Note that the N2 effect remained significant when the N2 relative to the preceding P2 peak was considered ($F(1,17) = 6.85$, $p < .025$). Moreover, peak latencies were somewhat delayed on shift compared to repeat trials for the N2 ($F(1,17) = 4.69$, $p < .045$) and mores so for the P3 ($F(1,17) = 10.26$, $p < .005$), but not P2.

4.3.4.2 Effects of shift type: Single versus dual shifts

A Shift Type x Trial Type interaction for P3 amplitude ($F(2,34) = 12.84$, $p < .001$) indicated that the shift-repeat difference in P3 amplitude was increased for dual shifts compared to

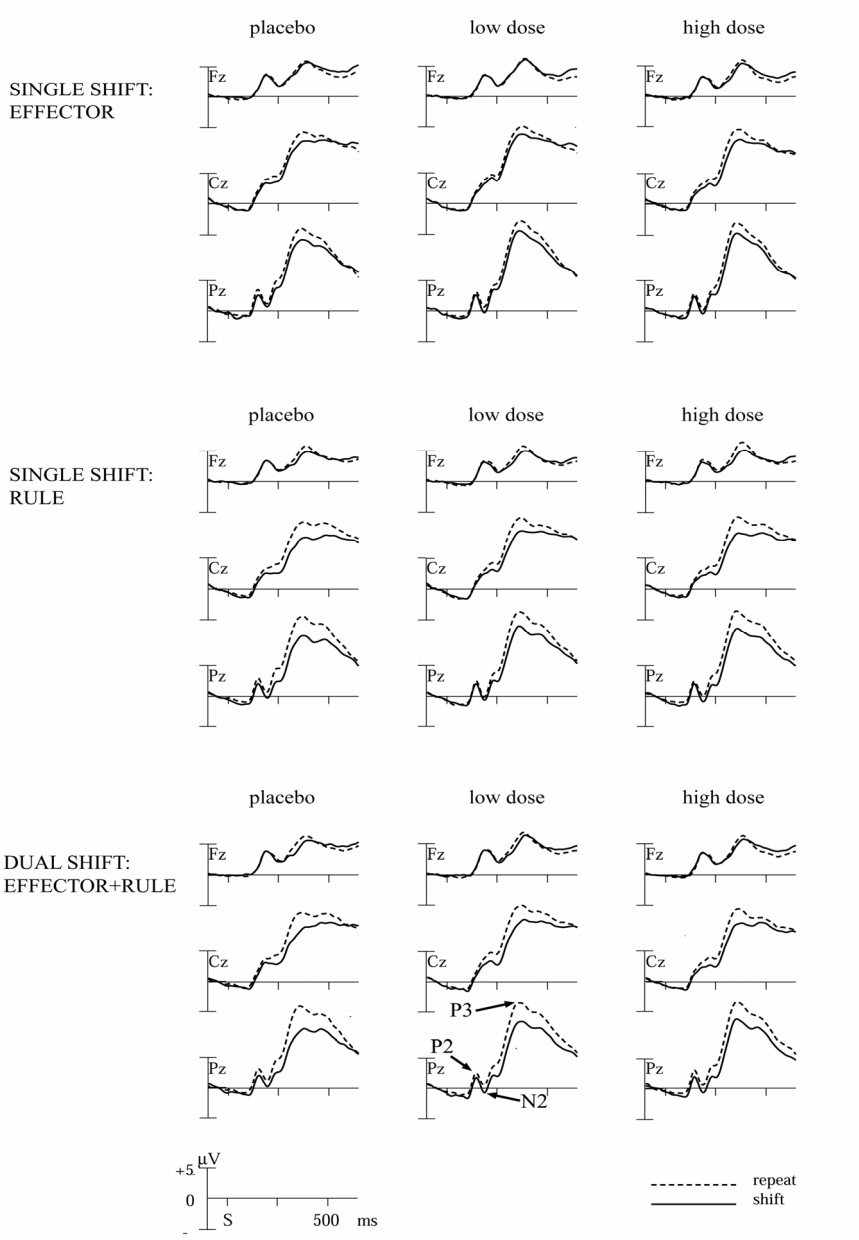

Figure 6. Average event-related potential (ERP) waveforms time-locked to onset of the stimulus, as recorded from Fz, Cz, and Pz. ERPs are shown for effector shift (upper panel), rule shift (middle panel), and dual shift (bottom panel) conditions, elicited on repeat trials (dashed lines) and shift trials (solid lines). P2 and P3 components were defined as the most positive peaks in the segments 150-300 ms (P2) and 300-600 ms (P3) post-cue; N2 was defined as the negative peak in the segment 200-350 ms.

effector shifts ($F(1,17) = 31.95$, $p < .001$). However, additional analyses did not reveal any significant effects of shift type for either repeat or shift conditions. No other effects of shift type were found.

4.3.4.3 Effects of caffeine

An effect of treatment on N2 amplitude ($F(2,34) = 4.38$, $p < .025$) as well as on latency ($F(2,34) = 4.86$, $p < .025$) showed that caffeine conditions produced an enhanced (i.e., more negative) N2 with a shorter latency, relative to placebo (N2 amplitude: $F(1,17) = 6.46$, $p < .022$; N2 latency: $F(1,17) = 8.05$, $p < .025$). However, when considering the N2 relative to the preceding P2, the effect of caffeine was no longer significant ($F(2,34) = 3.98$, $p < .029$). With respect to the P3, caffeine influenced its latency ($F(2,34) = 4.48$, $p < .025$), such that the P3 peaked earlier in caffeine conditions compared to placebo ($F(1,17) = 6.76$, $p < .025$). P3 amplitude was unaffected by caffeine, as was P2 amplitude. None of the interactions of treatment with other factors were significant for the different poststimulus components. This implies that, as in our previous study (Tieges et al., 2006), caffeine's effects on ERP correlates of task switching (i.e., shift-repeat differences) did not extend into the period after stimulus presentation, but instead were largely restricted to the preparation period.

To summarize, all stimulus-related components were smaller (or more negative) and peaking later (except for the P2) on shift compared to repeat trials. Moreover, the amplitude effect for the P3 was enhanced in dual shift conditions, relative to effector shifts. Lastly, caffeine increased N2 amplitude and reduced N2 and P3 peak latencies, but did not interact with other factors.

4.4 Discussion

The current study utilized both behavioral and electrophysiological measures to investigate effects of caffeine on anticipatory processes in task switching. Consistent with our main prediction, caffeine improved task-switching performance as evidenced by reduced RT switching costs after caffeine compared to placebo. A slow negativity developed within the preparation interval that was larger in advance of an upcoming shift of task compared to repeating the same task. Importantly, this shift-induced modulation in anticipatory processing was enhanced in both caffeine conditions compared to placebo. These data corroborate and extend the findings from our previous study (Tieges et al., 2006).

However, the prediction that effects of caffeine would increase parametrically with task shift load was not confirmed in the behavioral results or the slow negativity (although additional analyses showed a trend toward the predicted pattern in RTs). Therefore, it is concluded that caffeine apparently has a more general effect on task switching related to task-nonspecific processes (e.g., actively maintaining the task set in working memory and

protecting it against interference), rather than affecting task-specific processes (e.g., the retrieval and updating of task sets and their associated S-R assignments).

With respect to the nonsignificant trend toward the predicted pattern in RTs for dual compared to effector shifts, we acknowledge that this may be due to a lack of power in the data. Nevertheless, the present data were obtained from a larger sample (N = 18) and ERP data were based on larger trial counts (>60 per condition) than typically used in this type of study. Statistical power was sufficient to expose even moderate interaction effects. Most importantly, this trend in the behavioral data was entirely absent in the ERP findings. In sum, it is concluded that the observed pattern of increased shift-induced modulations in dual shift conditions (compared to effector shifts) simply did not reflect a strong effect.

In addition to the slow negativity, a number of other shift-sensitive components were found during the preparation interval, consistent with previous studies. First, presentation of the cue evoked a sequence of centro-parietal P2, N2, and P3 components (Kieffaber & Hetrick, 2005; Nicholson, et al., 2005; Rushworth et al., 2002). It was striking that the P3 peaked quite early, considering the complexity of the cues. This might be related to the fact that the task was extensively practiced prior to testing, and also because task instructions emphasized speed. It is noteworthy that early P3 components elicited by complex cues have been previously reported (e.g., Barcelo et al., 2006; Slagter, Kok, Mol, Talsma, & Kenemans, 2005).

Cue-related P3 amplitudes were increased on shift compared to repeat trials (with a trend for P2). The existence of a shift-sensitive anticipatory P3 is consistent with cue-related P3-like positivities in other studies (e.g., Karayanidis et al., 2003; Rushworth et al., 2002). This finding might be taken to reflect anticipatory processes directly related to the upcoming shift of task (such as task-set updating). Alternatively, it may reflect greater demands on cue processing, such as translating the cue into a task set. That is, cues on shift trials may have placed greater demands with respect to identification of the cue and translating the cue into the currently relevant task and its S-R assignments.

In sum, the presently used cued switching task yielded a number of ERP effects in the preparation interval: Switching between tasks was mainly associated with enhanced P3 amplitudes and an enhanced slow negativity (700-1000 ms postcue), compared to task repetitions. Furthermore, these effects of switching were further increased on dual compared to single shift conditions, although for the slow negativity this effect occurred only in the 700-800 ms time segment.

Importantly, we expected caffeine to enhance these shift-induced effects for the P3 and, in particular, the slow negativity. The prediction was confirmed in terms of the last portion of the slow negativity: The shift-induced increase in slow negativity was further enhanced by caffeine. For the P3, however, this effect was not seen. Nonetheless, a three-way interaction effect was found for the P3, indicating that the shift-induced increase of P3 amplitude was further enhanced on dual compared to single (i.e., rule) shift trials, and more so in low (compared to high) dose conditions. Although this finding may be taken to reflect the fact that the low dose was more optimal than the high dose with respect to stronger

encoding and updating of the task set on shift trials (possibly related to the inverted U-shaped function for DA in cognition; e.g., Cools, 2006), this interpretation should be made with caution. In particular, low and high dose conditions did not differ in terms of behavioral shift costs. Moreover, caffeine effects are usually most pronounced when comparing caffeine conditions to placebo, but here we did not find such an effect for the P3.

Unexpectedly, we found a caffeine-induced effect on the P2 as well, indicating that a shift-related increase in P2 amplitude was reduced by caffeine, mainly by enhancing its magnitude on repeat trials. This effect was unexpected and seems a bit puzzling. In the present study, the P2 may reflect early perceptual or attentional processing of the cue. For instance, it may index processing of the similarity of the current cue to the previous cue, which is an important feature of the cue because it indicates whether the current trial involves a task shift or task repetition. However, the functional significance of the cue-P2 in the context of task switching is as yet poorly understood and we therefore cannot offer a viable explanation for the presently found cue-P2 effects.

To conclude, although effects of caffeine on shift-induced modulations following the cue were found for the P2, P3, and slow negativity, these effects were most convincing for the latter component.

With respect to target-related ERPs, a sustained amplitude reduction was observed on shift relative to repeat trials, such that P2, N2, and P3 amplitudes were reduced on trials in which the task was switched. Similar effects of switching in P3-like components were reported by others (Karayanidis et al., 2003; Kieffaber & Hetrick, 2005). As mentioned in the introduction, these shift-induced attenuations of poststimulus components, specifically the P3 (or a positive waveform superimposed on the P3), may reflect a weaker or unstable task-set on shift compared to repeat trials (e.g., Barcelo et al., 2000). Alternatively, as Waszak et al. (2003) have proposed, stronger associations between stimulus and task set in repeat compared to shift conditions may also have accounted for these effects. Finally, it cannot be ruled out that these effects may reflect shift-induced modulations in anticipatory ERP components (i.e., slow negativity), extending into the period beyond stimulus presentation and overlapping with stimulus-related brain activity.

Although caffeine served to enhance poststimulus N2 amplitudes as well as shorten N2 and P3 latencies, the shift-induced modulations of these components were not affected by caffeine, in accordance with our prediction. The implication of this finding is that the perceived effects of caffeine on cue-related components and the following slow negativity cannot be explained by general caffeine-induced enhancements in ERP components, but instead, appear to be specific to anticipatory processing.

To summarize, we replicated and extended our previous findings. That is, we showed that the ability to shift voluntarily and dynamically between two tasks is improved by caffeine. Furthermore, the main prediction that these effects of caffeine would be most pronounced in dual shift conditions and that, in turn, this effect would be reflected in the slow negativity was not confirmed. Hence, it is concluded that the effects of caffeine on

anticipatory processes of task switching are linked to caffeine-mediated increases in task-nonspecific anticipatory processes associated with a shift of task.

A speculative, but interesting alternative explanation for the present findings concerns the binding processes that contribute to shift costs (Waszak et al., 2003). In a recent study by Colzato, Fagioli, Erasmus, and Hommel (2005) it was shown that caffeine, by stimulating the muscarinic cholinergic system, increased the binding of visual objects (S-S feature binding), whereas S-R feature bindings were spared. In the present experiment, S-R bindings (but not S-S bindings) were manipulated; that is, switching between one or two aspects of the task sets affected S-R bindings between a stimulus (e.g., the letter A printed in red) and its required response (e.g., a response made with the right index finger). Because the present study showed no interactions between caffeine and the task-set load to be switched (S-R bindings), it may be that caffeine influenced control (top-down) processes involved in task switching rather than binding (bottom-up) processes. This is an interesting, but purely theoretical, suggestion that requires further studying.

A final remark should be made regarding the functional significance of the slow negativity. Caffeine affected shift-sensitive modulations in this component that were comparable in single shift and dual shift conditions. If we assume that the slow negativity may have reflected processes related to inhibiting the currently relevant task set from the previously relevant, now irrelevant task set, this may very well have been similar for inhibition of task sets comprising only one element or two elements, yielding comparable findings in the single and dual conditions. At present, this idea cannot be confirmed or rejected.

4.4.1 ERP correlates of anticipatory control processes in task switching

Although the present study replicated our previous findings of a shift-induced enhancement in the anticipatory slow negativity, there were some important differences between the two data sets. Using a predictable task-switching paradigm, we have previously shown a negative component early on in the preparation interval, that was reduced for shift compared to repeat trials. Within roughly the same time period (200-600 ms postcue), we now observed a shift-induced increase in cue-evoked P2 and P3 in the present study. Whereas our previous results regarding the early negativity were possibly confounded by response-related processing, the present study clearly showed enhanced cue processing when the cue indicated an upcoming shift of task.

Recently, some researchers have argued that shift costs can be fully accounted for by cue processing instead of processes related to task switching, because conditions in which the task is shifted are usually confounded with a shift in cue (Logan & Bundesen, 2003). Indeed, we cannot rule out that the shift effects in cue-related P2 and P3 components were merely caused by cue processing, regardless of the cue meaning. Nonetheless, it is unlikely that the shift-induced effect on slow negativity can be accounted for by cue processing. This is informed by a recent fMRI study that has explicitly compared effects of a change in cue

with a change in task, showing that activation in the lateral PFC during task preparation was not related to cue encoding but instead to the updating of the relevant task representation (Brass & von Cramon, 2004). In addition, Nicholson et al. (2005) reported preparatory ERP activity specific to task switching while changing the cue on every trial, such that both task shift and task repeat trials were preceded by a change in cue position. Their results can therefore not be accounted for by differential cue processing, but instead appear to reflect an endogenous act of control whereby the task set is updated.

Consistent with previous task-switching studies, we found no evidence of an ERP component that was uniquely associated with switching. Rather, switching evoked modulations in ERP component amplitudes that were evident in both repeat and shift conditions. Our data are therefore in line with the view that a shift of task calls upon many of the same processes that are involved when repeating the task, instead of activating additional neural circuits. It should be noted, though, that the equal probability of repeat and shift trials might have encouraged subjects to prepare on both types of trials, which would have minimized differential processing between repeat and shift trials (see Brass & von Cramon, 2002).

One problem in interpreting the results with respect to single and dual shifts concerns the nature of responding in these conditions. That is, the rule shift conditions required bivalent responses (i.e., the same set of effectors was used in both tasks), whereas effector shift and dual shift conditions were associated with a separate set of response effectors for each task (univalent responses). Performing a rule shift therefore required an additional process of recoding the response meaning (Brass et al., 2003). This was, however, not evident from the behavioral and ERP results. As predicted, rule shift conditions yielded better overall responding and smaller shift costs, relative to dual shift conditions. We do not deny that an additional process of recoding the response meaning occurred in rule shift conditions, but we doubt whether this process placed high demands on anticipatory processing of rule shifts. Instead, the results are suggestive of greater demands placed on anticipatory processing when shifting two task-set elements (instead of one).

To conclude, there is still considerable debate with respect to how the brain achieves task switching, but it seems likely that a number of component processes must be proposed, both active and passive, in order to provide an adequate account of task switching. ERP components that index these component processes are only beginning to be understood.

4.4.2 Caffeine's actions on neural mechanisms involved in task switching

The caffeine-induced improvements in task-switching performance, as seen in the present study, may result from boosting DA activity (Garrett & Griffiths, 1997). Specifically, it has been reported that caffeine selectively stimulates DA transmission in the PFC of rats (Acquas et al., 2002), suggesting that caffeine can directly target the frontal cortex. Alternatively, the beneficial effects on task switching may be attributable to caffeine-mediated DA changes in the striatum, which is highly sensitive to caffeine (Fredholm et al.,

1999; Nehlig, 1999). Evidence for striatal involvement in task switching comes from studies with Parkinson patients, who suffer from DA depletion in the striatum, disrupting the striato-cortical circuits that are believed to subserve task switching (Monchi et al., 2004; Owen et al., 1998). These patients show impaired task-switching performance (Cools et al., 2001; Marie et al., 1999; Monchi et al., 2004), which is remediated by DA medication (Cools et al., 2001). Moreover, Monchi et al. (2006) reported an increase in neural activity in the striatum when activated in shifting conditions, but only when cognitive planning was required to perform a shift of task. This further points to a possible role for caffeine in strengthening preparatory activity related to task switching, especially because this effect was found for the caudate nucleus (but not the subthalamic nucleus), which is highly sensitive to caffeine (Fredholm et al., 1999).

A further notion regarding the brain areas involved in mediating caffeine's effects on switching tasks is informed by the topographical distribution of the slow negativity in the 900-1000 ms interval (see Figure 5). These distributions appear to show a fronto-central maximum that closely resembles the topography of the early frontal CNV (e.g., Falkenstein, Hoormann, Hohnsbein, & Kleinsorge, 2003) and of medial frontal negativity components, such as the error-related negativity (ERN; Gehring et al., 1993). These latter components have been linked to cognitive control processes and are believed to be generated in or near the ACC (e.g., van Veen & Carter, 2002). The fact that the ACC has been shown to be active when there is increased processing in general, as well as in tasks requiring a variety of different monitoring and control processes (Paus, 2001), implies that these types of processes would presumably be performed in the anticipatory interval when the task set and S-R assignments are retrieved and updated. Importantly, we have previously found an enlarged ERN after caffeine, which we interpreted as a specific effect of caffeine on action monitoring (Tieges et al., 2006). Therefore, it is conceivable that the presently found effects of caffeine may have been mediated, in part, by modulating activity in the ACC. This notion is further supported by a study showing that caffeine selectively stimulates DA transmission in the medial PFC, but not the nucleus accumbens of rats (Acquas et al., 2002).

In a study by Parris, Thai, Benattayallah, Summers, and Hodqson (2007), a phasic increase in ACC activity was observed when S-R associations had to be modified, in addition to a tonic increase in activity under conditions where S-R associations were labile. If, for instance, these phasic increases in ACC activity were modulated by caffeine in the present study, this could be the mechanism that gave rise to the presently found general effect of caffeine on task switching, related to task-nonspecific processes. It is also noteworthy that the ACC is closely connected to the lateral PFC, and both have been associated with preparatory processing (e.g., Luks et al., 2002). Thus, the lateral PFC may be another candidate for mediating caffeine's effects on anticipatory processing, perhaps in concert with the ACC. It should be noted, though, that the slow negativity in our previous study on task switching (Tieges et al., 2006) had a more posterior distribution, not consistent with mediofrontal activation. Nonetheless, the idea of ACC involvement in generating the effects of caffeine on task switching is intriguing and deserves attention in future research.

Finally, a recent theory as proposed by Braver et al. (in press) may shed light on the present findings regarding caffeine from a more cognitive perspective. Braver et al. made a distinction between proactive and reactive control. Proactive control is a resource-demanding type of control concerned with preparation and maintaining goals in working memory; reactive control deals with a stimulus-driven, conflict-resolving type of control. They further state that proactive control is metabolically costly and is most likely to be used if sufficient capacity is available. From this point of view, it makes sense that caffeine, by providing additional energetic resources, specifically enhanced proactive control processes during the preparation phase of task switching. Because caffeine mainly affected the shift-sensitive slow negativity in the present study, we propose that this component may be linked to proactive control in the present study.

In conclusion, the present study showed that anticipatory control in task switching was improved by caffeine, most likely by increasing more general effects on task switching, related to task-nonspecific anticipatory processes (e.g., actively maintaining the task set in working memory and protecting it against interference), rather than affecting task-specific processes (e.g., rule retrieval and rule-based response selection). These actions of caffeine may be mediated by DA changes in the striatum, which is highly sensitive to caffeine, or may result from increased ACC activity, both of which have been related to preparatory activity in task switching.

5

No effects of caffeine on response inhibition

The effects of a habitual dose of caffeine were assessed on behavioral indices of response inhibition. To meet this aim, we selected a modified AX version of the Continuous Performance Test (CPT), the stop task, and the flanker task. In three double-blind, placebo-controlled, within-subjects experiments, these tasks were administered to groups of healthy participants. Whereas the results for the AX-CPT were indicative of improved response inhibition after caffeine, they might also reflect caffeine-induced changes in mechanisms other than response inhibition (i.e., attentional processes). The results for the stop task and flanker task were more straightforward. That is, overall flanker performance and selective response suppression as revealed by distribution-analytical techniques were unaffected by caffeine. In the stop task a global effect of caffeine on processing speed was seen, rather than specific effects on response inhibition. Taken together, these experiments showed that response inhibition was fairly insensitive to a habitual dose of caffeine. The present results are linked to neural circuits that underlie inhibitory control and the role of caffeine-induced strategic changes.

Chapter 5 has led to the following paper, submitted for publication:

Tieges, Z., Snel, J., Kok, A., & Ridderinkhof, K.R. (submitted). No effects of caffeine on response inhibition. Manuscript submitted for publication.

5.1 Introduction

Caffeine (1,3,7-trimethylxanthine) is the best-known pharmacologically active constituent of coffee. That is, low doses of caffeine block inhibitory adenosine A_1 and A_{2A} receptors, which increases central nervous system activity. Adenosine A_1 receptors are present in almost all brain areas, whereas A_{2A} receptors are found mainly in the dopamine (DA)-rich regions of the brain (e.g., striatum) where they are co-localized with DA receptors (Acquas et al., 2002; Ferré, 1997). The stimulation of DA activity through these antagonistic A_{2A}-DA D_2 receptor-receptor interactions appears to underlie most behavioral effects of caffeine (Garrett & Griffiths, 1997).

In doses that are consumed normally, caffeine leads to subtle improvements in cognitive operations, the most reported of which are faster reactions, sometimes accompanied by fewer errors (e.g., Lorist et al., 1996; Ruijter et al., 2000a). These improvements result from both general caffeine effects on arousal, such as enhanced alertness and wakefulness, and from more specific effects on perceptual, attentional, and motor processes (Barthel et al., 2001; Lorist & Snel, 1997; Snel et al., 2004; Warburton et al., 2001). In addition to these lower-level processes, recent studies suggest higher-order control processes involved in the coordination and control of behavior (cf. Miller & Cohen, 2001) are also affected by caffeine. Specifically, caffeine has been shown to enhance the ability to monitor ongoing actions for signs of conflict or erroneous outcome (Tieges et al., 2004) as well as improve task-switching performance (Tieges et al., 2006). Both of these functions are central to the efficient control of behavior (e.g., Kok, Ridderinkhof, & Ullsperger, 2006).

Numerous theories have postulated that the control of behavior requires two distinct systems: One that activates behavior and one that inhibits behavior (e.g., Logan & Cowan, 1984). As such, response inhibition is another key instrument of cognitive control. Inhibitory control is invoked when the tendency to make a reflex-like, premature, inappropriate, or incorrect response must be suppressed. Furthermore, inhibitory control can be general (serving to inhibit any ongoing motor activity, such as in stop tasks; Logan & Cowan, 1984) or selective (serving to inhibit the activation for one response but not the other, such as in conflict tasks), depending on where in the system the effect is exerted (Band & van Boxtel, 1999).

Neuroimaging studies support the notion that response inhibition may be mediated by the basal ganglia and its connections to the prefrontal cortex (PFC; Mink, 1996; van den Wildenberg et al., 2006), in particular the right inferior frontal cortex (IFC; e.g., Aron & Poldrack, 2006; Kelly, Hester, Murphy, Javitt, Foxe, & Garavan, 2004). Since DA in particular influences these circuits, it has been hypothesized that DA modulates response inhibition (Cropley et al., 2006; Hershey et al., 2004; Mink, 1996).

The goal of the present study was to examine effects of caffeine on response inhibition. At first glance, we would expect caffeine to strengthen inhibitory control, consistent with previous reports of caffeine-mediated improvements in controlled processing

(Tieges et al., 2004; 2006) and its stimulation of striatal DA transmission (e.g., Fredholm et al, 1999). In this respect, it is interesting to note that Kaasinen, Aalto, Någren, and Rinne (2004) observed *in vivo* effects of caffeine on DA-D_2 neurotransmission in the human brain, such that it was decreased in the thalamus with an opposite trend-level increase in the ventral striatum. This is in line with preclinical studies showing that the striatum, particularly the caudate nucleus, is very sensitive to caffeine due to its high concentration of adenosine A_2 receptors (Fredholm et al., 1999; Nehlig, 1999). Since striatal (especially caudate) DA activity might be particularly important for response inhibition (see Cropley et al., 2006), this brain area may be a possible candidate for mediating caffeine's effects on response inhibition. However, such caffeine-induced striatal DA modulations might not directly interfere with specific cognitive performance, but may do so indirectly by disrupting the fronto-striato-thalamic circuitry.

Alternatively, caffeine may alter response inhibition by modulating activity in brain areas other than the striatum. Specifically, it has been reported that caffeine selectively stimulates DA transmission in the prefrontal cortex of rats (Acquas et al., 2002), suggesting that caffeine can directly target this area. However, it has yet to be shown whether the human frontal cortex is sensitive to caffeine as well. Also, a direct link between caffeine's behavioral effects in humans and concurrent DA alterations in brain areas (e.g., basal ganglia) has not yet been demonstrated. In sum, the cited studies provide only indirect clues for dopaminergic mechanisms by which caffeine may affect response inhibition.

Whereas stimulants are generally associated with enhanced information processing, reports of stimulant effects on inhibitory processes have been inconsistent. Marczinsky and Fillmore (2003) reported that habitual doses of caffeine (2.0 and 4.0 mg/kg BW) facilitated execution but not inhibition of responses (as measured with different tasks), either alone or by antagonizing the effects of alcohol. They interpreted these results in terms of an effect of caffeine on nonspecific arousal, but not on response inhibition. In contrast, Kenemans, Wielemans, Zeegers, and Verbaten (1999) reported beneficial effects of 250 mg caffeine on Stroop interference (possibly reflecting inhibitory control). In a number-digit variant of the Stroop task, caffeine reduced interference effects at the level of error rates, whereas beneficial effects of caffeine in a color-word variant of the task were limited to conditions in which the occurrence of high-interference stimuli was 100% predictable (i.e. when high-interference stimuli were presented blockwise).

Studies on effects of stimulants such as d-amphetamine and methylphenidate also produced mixed results. It appears that these stimulants may have an effect on the ability to inhibit behavior, but only in subjects with suboptimal levels of inhibitory control. For instance, response inhibition in healthy adults did not benefit from acute administration of d-amphetamine in one study (Fillmore, Kelly, & Martin, 2005), whereas others reported slight improvements in inhibitory efficiency after d-amphetamine, but only in subjects with poor baseline levels of inhibitory control (de Wit, Enggasser, & Richards, 2002). Similarly, response control was improved by methylphenidate in children with ADHD, whose ability to

inhibit responses is often compromised (e.g., Lijffijt et al., 2006; Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005; Scheres et al., 2003).

Here we investigate more rigorously whether processes of response inhibition are modulated by caffeine. The current study was aimed at investigating the effects of a habitual dose of caffeine and a placebo on response inhibition, as measured in three experiments using a modified version of the AX-CPT (Braver et al., 1999), a stop-signal task (Logan & Cowan, 1984), and a flanker task (Eriksen & Eriksen, 1974). The rationale and predictions for each of these experiments will be elaborated consecutively.

5.2 Experiment 1: Inhibition of a prepotent response in the AX-CPT

In the first experiment, we used a cued version of the continuous performance test, the AX-CPT (e.g., Braver et al., 1999). In the AX-CPT, participants are presented with sequences of two letters. They are instructed to respond to the sequence A-X by pressing a target button. A nontarget response has to be made to all other letter combinations, i.e., AY, BY, and BX (where cue B and probe Y refer to the collection of letters other than A and X). The AX-CPT resembles a cued go/no-go paradigm, since both tasks involve the execution (AX trials) and inhibition (AY trials) of a prepared motor response.

The high probability of AX (target) trials (usually 70%) induces two types of bias in participants. The first is to make a target response to the occurrence of an X probe. On those trials in which a target response should not be made to the X probe (i.e. BX trials), context information provided by the cue must be used in an inhibitory fashion to suppress the tendency to produce a false alarm. The second bias involves an expectancy to make a target response following the occurrence of an A cue. In this case, the cue serves a predictive function which directs attention to a particular response (cf. attention-to-action; Norman & Shallice, 1986). On those trials in which the cue is an invalid predictor of the response (i.e., AY trials), this attentional function of context creates the tendency to produce a false alarm (Braver et al., 1999). Thus, correct performance in the AX-CPT has been argued to require correct encoding of cue and probe instruction and inhibitory control (Dias et al., 2006).

Previous investigations with a classical version of the CPT revealed slight or no effects of caffeine consumption on CPT performance (e.g., Bernstein et al., 1994). However, the classical CPT does not involve as strong and as specific a response bias as does the AX-CPT (cf. Braver et al., 1999). The purpose of the present study was therefore to investigate the effects of caffeine on the AX-CPT, so as to have more power to reveal modulatory effects on inhibitory control.

First, we predicted performance decrements (in terms of response speed and/or error rate) on both AY and BX trials compared to BY trials. BY rather than AX trials were selected as a reference for comparison, because of the better comparability in terms of trial frequencies (cf. Braver et al., 1999). It was further hypothesized that a beneficial effect of

caffeine on inhibitory control would be reflected in smaller performance decrements on both AY and BX trials (relative to BY) compared to placebo.

In the standard AX-CPT, the contextual value of the cues (A and B) is arbitrary. That is, the association between target cue and probe (AX) is not evident, but instead is to be learned through practice. We modified the task by replacing letter stimuli with pictures, so that the content of cue and target pictures were intrinsically related to each other.

5.2.1 Methods

5.2.1.1 Participants

Fifteen undergraduate students (9 men, 6 women) participated in the AX-CPT (mean age = 21.1, SD = 3.0). All reported to be healthy, nonsmoking, habitual coffee drinkers. They had normal or corrected-to-normal vision, did not use prescription medication except for birth control, had normal sleep patterns (Mulder-Hajonides van der Meulen et al., 1980), and reported no history of brain damage or mental illness. Written informed consent was obtained from all participants, and they received course credits for participation.

5.2.1.2 Treatment manipulation

A double-blind, placebo-controlled, cross-over design was used, in which each participant completed two experimental sessions. Treatment condition consisted of 3 mg/kg BW lactose (placebo) or 3 mg/kg BW caffeine dissolved in a cup of normally brewed decaffeinated coffee. These substances could not be detected by taste or smell. Milk powder and sugar were added to suit the participants' taste. They were asked to abstain from all caffeine-containing foods and beverages for 12 h prior to testing, and to take a good night's rest. The order of sessions was counterbalanced across participants. Saliva samples were taken at the beginning of the experimental sessions in order to encourage compliance to the abstinence instructions.

5.2.1.3 Modified AX-CPT

Participants had to make a target response to a picture of a *readable object* (e.g., book, magazine), but only when it was preceded by a picture of a *reading environment* (e.g., library, bookshop). Nontarget cues and nontarget probes consisted of pictures of landscapes and vehicles, respectively. Ten different pictures were used for each of the four stimulus categories (reading environment, readable object, landscapes, and vehicles). Distractor words, representing 42 different food items (e.g., spaghetti, curry) appeared in the interval between cue and probe (printed in a 32 point Times New Roman font of red color), in order to make the task sufficiently difficult (cf. Braver et al., 2001).

Each trial started with a centrally presented fixation cross of 1000 ms duration. Next, a cue appeared for 500 ms, followed 1000 ms after cue onset by a distractor word of 2500 ms duration. Probe stimuli appeared 3000 ms after distractor onset, and remained on the screen until participants gave a response or until 6000 ms had elapsed. An inter-trial interval of 500 ms was used.

Target trials (AX) occurred on 63,75% of the trials, whereas all other picture combinations (AY, BX, and BY) appeared on 8,75% of the trials. On the remaining 10% of trials, the probe consisted of the Dutch equivalents of the words "press left" (5%; AZ) or "press right" (5%; BZ). These "catch" trials were included to ensure that participants continued to pay attention to the probe after a B cue. Correct responding on catch trials was highly emphasized.

Participants were instructed to make a target (right-hand) response to AX trials and a nontarget (left-hand) response otherwise using two external button boxes.

5.2.1.4 Subjective measurements

Three questionnaires were used to assess subjective feelings before each experimental session: A sleep quality inventory (Mulder-Hajonides van der Meulen et al., 1980) to measure participants' self-reported sleep duration and quality on the nights before the experimental sessions; the shortened version of the profile of mood states (POMS; Wald & Mellenbergh, 1990) containing 32 adjectives to be rated on a 5-point scale ranging from 0 (not at all) to 4 (very much), representing five specific mood states: Depression, anger, fatigue, vigor, and tension; the 20-item state part of the Dutch version of the state-trait anxiety inventory (STAI; van der Ploeg et al., 1980) to assess state anxiety on a four-point scale ranging from 1 (not at all) to 4 (almost always).

5.2.1.5 Procedure

The experiment consisted of an intake session (which also served as practice session) and two experimental sessions that were identical except for treatment (placebo or caffeine). The interval between sessions was kept constant at approximately one week, and the time-of-day for the measurement was kept constant across participants.

In the intake session, the purpose of the experiment was explained to the participants and they filled out an informed consent form. After verification that they met all inclusion criteria, participants familiarized themselves with the experimental task in a series of short practice blocks: First a block of 10 AX trials to induce a strong bias to target responses, followed by a block of 3 nontarget trials (one of each type), and a block of 10 catch (5 AZ and 5 BZ) trials. Next, they completed a practice block of 40 trials in which all trials (except for catch trials) occurred with equal probability. Finally, they completed two blocks of 80 trials each with the same structure as the blocks used during the experimental sessions (as described in the 'Modified AX-CPT' section above).

Each experimental session started with a saliva sample that was taken from the participant in order to reinforce compliance to the caffeine abstinence instructions. Next participants filled out the questionnaires after which they consumed their coffee. Subsequently, they completed a block of 10 AX trials, a block of 10 catch trials, and finally a complete block of 80 trials, to familiarize themselves with the task at hand. The testing phase consisted of 8 blocks of 80 trials each.

The experimental task started about 40 minutes after drinking the coffee. Questionnaires were filled out at the beginning of each session (to test for differences in pre-existing subjective feelings between treatment conditions). Participants were fully debriefed at the end of the last session.

All experimental procedures were conducted in compliance with relevant laws and institutional guidelines, and were approved by the departmental ethical committee.

5.2.1.6 Statistical analyses

Responses were defined as correct when made with the correct hand between 100 and 6000 ms after probe onset. Errors were defined as responses made with the wrong hand, regardless of speed, or as responses not made. Individual averages for subjective measurements, reaction time (RT), and error rate were analyzed with repeated-measures analyses of variance (ANOVA). Target (AX) and nontarget (AY, BX, BY) trials were analyzed separately because of their different response requirements and/or different frequencies of occurrence. Performance on catch trials was analyzed as well.

Statistically significant effects in the analyses of nontarget trials were followed by contrasts analyses, involving two orthogonal contrasts for the factor 'trial type' (simple contrasts). The first contrast evaluates performance on AY trials against BY trials; the second contrast tests BX trials against BY trials.

	Reaction Time (ms)				Error Rate (%)			
	AZ		BZ		AZ		BZ	
Placebo	428	(64)	419	(75)	4.1	(4.8)	2.6	(3.0)
Caffeine	410	(40)	385	(63)	1.2	(2.5)	2.6	(3.0)

Table 1. Performance on catch trials in the modified AX-CPT. Mean reaction times (RTs) in ms and error rates (%) are depicted as a function of trial type (AZ, BZ) and treatment (placebo, caffeine). Standard deviations are given in parentheses.

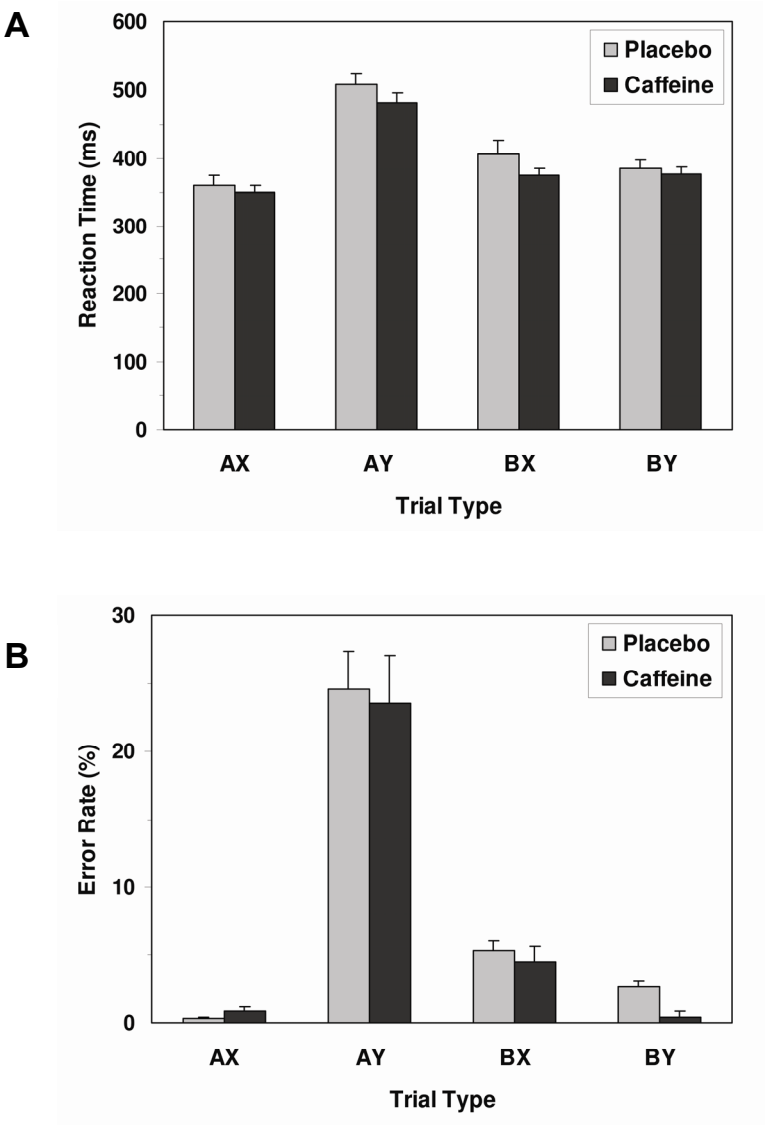

Figure 1. Performance in the modified AX-CPT task. Mean reaction times (*A*) and mean error rates (*B*) for trial types AX, AY, BX, and BY are shown (where AX represents the target sequence, and the cue B and probe Y represent the collection of stimuli other than A and X). Light and dark grey bars represent performance in placebo and caffeine conditions, respectively. Error bars represent standard error of the mean.

5.2.2 Results

5.2.2.1 Subjective measurements

Participants reported no differences in sleep length and quality on the nights before the experimental sessions, or in state anxiety. Relative to placebo conditions, caffeine conditions were associated with increased feelings of vigor ($F(1,14) = 7.72$, $p < .05$) and tension ($F(1,14) = 6.32$, $p < .026$) upon arrival[1]. No differences between sessions were found for the other mood states (depression, anger, and fatigue).

5.2.2.2 Behavioral data

Treatment had no effect on RT or error rate for AX trials, but it did so for nontarget trials (see Figure 1). That is, caffeine increased overall response speed on nontarget trials ($F(1,14) = 7.42$, $p < .05$) compared to placebo, while error rate remained unaffected.

Simple tests revealed that, compared to BY trials, performance was significantly worse for AY in terms of response speed ($F(1,14) = 322.49$, $p < .001$) and error rate ($F(1,14) = 67.19$, $p < .001$). Treatment interacted with this effect of trial type, such that the performance deterioration on AY trials decreased after caffeine relative to placebo, but only for RT ($F(1,14) = 6.02$, $p < .05$).

BX trials were associated with higher error rates (but no effect on RT) compared to BY trials ($F(1,14) = 20.65$, $p < .001$). After caffeine (compared to placebo) there was a trend towards smaller performance decrements on BX trials relative to BY trials, in terms of response speed (but not error rate; $F(1,14) = 3.55$, $p < .082$).

No differences between catch trial conditions AZ and BZ were found for RT or error rate (see Table 1). AZ (but not BZ) trials were speeded up by caffeine ($F(1,14) = 11.16$, $p < .01$). No other effects were found for catch trials.

5.2.3 Discussion

As expected, performance was significantly worse for BX (higher error rates) and AY (higher error rates and slower responding) trials compared to BY trials. Caffeine reduced the performance decrement in RT as seen on AY trials (with a trend for BX trials). These results

[1] It could be argued that the effects of session (caffeine versus placebo) on test scores of the POMS subscales 'vigor' and 'tension' contributed to the RT effects of caffeine as found in the modified AX-CPT. To test this possibility, we used the difference between caffeine and placebo conditions in scores on the vigor and tension subscales, and entered these covariates separately in repeated measures ANOVAs. These additional analyses largely replicated the findings obtained in the main analyses, indicating that the RT effects of caffeine could not be explained merely by changes in vigor and tension after caffeine intake. For reasons of clarity, we did not include these additional analyses in the text.

support the hypothesis that caffeine improves inhibitory control in the present study. Specifically, participants were faster after caffeine (compared to placebo) in overriding a prepared target response, as was the case on AY trials, but this was not corroborated by a statistically significant effect of caffeine on inhibitory processing on BX trials.

Whereas some studies support the role of inhibitory control in successful performance on the AX-CPT (e.g., Dias et al., 2006), others have called into question whether inhibitory processes are strongly engaged in this task (e.g., Rush, Barch, & Braver, 2006). Instead, it has been suggested that task demands on the AX-CPT are multifactorial and it is possible that caffeine-related changes in AX-CPT performance primarily reflect cognitive mechanisms other than inhibition (e.g., context processing; Braver et al., 1999). Thus, we cannot rule out that effects of caffeine on processes besides response inhibition contributed to the present findings.

One specific possibility is that the present findings were caused by stronger attention to targets after caffeine (e.g., Ruijter et al., 2000b). If this were the case, one implication could be weaker activation of nontarget responses in the case of AY trials. Consequently, less incorrect activation would require less inhibitory control to suppress these incorrect response activations (for a discussion of these interpretational issues see Rush et al., 2006). This is in line with the view that measurements of response inhibition (such as speed of stopping) represent a combination of cognitive processes, one of which may be target detection (Aron & Poldrack, 2005).

In sum, although the results appear to offer some support for improved inhibitory control by caffeine, we cannot draw firm conclusions regarding caffeine's effects on response inhibition based on these findings alone. Therefore, we conducted a second experiment using a simpler and more established task that provides a widely used and accepted measure of the efficiency of inhibitory motor control: The stop-signal task (Logan & Cowan, 1984).

5.3 Experiment 2: Inhibitory motor control in the stop task

The stop-signal task is designed to measure the subjects' ability to stop a planned or ongoing motor response. In the stop-signal paradigm (Logan & Cowan, 1984), subjects perform a choice RT task. In addition to the primary stimulus ("go" stimulus), a stop signal is occasionally presented after a variable delay. The stop signal requires subjects to withhold the initiated response to the choice RT task. Go and stop signals elicit activating and inhibitory processes, and the time in which each process is completed determines the probability of successfully inhibiting a response to stop signals. The stop task yields an

estimate of the duration of the covert response-inhibition process, termed the stop-signal reaction time (SSRT)[2].

SSRT has been argued to be sensitive specifically to the efficiency of response inhibition and to be insensitive to attentional and other factors (e.g., Logan, 1994). Thus, the stop task provides a more selective measure of response inhibition than does the AX-CPT. Being a speed measure, however, SSRT may be sensitive to nonspecific effects of caffeine on processing speed. Thus, the analysis of SSRT typically involves procedures to control statistically for global speed effects (e.g., Ridderinkhof et al., 1999).

A few studies have assessed the effects of stimulants on stopping. In healthy adults, little or no effect of d-amphetamine on stop speed was found (de Wit et al., 2002; Fillmore et al., 2005), but methylphenidate improved response inhibition in children with ADHD (Lijffijt et al., 2006; Scheres et al., 2003). As pointed out in the introduction, stimulants may have more pronounced effects on inhibitory control in individuals with suboptimal levels of inhibitory control.

The purpose of the present experiment was to assess the influence of caffeine on inhibitory motor control, as measured with the stop task. If caffeine consumption were to improve response control, then this should be evident in faster SSRTs in caffeine conditions relative to placebo, after controlling for global processing speed.

5.3.1 Methods

5.3.1.1 Participants

Participants were seventeen undergraduate students (11 men and 6 women; mean age = 20.9, SD = 2.3). None of them had participated in the previous experiment.

5.3.1.2 Stop task

The stop task was adopted from Ramautar, Kok, and Ridderinkhof (2004), with the modification that the proportion of stop trials was set to 30%.

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[2] The stop-signal reaction time (SSRT) can be derived mathematically from the reaction time (RT) distribution of the primary task, the observed probability of responding on stop-signal trials, and the stop-signal delay (the time interval between go and stop signals). First, RTs on go trials were rank ordered on a time axis from fastest to slowest responses. Second, the *n*th RT was picked, where *n* was defined by the product of the number of RTs in the distribution and the probability of responding given a stop signal. For example, if there were 100 RTs in the distribution and the probability of responding given a stop signal was .4, the *n*th RT would be the 40th in the rank-ordered distribution. Thus, the *n*th RT is an estimate of the time at which the stop process runs to completion, relative to the onset of the go signal. Third, the stop-signal delay was subtracted from the *n*th RT to estimate SSRT (Logan, 1994; Logan & Cowan, 1984).

Participants were tested individually in a dimly lit, sound-attenuated room. They were seated in a comfortable chair with response buttons attached to both armrests, facing a VGA color monitor at a viewing distance of 90 cm. They were instructed to focus on a fixation sign (+) that was continuously presented in the center of the screen (as were all stimuli), subtending a 0.15˚ visual angle. The go stimuli consisted of blue circles and squares, subtending a 0.4˚ visual angle. Each trial started with presentation of the fixation sign for a duration of 250 ms, followed by one of the go stimuli (circle or square) that was displayed for 100 ms. In the stop task, a blue cross (stop signal) was presented after onset of the go stimulus on 30% of the trials, with a visual angle of 0.4˚ and a duration of 100 ms. The delay between onset of the go and stop stimulus was randomly chosen from a set of 5 fixed delays (100, 150, 200, 250, or 300 ms). A choice RT task, which was used to measure processing speed without the presence of stop trials, consisted solely of go stimuli. Trial duration of the choice RT task and stop task varied between 3.5 and 4.5 sec. Responses were made with the left and right index finger, and stimulus-response mappings were counterbalanced across participants.

5.3.1.3 Procedure

The design and procedure were the same as in the first experiment, unless stated otherwise. In the intake session, participants practiced the choice RT task and the stop task in order to achieve stable response levels. With respect to the stop task, participants were instructed to respond as quickly as possible to the go stimulus and not to wait for possible stop stimuli, but to try and withhold their response to a go stimulus as soon as they perceived the stop signal. In both experimental sessions, participants completed two blocks of the choice RT task, to assess their individual speed level. Then, mean RT in the choice RT task was calculated and subsequently used as a baseline for evaluating the RTs to the go signals of the stop task (i.e., go RTs in the stop task should not deviate substantially from RTs in the choice RT task). They completed 7 blocks of the stop task containing 100 trials each, with a short break after the fourth block.

5.3.1.4 Statistical analyses

RT and accuracy scores were analyzed as measures of overall performance, whereas SSRTs for each of the 5 stop-signal delays were used as measures of stop speed. Each dependent variable was analyzed with repeated measures ANOVAs with the within-subjects factor “treatment” and “delay”. An additional ANCOVA on SSRT, with the same analysis design, included the effect of caffeine on go-RT as a covariate.

	Overall performance		SSRT (ms)				
	Go-	Commission	Stop-signal delays (ms)				
	RTs (ms)	errors (%)	100	150	200	250	300
Placebo	413 (31)	57.9 (13.1)	263 (50)	248 (51)	235 (51)	239 (68)	235 (57)
Caffeine	396 (34)	61.6 (14.6)	247 (48)	221 (48)	227 (37)	216 (42)	223 (57)

Table 2. Performance parameters in the stop task. Mean reaction times (RTs) in ms, commission errors (%), and SSRT (stop speed) for each of the five stop-signal delays (100, 150, 200, 250, 300 ms) are depicted for placebo and caffeine conditions. Standard deviations are given in parentheses.

5.3.2 Results

5.3.2.1 Subjective measurements

Participants reported no differences in sleep quality on the nights before the experimental sessions, or in state anxiety (as measured with the STAI). The POMS was not filled out in this experiment.

5.3.2.2 Behavioral data

The choice RT task produced faster responses in caffeine sessions (mean = 362 ms, SD = 30.9) relative to placebo (mean = 384 ms, SD = 39.9 ; $F(1,16) = 7.31$, $p < .05$). Similarly, go RTs in the stop task were faster after caffeine (mean = 369 ms , SD = 8.4) compared to placebo (mean = 413 ms, SD = 7.6; $F(1,16) = 9.21$, $p < .01$; see Table 2 and Figure 2A). Caffeine did not modulate the proportion of commission errors.

SSRTs obtained in both treatment conditions were in the order of 200-250 ms, as is commonly found in stop-signal studies (see Figure 2B). Caffeine did not affect SSRT ($F(1,16) = 2.01$, ns), whereas the interaction with delay reached a trend ($F(1,16) = 3.39$, $p < .062$). Despite the fact that treatment effects on this dependent variable failed to reach statistical significance, the pattern of SSRTs was in the direction of faster SSRTs in caffeine conditions compared to placebo, especially for the 150 ms and 250 ms delay. To ensure that possible subtle effects of caffeine were not overlooked, we performed additional ANOVAs separately for each delay. A trend towards shorter SSRTs in caffeine conditions compared to placebo was observed only for the 150 ms delay ($F(1,16) = 3.87$, $p < .068$), while SSRTs obtained in other delays remained unaffected by caffeine.

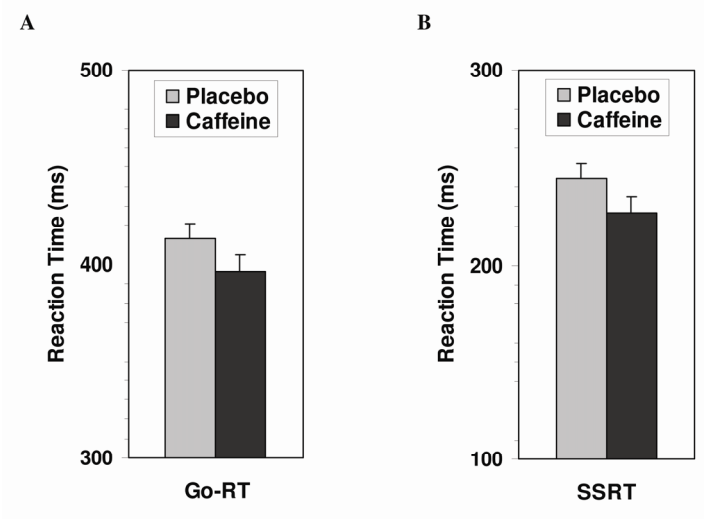

Figure 2. Performance in the stop-signal task. Mean reaction times for go-trials *(A)* and overall SSRT (*B*; averaged over the 5 delays) are shown. Light and dark grey bars represent performance in placebo and caffeine conditions, respectively. Error bars represent standard error of the mean.

We have raised the possibility that the global caffeine-induced increase in processing speed, as expressed in RT, may account for the effects on SSRT as well. Thus, rather than an effect on response inhibition, the trend towards a decreased SSRT at the 150 ms delay may simply reflect a global effect of caffeine on processing speed. To test this possibility, we re-analyzed the effect of caffeine on SSRT (for the 150 ms delay) in an ANCOVA, the covariate being the difference in go RTs between caffeine and placebo. The outcome was that the caffeine effect on SSRT disappeared completely ($F(1,16) = .19$). Apparently caffeine modulated global processing speed, but not response inhibition in the present study.

5.3.3 Discussion

Caffeine had no specific effect on inhibitory control in the stop task[3]. Rather than selectively affecting response inhibition, caffeine had a global effect on processing speed, which is consistent with well-known effects of caffeine on perceptual, attentional, and motor processes (e.g., Snel et al., 2004).

[3] A similar finding was observed in a nonpublished investigation by Lijffijt (personal communication).

Thus far, we have considered effects of caffeine on global forms of inhibition. Although interpretation of the AX-CPT findings was constrained by possible confounding factors (e.g., caffeine-mediated changes in attention to the targets), results from the stop task provide more unequivocal support for the conclusion that caffeine does not affect global inhibitory control. Therefore we tested whether caffeine might be able to affect more selective forms of inhibition in the third experiment.

5.4 Experiment 3: Inhibition of irrelevant information in the flanker task

Adequate performance in the flanker task (Eriksen & Eriksen, 1974) relies on effective engagement of interference control processes, such as the selective inhibition of inappropriate responses. In such tasks, the designated response is indicated by one aspect of the stimulus, but competing response tendencies may be elicited by other aspects of the stimulus, even if the latter are to be ignored. Responses are typically slowed when the irrelevant stimulus features elicit the response opposite to the one elicited by the target stimulus feature (the congruency effect). To account for these interference effects, many authors have invoked a processing model that involves two distinct pathways: An automatic, reflex-like direct pathway and a parallel indirect, attention-controlled pathway of stimulus-response translation (e.g., de Jong, Lian, & Lauber, 1994). These two routes converge at the level of response activation. The automatic route will facilitate the correct response on congruent trials, but interferes with the correct response on incongruent trials (Ridderinkhof et al., 2005).

In the present experiment, we used the flanker task to examine effects of caffeine on selective inhibition. Previous studies employed comparable flanker paradigms to assess effects of caffeine on information processing (Lorist & Snel, 1997; Kenemans & Verbaten, 1998), but both could not show modulations of interference control or response inhibition by caffeine. It is noteworthy that these studies focused on attentional rather than inhibitory processing. More important, behavioral analyses in these studies were confined to overall performance. In our present experiment, we used additional RT distribution analyses that have proven to be more sensitive to selective response inhibition than classical performance measures (e.g., de Jong et al., 1994). Specifically, we used the delta plot technique (Ridderinkhof et al., 2005).

Delta plot techniques are based on the notion that performance fluctuates from trial to trial. In the case of slow responses, selective inhibition processes along the controlled route have more time to build up relative to trials with fast responses. This implies that activation of the incorrect response along the direct route will be reduced through selective inhibition along the indirect, controlled route. This, in turn, will be reflected in larger congruency effects associated with slow responses. Delta plots are constructed by plotting these congruency effects as a function of response speed (for a detailed description, see

Ridderinkhof et al., 2005). The delta-plot technique has proven useful in studying the sensitivity of selective response inhibition to individual differences (Bub, Masson, & Lalonde, 2006; Ridderinkhof et al., 2005; Wylie, Ridderinkhof, Eckerle, & Manning, 2007) as well as pharmacological intervention (Ridderinkhof et al., 2002; 2005).

In the present experiment, we examined effects of caffeine on selective inhibition in a flanker task using both overall performance analyses and delta-plot techniques. The point of divergence between two delta plots (representing different levels of inhibitory strength) was the critical variable in comparisons between treatment conditions.

5.4.1 Methods

5.4.1.1 Participants

Eighteen fresh undergraduate students participated in the flanker experiment (2 men, 16 women). Age ranged from 18 to 26 (mean = 21.6, SD = 2.6). None of them had participated in the previous experiments.

5.4.1.2 Flanker task

Participants performed an arrow version of the Eriksen flanker task as used previously by Ridderinkhof et al. (2002), in which they had to respond with either their left or right index finger to the central arrow of a congruent or incongruent stimulus array. First, a horizontal rectangular contour was continuously displayed in the center of a computer screen, in which a stimulus array of five stimuli appeared for 100 ms: A target arrow in the center that was flanked on each side by two arrows pointing in the same direction as the target (congruent; e.g., >>>>>) or in the opposite direction (incongruent; e.g., <<><<). Congruent and incongruent arrow arrays were presented randomly but equiprobably. Participants were to respond to the direction of the target and to ignore distractor arrows. Responses are typically slowed on incongruent compared to congruent trials, that is, when the flanking arrows point in the opposite direction. Participants indicated their choice by pressing the *q* button (left index finger) on a keyboard to a target pointing to the left or the *p* button (right index finger) to a right-pointing target. The fixation contour was shown in black against a light gray (10% black) background. The target arrow was presented in dark gray (80% black). To maximize flanker interference effects, the immediately surrounding arrows were slightly darker (90% black) and larger (10%), while the outmost flankers were still darker (100% black) and larger (20%). Interstimulus intervals (ISI) were varied randomly but equiprobably between 1811 ms, 2211 ms, or 2611 ms. These ISIs were prolonged relative to the original arrow flanker task to maximize interference effects, in accordance with a report of larger Stroop interference effects with long compared to short intervals (de Jong, Berendsen, & Cools, 1999).

5.4.1.3 Procedure

The design and procedure were the same as in the previous experiments, unless stated otherwise. In the intake session, participants practiced two flanker task blocks of 240 trials each. In each experimental session, they practiced with an additional block of 240 trials. The testing phase consisted of eight task blocks with a short break after the fourth block. At the end of each block, participants were informed about their performance in terms of processing speed and accuracy. Verbal encouragements were given to keep performance accuracy around 90%.

5.4.1.4 Statistical analyses

Repeated measures ANOVAs were conducted to test the effects of treatment on the various aspects of flanker task performance, as detailed below.
Overall performance. The first trial within each block was regarded as warm-up trial and was therefore excluded from analysis. For the remaining trials, responses were defined as correct when made with the correct hand between 50 ms and 1000 ms after stimulus onset. Errors were defined as responses made with the wrong hand, regardless of speed. Effects of treatment on overall performance and interference control were analyzed by including the within-subject factors treatment (placebo, caffeine) and congruency (congruent, incongruent).
Distributional analyses. For each participant, RTs of all responses (correct and incorrect responses) were rank ordered for each condition and then divided into five speed bins (quintiles) containing equal numbers of observations. Mean RT was determined for each quintile separately for each condition. Delta plots were constructed by plotting, quintile by quintile, the difference in mean RT between incongruent and congruent conditions (i.e., magnitude of interference effect) against the average of these quintile RTs. Thus, delta plots reflect the development of the interference effect as a function of response speed. Slopes were computed for the delta plot segments connecting the data points of two consecutive quintiles (segments q1-2, q2-3, q3-4, and q4-5). RT effects of caffeine on slopes were then analyzed with factors “treatment” and “segment”.

5.4.2 Results

5.4.2.1 Subjective measurements

Participants reported no differences in sleep length and quality on the nights before the experimental sessions, or in reported feelings of mood and anxiety.

	Reaction times (ms)				Accuracy (%)			
	CG		IG		CG		IG	
Placebo	370	(34)	403	(39)	96.3	(21)	84.3	(5.8)
Caffeine	354	(28)	385	(35)	97.2	(1.9)	84.7	(6.6)

Table 3. Performance parameters in the flanker task. Mean reaction times (RTs) in ms and accuracy scores (%) are depicted as a function of correct responses of congruent (CG) and incongruent (IG) stimulus type and treatment (placebo, caffeine). Standard deviations are given in parentheses.

5.4.2.2 Overall performance

Again, processing speed was enhanced by caffeine (placebo: mean = 387 ms, SD = 36.0, caffeine: mean = 360 ms, SD = 31.4; $F(1,17) = 12.98$, $p < .005$) whereas accuracy remained unaffected ($F(1,17) = 1.25$; see Table 3). Thus, the effect of caffeine on RT could not be explained in terms of a speed-accuracy trade-off. Compared to congruent trials, incongruent stimuli were associated with slower responses (congruent: mean = 362 ms, SD = 29.9; incongruent: mean = 394 ms, SD = 35.3; $F(1,17) = 155.12$, $p < .001$) and reduced accuracy (congruent: mean = 96.8 %, SD = 1.9; incongruent: mean = 84.5 %, SD = 5.9; $F(1,17) = 95.57$, $p < .001$). The magnitude of these congruency effects was not modulated by caffeine ($F(1,17) = .73$ and .30 for RT and accuracy, respectively).

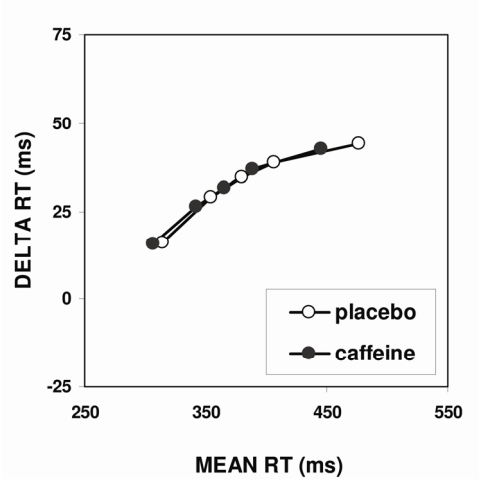

Figure 3. Delta plots for reaction times, for placebo and caffeine. Delta plots display the magnitude of the flanker congruency effect on RT as a function of response speed (as expressed in RT quintile scores).

5.4.2.3 Distributional analyses

A main effect of segment was found ($F(3,51) = 7.65$, $p < .005$), showing that delta plots levelled off towards the slow end of the RT distribution (see Figure 3). Consistent with the literature, this levelling off is taken to reflect selective response suppression (e.g., Ridderinkhof et al., 2005). Importantly, caffeine had no effect on delta slopes ($F(2,51) = 1.48$). To ensure that no specific effects of caffeine were overlooked, we also analyzed effects of caffeine separately for each segment. Among a series of null findings, these analyses revealed an effect of caffeine on delta plot slopes for the q3-4 segment ($F(1,17) = 4.77$, $p < .05$). The slope in this segment remained slightly steeper for caffeine conditions (ES = .22) compared to placebo (ES = .16), suggesting (if anything) weaker response inhibition (stronger interference effects) in caffeine conditions. This effect did not extend into the slower segment ($F(1,17) = .63$). No effects of treatment on the slopes for the faster segments were found ($F(1,17) = .86$ and .04 for q1-2 and q2-3, respectively).

5.4.3 Discussion

In accordance with previous findings (Kenemans & Verbaten, 1998; Lorist & Snel, 1997), overall performance in the flanker task appeared to be unaffected by caffeine. More specific, caffeine failed to modulate the efficiency of selective response suppression, as evidenced by analyses of delta plot slopes. Despite the lack of interaction between caffeine and delta-plot segments, we zoomed in on caffeine effects per segment to ascertain that no effects of caffeine on response inhibition were overlooked. No effects of caffeine were observed, except for slightly less efficient response inhibition in the second slowest segment of the RT distribution. However, this effect failed to extend into the slowest segment and appeared incidental and nonsystematic. In all, selective inhibition processes appear to be fairly insensitive to a habitual dose of caffeine in the third experiment.

5.5 General discussion

The present study assessed the effects of caffeine on behavioral indices of response inhibition. Three paradigms were used: The stop task, the AX-CPT, and the flanker task. Successful performance in each paradigm requires a different form of response inhibition. The general conclusion from these experiments is that response inhibition is fairly insensitive to a habitual dose (3 mg/kg) of caffeine.

While performance in the AX-CPT task seemed to benefit from caffeine (as revealed by more efficient performance on AY trials compared to placebo), this small effect was not accompanied by a comparable effect on BX performance. Furthermore, possible caffeine-mediated changes in mechanisms other than response inhibition (e.g., attention to target, context processing; cf. Braver et al., 1999; Rush et al., 2006) might have contributed

to the present findings. Results from the stop task and flanker task were more straightforward. The stop task yielded a global effect of caffeine on processing speed (consistent with well-known effects of caffeine on e.g., attentional processing; Snel et al., 2004), but did not selectively affect stop-signal inhibition. Furthermore, result; from the flanker task showed no effects of caffeine on overall flanker performance or more specific forms of response inhibition. Taken together, the presently studied domains of response inhibition were not susceptible to effects of caffeine.

The converging evidence brought about by these experiments (that is, we found null effects in all experiments, each using different paradigms and subject groups) justifies acceptance of the null hypothesis in the present study. Furthermore, we found effects of caffeine in each experiment (i.e., all tasks were sensitive to caffeine), but these effects were general rather than specific to response inhibition.

The present findings build on the notion that beneficial effects of stimulants on response inhibition appear to be limited to subjects whose inhibitory efficiency is less than optimal (e.g., de Wit et al., 2002; Scheres et al., 2003). That is, participants in the present study reported to have good physical and mental health, and therefore were not expected to show deficient inhibitory control. Accordingly, caffeine (in the used dose) barely affected response inhibition in these participants. Note, however, that we have previously shown specific effects of caffeine on task switching in a comparable group of participants (e.g., Tieges et al., 2006). It therefore appears that response inhibition is simply not as sensitive to the effects of caffeine as are other types of higher-order cognitive processes, a conclusion in line with previous studies (Lorist & Snel, 1997; Marczinsky & Fillmore, 2003). From this it follows that those persons who have deficient inhibitory control may very well benefit from caffeine.

Based on the neuroimaging literature on response inhibition, which assigns an important role to DA in inhibitory control (especially in the striatum; Cropley et al., 2006), one would predict substantial effects of caffeine in the present experiments, since stimulation of DA activity appears to underlie most behavioral effects of caffeine. However, this was clearly not the case. One must keep in mind, though, that the neural circuits underlying response inhibition are only beginning to be understood (cf. Aron & Poldrack, 2006; van den Wildenberg et al., 2006). Moreover, it is not known to what extent inhibition across different tasks is mediated by common mechanisms or unique task-specific mechanisms. Wager et al. (2005) provide some support for a common set of frontal and parietal regions engaged in response inhibition across different tasks (i.e., go/no-go task, flanker task, and stimulus-response compatibility task). However, correlations among tasks were low, both for measures of brain activity and performance (see also Rush et al., 2006). This is hardly surprising when we take a close look at the different tasks used in the present study. Response inhibition in the AX-CPT task (with AY conditions being equivalent to no-go trials in a go/no-go task) may be different from that in the stop task with respect to the point of contact with the motor system (see Aron & Poldrack, 2006). More specific, canceling an already initiated response to a stop signal and canceling the development of a motor plan to a

no-go stimulus (or Y probe) involve different processes, at least in part. Furthermore, response inhibition in the stop task may differ from that in the flanker task as it involves the withholding of a prepotent response, rather than the production of an alternate response. In conclusion, the three tasks in this study may have addressed different types of inhibitory control, at least to a certain extent. Clearly, more research is needed to unravel the mechanisms involved in inhibitory control, and studying the effects of stimulant drugs on response inhibition might contribute to the understanding of these mechanisms.

With respect to stopping, a recent theory has been postulated suggesting that inhibiting a prepotent response is achieved through activation of a "hyperdirect pathway", whereby the frontal cortex through the subthalamic nucleus excites the output structures of the basal ganglia and suppresses thalamo-cortical output, thus blocking execution of the initiated go response (Aron & Poldrack, 2006; Nambu, Tokuno, & Takada., 2002). Indeed, in Parkinson's patients with deep brain stimulation micro-electrodes implanted in the subthalamic nucleus, SSRTs in the stop task show impaired inhibitory control when the stimulators are on compared to off (van den Wildenberg et al., 2006). According to this theory the striatum (which is the primary site of action for caffeine) is not critical for stop-signal inhibition. If true, it makes sense that in our study caffeine did not modulate stop-signal response inhibition.

Our data are in line with those of Kenemans et al. (1999) who found that beneficial effects of caffeine on Stroop interference (reflecting inhibitory control) were restricted to conditions in which predictability of high-interference stimuli (incongruence between color and word) was 100% (i.e., blocked). Within mixed block conditions, caffeine still reduced overall RTs, but did no longer specifically affect interference. Apparently, an active inhibition process (directed at the irrelevant-feature representations) was invoked strongly in blocked incongruent conditions, but less so in mixed conditions. These findings led Kenemans et al. to suggest that caffeine improves inhibitory control only when it could be deployed at a strategic level, e.g., when knowing in advance that high-interference stimuli were going to be presented. This logic could be applied in reverse to the present findings, since our participants could not predict when response inhibition was required (i.e., in the case of stop-signal trials, AY and BX trials, and incongruent flanker trials). As such, they might have resorted to a stimulus-driven approach rather than a goal-directed one. The former approach would not be amenable to modulation by caffeine.

This suggestion fits well within the framework of a recent theory by Braver et al. (in press). They made a distinction between proactive and reactive control. Proactive control is a resource demanding type of control concerned with preparation and maintaining goals in working memory, whereas reactive control deals with a stimulus-driven, conflict-resolving type of control. We have recently found specific effects of caffeine in a task-switching paradigm that employed either a predictable trial sequence or valid cues that preceded target stimuli (Tieges et al., 2006; Tieges, Snel, Kok, Plat, & Ridderinkhof, 2007). As such, these tasks invoked a high degree of proactive control. We therefore argue that specific effects of caffeine may be largely mediated by proactive control strategies, which appear not to be

strongly involved in inhibitory control as measured in the present study. Rather, reactive control was required for succesful performance in the presently used tasks, and this type of control was apparently not sensitive to caffeine (see Braver et al., in press).

In conclusion, our results show that caffeine does not modulate response inhibition. It may be that specific effects of caffeine on control processes largely involve proactive control, whereas the tasks used in the present study mainly invoke reactive control.

6

General Discussion and Summary

The primary objective of the studies described in this thesis was to assess the effects of caffeine on cognitive control processes. To achieve this goal, both behavioral and ERP correlates of cognitive control as involved in action monitoring, task switching, and response inhibition were investigated. This section starts with a summary and discussion of the main outcomes in light of the three research questions as postulated in the Introduction (section 1.4). Subsequently, some additional issues will be addressed, i.e. the role of energetical mechanisms, generalization of the findings to coffee drinking in daily life, and recommmendations for future research.

6.1 Caffeine and action monitoring

6.1.1 Summary of findings

The first question addressed in this thesis was concerned with evaluative control, which pertains to the type of control responsible for monitoring the need for executive control and signaling when adjustments in control are needed. The impact of caffeine on this action-monitoring system was examined, as described in Chapter 2. In a double-blind, within-subjects experiment, nonsmoking, habitual coffee drinkers performed an alternating-runs switch task (Rogers & Monsell, 1995), in which two caffeine doses (3 and 5 mg/kg body weight) and a placebo were administered. It was demonstrated that the amplitude of the error-related negativity (ERN), a psychophysiological index of action monitoring (Gehring et al., 1993), was enhanced by caffeine. As such, this study showed a beneficial effect of caffeine on the monitoring of ongoing cognitive processes for signs of erroneous outcomes.

In addition to the ERN, caffeine enhanced another error-related ERP component, namely the error positivity or Pe. Although debate remains about the functional significance of this component, there is evidence to suggest that the Pe is related to the conscious evaluation of an error as such (Nieuwenhuis et al., 2001). Its signal has been hypothesized to be useful for post-error speed-accuracy adjustments. These adjustments were seen in our study as post-error slowing, but caffeine did not modulate this effect. This suggests that the perceived strengthening of processes related to error awareness by caffeine, as indexed by an enhanced caffeine-induced Pe, appears to have no effect on subsequent corrective behavior. Nevertheless, it should be noted that overall performance in terms of response speed and error rate was indeed improved after caffeine, which has been reported quite consistently in caffeine studies.

Contrary to expectations, ERN and Pe amplitudes were not different for low and high caffeine conditions. In fact, almost no dose-dependent effects were found throughout the studies described in this thesis. This puzzling finding is further discussed in section 6.4.

To summarize, evaluative control as seen in action monitoring was strengthened by caffeine. An intriguing implication of this finding is, that the commonly found effects of caffeine on human behavior, which have been attributed to a wide variety of cognitive

processes, may depend in part on caffeine's actions on the action monitoring system. Future studies are needed, however, to provide further support for this idea.

6.1.2 Caffeine's actions on neural mechanisms involved in action monitoring

An additional goal of the present thesis was to gain insight into the neural mechanisms that underlie the effects of caffeine on cognitive control. The neurobiological reinforcement-learning model of the ERN (Holroyd & Coles, 2002) constitutes a useful framework for interpreting caffeine's effects on the ERN. To reiterate, the model postulates that the ERN reflects the transmission of a dopamine (DA) reinforcement learning signal that is carried from the midbrain DA system to the anterior cingulate cortex (ACC) and is subsequently used to train the ACC to optimize task performance. It was proposed in Chapter 2 that caffeine's effects on action monitoring may have been caused by boosting this mesencephalic DA system, in accordance with the well-established notion that DA neurotransmission mediates caffeine's behavioral effects (Garret & Griffiths, 1997). This could be achieved either by stimulating activity in the ventral tegmental area (VTA), resulting in strengthening the error signal carried to the ACC, or by directly targeting the ACC. This idea receives some support from animal studies showing, in rats, caffeine-induced increases in glucose utilization in the VTA and ACC (Nehlig & Boyet, 2000) and increased stimulation of DA transmission in medial PFC (Acquas et al., 2002). It is unknown, hoewever, whether such activations reflect the cause or effect of the psychostimulant properties of caffeine (i.e. caffeine may directly stimulate the ACC or this may result from e.g. increased striatal activation). Also, findings from rat studies on the neurochemical effects of caffeine cannot be easily generalized to humans. It is particularly difficult to relate doses of caffeine as injected in rats to a habitual dose of caffeine as ingested through coffee by humans. This is a relevant issue, since low and higher doses of caffeine are believed to act on the brain through different mechanisms. That is, whereas low doses of caffeine occur at the level of adenosine A_{2A} receptors that are co-localized with DA-D_2 receptors in the striatum (which is believed to underlie most of the central effects of caffeine), higher doses of caffeine also bind to adenosine A_1 receptors. Even so, rat studies provide valuable information about the brain regions sensitive to caffeine, but neuroimaging studies with human subjects are necessary to further clarify the neurochemical effects of caffeine.

Clearly, this error-driven learning account of the ERN (Holroyd & Coles, 2002) draws on principles of reinforcement (reward) processing. The mesocortical pathway, as described in this model, is closely connected to the mesolimbic pathway, and both pathways are involved in reward processing (Schultz, 2000). Despite the fact that caffeine's reinforcing and addictive properties, if any, appear to be mild (Nehlig, 1999), and consequently caffeine may be a weak reinforcer (reward) in itself, this does not preclude any effects of caffeine on the neural ciruits involved in reward processing. Rather than being limited to basic (primary) rewards (satisfying vegetative needs), reward systems in humans

extend to different classes of 'higher' cognitive (secondary) rewards (e.g., novelty, money, power, and challenge) that typify human behavior. The current findings of boosting mesocortical activity by caffeine may have implications for caffeine's effects on reward-related processing. Interestingly, it has been widely accepted that the striatum (specifically the caudate nucleus) is involved in reward processing in humans (e.g., Haruno & Kawato, 2006), and consequently striatal reward activities might influence widespread cortical behavior-related activity through striato-cortical loops (Schultz, 2000). It should be noted though that the Holroyd & Coles' model does not incorporate the striatum.

Taken together, the ERN study indicates a role for caffeine in the neural circuit involved in action monitoring. The implications of these findings are relevant for the discussion of caffeine's effects on reward-related processing in humans, which is an intriguing direction for future studies on caffeine.

6.2 Caffeine and executive control in task switching

6.2.1 Summary of findings

The main portion of this thesis dealt with effects of caffeine on executive control as involved in task switching (Chapters 3 and 4).

The double blind, within-subjects study described in Chapter 3 was concerned with the effects of 3 and 5 mg/kg BW caffeine on behavioral and ERP measures of task switching in habitual coffee drinkers. To meet these aims, an alternating-runs paradigm was used (Lorist et al., 2000), with both single-task blocks (performing only one task throughout a block) and mixed-task blocks (alternating predictably between two tasks). This design allowed us to disentangle effects of caffeine on processes of task-set maintenance from processes of task-set reconfiguration (or updating). The findings provided some support for the notion that caffeine improves task-set maintenance, as evidenced by reduced mixing costs after caffeine (mainly seen for errors). Caffeine's effects were most clearly seen with respect to task-set updating, as evidenced by reduced RT switch costs after caffeine. Within the ERPs, an early negativity was reduced in switch (compared to repeat) conditions, followed by a late slow negativity for which the reverse pattern of a shift-induced enhancement was seen. Caffeine further enhanced the switch-induced effect on the slow negativity (but not the early negativity). This effect of caffeine was interpreted as reflecting improved anticipatory control. Furthermore, length of the preparation interval was manipulated and, as expected, caffeine's effects were most pronounced on RTs when the opportunity for preparation was greatest, providing further support for the notion that caffeine's effects are specific to anticipatory processing. However, the slow negativity was not clearly seen in shorter preparation conditions, and a direct investigation of the slow negativity effects between RSI conditions was therefore not possible.

Taken together, these complementary behavioral and ERP findings provided the first evidence that coffee consumption may improve task-switching performance, in particular by enhancing anticipatory processing. Nevertheless, a few problems occurred with respect to interpretation of the findings. These mainly concerned the fact that a response was always immediately followed by the preparation period of the next trial, and therefore response-related and preparation-related processes may have partially overlapped. In addition, the onset of anticipatory processing was not sufficiently controlled for. In other words, due to the predictable nature of the task, participants could have prepared prior to the onset of the preparation period (that is, on the preceding repeat trial).

Therefore, a second study was performed that dealt with these methodological issues, by using unpredictable (cued) rather than predictable switches. Furthermore, this study was concerned with a more in-depth exploration of effects of caffeine on anticipatory control in task switching. Specifically, it was hypothesized that the shift-sensitive effects of caffeine are task-specific (e.g., retrieval and updating of task sets and S-R assignments), and hence should be related to the characteristics of the tasks that have to be switched. To this end, the extent to which the task appeals to anticipatory processing was manipulated by varying the number of task items that have to be prepared (mapping rule, response effectors, or both). The data largely replicated the previous findings, showing once more a caffeine-induced reduction in behavioral shift costs, and a concurrent caffeine-induced enhancement of the shift-effect in the slow negativity. Contrary to our predictions, however, behavioral and ERP results did not confirm the task-specificity hypothesis, since these effects of caffeine did not increase parametrically with task shift load. In other words, the caffeine effects on behavioral shift costs and on anticipatory ERP components were not significantly larger for dual shift conditions, relative to single shifts. Hence, it was concluded that caffeine apparently has a more general effect on task switching related to task-nonspecific processes (e.g., goal setting or active task-set maintenance), rather than being task-specific.

Interestingly, active maintenance of currently relevant information (from specific stimulus features, to instructional cues, to motivational goals) is an important subcomponent of working memory, and the present findings suggest that these working memory processes can be modulated by caffeine. This notion has received only limited support in the literature (see Snel et al., 2004). Interestingly, though, it has been suggested that working memory may be highly involved in the control of visual selective attention (de Fockert, Rees, Frith, & Lavie, 2001), and accordingly the previously reported caffeine effects on visual selective attention (Ruijter et al., 2000a) may perhaps have reflected, in part, caffeine-induced changes in working memory.

Again, dose-dependent effects were almost absent in both of these studies, even though the high dose in the second switch experiment was higher (6 mg/kg) compared to the previous studies (5 mg/kg BW).

Taken together, the main conlusions from these task-switching studies are that a) caffeine improves task-switching performance; b) this is achieved by caffeine-related

enhancements in anticipatory control of task switching; and c) these effects of caffeine appear to be task-nonspecific.

6.2.2 ERP components of task switching

The current task-switching studies may contribute to the understanding of processes involved in task switching and its neural correlates. In agreement with the bulk of ERP literature on task switching, we found no evidence of ERP components that were uniquely associated with switching. Rather, switching evoked modulations in ERP components that were evident in both repeat and shift conditions, consistent with the notion that a shift of task calls upon many of the same processes that are involved when repeating the task, instead of activating additional neural circuits.

One of the major findings of the present task-switching studies concerned the effects of caffeine on the slow negativity, and therefore this component merits some discussion. It has been proposed that it takes about half a second to prepare for an upcoming task (e.g., Rogers & Monsell, 1995). One might argue, therefore, that the slow negativity, with an onset of around 600 ms within the preparation interval, should reflect task-set maintenance rather than task-set updating. Yet, whereas repeat trials in the alternating-runs study (mixed-task blocks) were associated with increased active maintenance demands compared to single-task conditions, this effect was not reflected in differences between repeat and single-task trials in the slow negativity. This argues against an interpretation of the slow negativity exclusively in terms of task-set maintenance, but rather suggests that it may reflect, in part, processes related to task-set updating. In turn, this notion was just partly confirmed in the cued task-switching study, since the effect of shift-type (single vs. dual shifts) on the slow negativity was limited to the 700-800 ms time segment. Most likely, the slow negativity incorporates aspects of both active task-set maintenance (or goal setting), as well as processes related to the retrieval and updating of task sets and their associated S-R assignments. Moreover, the exact contribution of these processes to the slow negativity may depend to a large extent on the task requirements, which are known to differ a great deal between task-switching paradigms. In addition, trial-to-trial strategic changes may further complicate interpretation of the slow negativity. For instance, it has been proposed that preparation acts as a probabilistic all-or-none process, such that participants will prepare in advance on some trials but not on others, depending on task parameters and participant variables (de Jong, 2000). Yet, it can be concluded at the very least that the slow negativity represents aspects of anticipatory processing for an upcoming shift of task.

In addition to the slow negativity, we observed shift-induced effects in the early negativity as well in the cue- and stimulus-related P3. The early negativity is difficult to interpet due to the possible overlap with motor-related processes elicited by the preceding response, but one possibility is that it reflects early anticipatory processes, perhaps task-set retrieval. The cue-P3 could be interpreted in a similar fashion (i.e. task-set retrieval or updating; Kok, 2001) or it may reflect greater demands on cue processing (Johnson, 1986),

such as translating the cue into a task set. Lastly, the shift-induced reduction in the stimulus-P3 might indicate a weaker or unstable task set on shift compared to repeat trials (e.g., Barcelo et al., 2000), but it could also reflect stronger associations between stimulus and task-set on repeat (compared to shift) trials (Waszak et al., 2003). However, none of these shift-sensitive components were systematically affected by caffeine.

This discussion of shift-related ERP components shows all the more that it is difficult to arrive at a coherent account of the cognitive functions involved in task switching, let alone their neural correlates. This would be much less problematic if a widely accepted process model of task switching existed, which is unfortunately not yet the case.

6.2.3 Caffeine's actions on neural mechanisms involved in task switching

The converging evidence on the neural mechanims involved in task switching together with the neurocognitive effects of caffeine, may provide clues as to which brain areas could have mediated caffeine's effects on task switching. This has been extensively discussed in Chapters 3 and 4.

First, it was concluded that the effects of caffeine on task switching are most likely mediated by DA neurotransmission, a conclusion derived from the reported role of DA activity in the psychostimulant effects of caffeine on behavior (e.g., Garrett & Griffiths, 1997), combined with the observed DA involvement in task switching (e.g., Cools et al., 2001). One possibility is that caffeine may directly target DA activity in the (pre)frontal cortex (PFC; Acquas et al., 2002). Speculating further, these actions of caffeine on (pre)frontal DA activation may be located in regions such as the (left) lateral PFC and the ACC, both of which have been implicated in task switching (e.g., Braver et al., 2003; Luks et al., 2002). Specifically, the lateral PFC has been implicated in processes such as rule retrieval, online maintenance during task preparation, and rule-based response selection (Bunge, 2004). Some of these processes were supposedly reflected in the slow negativity and, hence, affected by caffeine in the present studies. In addition to the lateral PFC, the ACC may constitute another target for caffeine's actions (see also section 6.1.2), especially since it has been implicated in preparation-related activity (Parris et al., 2007). Furthermore, the ACC is among the proposed neural generators of the CNV, a component closely resembling the slow negativity (Brunia & van Boxtel, 2001), and its activation has been shown to correlate with CNV amplitude (Nagai et al., 2004). Nonetheless, the ACC has received much less attention in the task-switching literature than the lateral PFC. Note also that topographical distributions as obtained in the present studies provide only limited support for this notion of ACC involvement, with a fronto-central distribution of the slow negativity in the cued task-switching study (consistent with ACC activation) but a more posteriorly distributed effect in the alternating-runs study. However, interpretation of these topographical distributions is not straightforward, especially when they reflect a widespread activation.

Since the notion of lateral PFC and ACC involvement in generating the effects of caffeine on task switching is speculative, it deserves attention in future research. This is especially true since these two brain regions are closely connected.

In addition to the frontal cortex, the present effects may be attributable to caffeine-mediated DA changes in the striatum, in particular because the striatum (particularly the caudate nucleus) is highly sensitive to caffeine in humans (Fredholm et al., 1999; Kaasinen et al., 2004). Moreover, evidence for striatal DA activity in task switching comes from studies with Parkinson patients (e.g., Monchi et al., 2004). Specifically, the striatum has been assigned a crucial role in the voluntarily (or internally) initiated control of behavior. For instance, the caudate nucleus has been shown to be involved when cognitive planning is required to perform a shift of task (Monchi et al., 2006), but this was only true when self-initiated shifts were concerned and not when shifts were externally cued (as was the case in the present caffeine studies). Nevertheless, the sensitivity of the striatum to low or moderate doses of caffeine together with its involvement in task switching is suggestive of striatal involvement in mediating caffeine's effects on cognitive control.

6.3 Caffeine and executive control in response inhibition

6.3.1 Summary of findings

The third, and final, question addressed was concerned with caffeine's effects on executive control as involved in response inhibition, as described in Chapter 5. In three behavioral double-blind, within-subjects experiments, the effects of 3 mg/kg BW caffeine and a placebo were assessed on behavioral indices of response inhibition: Inhibition of a prepotent response in the AX-CPT, inhibitory motor control in the stop task, and inhibition of irrelevant information in the flanker task. Collectively, the findings of these experiments show that the presently studied domains of response inhibition are fairly insensitive to caffeine. The only exception to this was seen in the AX-CPT, which revealed more efficient performance on AY trials (relative to BY trials) after caffeine. However, this was not accompanied by a comparable effect on BX performance, and, furthermore, this effect might have reflected caffeine-induced changes in mechanisms other than response inhibition (i.e., attentional processes). It is noteworthy that caffeine affected performance in each experiment (i.e., all tasks were sensitive to caffeine), but these effects were general rather than specific to response inhibition, consistent with the well-known effects of caffeine on perceptual, attentional, and motor processes (e.g., Snel et al., 2004).

In contrast to the previous ERP experiments, only behavioral measurements were obtained in this study. Nevertheless, the converging evidence brought about by these experiments makes a strong claim for the notion that response inhibition is not susceptible to a habitual dose of caffeine. That is, we found null effects in all experiments, each using different paradigms and subject groups, which justifies acceptance of the null hypothesis in

the present study. Neverheless, psychophysiological studies may possibly shed more light on caffeine's effects on inhibitory control. For instance, caffeine might influence inhibitory control in ways not evident from behavioral measurements (e.g., an effect on the nogo-N2 in the stop experiment).

6.3.2 Caffeine's actions on neural mechanisms involved in response inhibition

The findings from this study on response inhibition appear to be at odds with the reported role of DA activity in response inhibition (especially in the striatum; see Cropley et al., 2006). A possible explanation of this apparent inconsistency may be related to the idea that, at least in the case of stopping, inhibitory control may be mediated by a *hyperdirect* pathway, whereby the frontal cortex through the subthalamic nucleus excites the output structures of the basal ganglia and suppresses thalamo-cortical output, thus blocking execution of the initiated go response (Aron & Poldrack, 2006; Nambu et al., 2002). Indeed, in Parkinson's patients with deep brain stimulation micro-electrodes implanted in the subthalamic nucleus, impaired inhibitory control was shown in the stop task when the stimulators were on compared to off (van den Wildenberg et al., 2006). According to this theory the striatum (which is the primary site of action for caffeine) is not critical for stop-signal inhibition. If so, it makes sense that in our study caffeine did not modulate stop-signal response inhibition. As yet, however, this is merely a speculative suggestion.

6.4 Absence of dose-dependent effects

The outcomes as reported in this thesis are characterized by an overall absence of dose-dependent effects. This was not due to failure of the caffeine manipulation, as evidenced by caffeine saliva analyses (in the first two studies). As for subjective and behavioral measures, no dose-dependent effects were observed at all. Regarding ERPs, the only difference between high and low dose conditions was seen for cue-related P3 amplitudes (Chapter 4), suggesting a stronger shift-effect in low (compared to high) dose conditions. However, the robustness of this effect was questionable, mainly because P3 amplitudes did not differ between caffeine and placebo conditions (which is commonly found). Thus, the overall pattern in the data indicates an overall absence of dose-dependent effects.

Obviously, the complex tasks as used in these studies did not benefit from relatively high doses of caffeine, nor did task performance deteriorate after a high dose. Though unexpected, this result is in line with previous studies showing a flat dose-response relationship in mood and psychomotor performance (Lieberman et al., 1987; Robelin & Rogers, 1998). One possibility is that performance reached optimal levels in low dose conditions, such that participants did not benefit from the additional boost given by a high dose. However, according to the "inverted-U hypothesis" (Yerkes & Dodson, 1908), performance should decline with doses that induce arousal levels beyond the optimum. This

appeared not to be the case. Nonetheless, it may be that lower and higher doses were below and beyond the optimum dose, respectively, resulting in comparable arousal levels. Arousal was not directly measured in the present studies, however, and this notion can therefore not be validated.

As discussed in Chapters 2 and 3, a viable explanation for the absence of dose-dependent effects concerns the between-subjects variability in reported caffeine intake. This could have resulted in performance deterioration in low users after a high dose because of induced arousal levels beyond the optimum, whereas high users benefited from the high dose. Unfortunately, subject groups were too small to corroborate this notion (based on a median split) with additional statistical analyses.

A final remark relates to the 'low' dose of 3 mg/kg BW caffeine (comparable to two cups of coffee), which is actually quite high when ingested in one serving. It may be that this dose already produced a diffuse stimulating effect in the central nervous system. As such, the neural substrates of a wide range of cognitive processes may have been stimulated by caffeine. Even though the reduced specificity in caffeine's actions due to higher doses in the brain has been shown in rats (Nehlig & Boyet, 2000), it is unknown how this finding relates to the human brain.

6.5 Conclusions

In sum, the current findings support the assumption that moderate amounts of caffeine improve certain aspects of cognitive control. Specifically, evaluative control as involved in action monitoring, and executive control as involved in anticipatory task-switching processes appear to benefit from caffeine. In contrast, response inhibition seems much less sensitive to caffeine's actions. It may be useful to discuss these findings in light of the proactive-reactive distinction proposed by Braver et al. (in press). As such, specific effects of caffeine on control processes may be largely mediated by proactive control (as involved in task switching), which is a resource demanding type of control concerned with preparation and maintaining goals in working memory. In contrast, reactive control (as involved in response inhibition), which refers to a stimulus-driven, conflict-resolving type of control, appears to be much less sensitive to caffeine. It is further proposed that a neural mechanism involving DA neurotransmission appears to mediate the presently found effects of caffeine on proactive control.

This conclusion contrasts sharply with previous studies by Lorist (1995) and Ruijter (2000), who concluded that higher mental functions were not sensitive to caffeine. As mentioned in the Introduction, though, the tasks used in those studies were very different from the presently used tasks, and hence a direct comparison of their studies with ours is tricky. Nonetheless, cognitive processes associated with planning and preparation were more strongly addressed in the current studies as compared with earlier studies, which may be a key process of higher-level control that is susceptible to caffeine.

A final issue that merits discussion is that, although the current findings certainly fit within a DA framework, the data are not specific enough to preclude the involvement of other neuromodulator systems in the effects of caffeine, such as noradrenaline, acetylcholine, and serotonine (Nehlig, Daval, & Debry, 1992). In fact, the locus coeruleus (noradrenaline) and the raphe nuclei (serotonine) are among the first brain areas to be stimulated by caffeine in rats at low doses (Nehlig & Boyet, 2000). The link between the cognitive effects of caffeine and these other neurochemical mechanisms is not well understood. Nevertheless, some interesting findings regarding the role of these neurotransmitter systems in cognitive control are relevant to the present data.

First, there is empirical evidence for a role of noradrenaline transmission in error processing. Riba, Rodriguez-Fornells, Morte, Munte, and Barbanoj (2005) found that the agent yohimbine, which stimulates firing in the locus coeruleus and noradrenaline release, led to an increase in ERN amplitude and a concurrent reduction of action errors in humans, while the N2 component and posterror adjustments were spared. This points to a rather specific effect of the locus coeruleus-noradrenaline system on human action monitoring, which provides an alternative account for the presently found effects of caffeine on the ERN. Further support for this notion comes from studies showing prominent, direct inputs from the ACC (which is involved in action monitoring) to the locus coeruleus of monkeys (see Aston-Jones & Cohen, 2005). Interestingly, noradrenergic neurotransmission in the medial PFC of rats has been implicated in attentional set-shifting ability as well (Lapiz & Morilak, 2006).

In addition to noradrenaline, serotonergic neurotransmission has also been linked to cognitive control. Specifically, it was demonstrated in rats that prefrontal serotonin depletion induced reversal learning deficits (Clarke, Walker, Dalley, Robbins, & Roberts, 2007), which requires flexible shifting of response patterns.

In sum, whereas current hypotheses have focused on DA, alternative hypotheses regarding the contribution of other neurotransmitter systems to the current findings seem also plausible. These post-hoc hypotheses may provide some directions for further research on the neurocognitive effects of caffeine.

6.6 The role of energetical mechanisms

So far, the outcomes of this thesis have been discussed in terms of effects of caffeine on structural processes, but the quality of human information processing is dependent on energetical factors as well. Here we focus on mental effort, and the possible role of effort in the present findings will now be considered briefly.

Generalizing from the notion that caffeine tends to counteract the effects of central fatigue, possibly by increasing DA functioning in striato-thalamo-cortical circuits (e.g., Lorist & Tops, 2003), it seems plausible that the present findings reflect, in part, compensation of mental fatigue by caffeine. In particular, the ERP expressions of differential engagement of anticipatory processes in switch and repeat trials, as obtained in the

alternating-runs study, were observed to be reduced with mental fatigue in a comparable paradigm (Lorist et al., 2000). Moreover, it has been suggested that the extra energy as provided by caffeine is used there were needed most (i.e. dependent upon the specific task requirements).

One of the mechanisms involved in compensating for the effects of fatigue during short time periods may be related to the investment of additional effort (Sanders, 1983). Such an effort mechanism has been argued to involve the mesolimbic DA system. Moreover, involvement of adenosine A_{2A} receptors (and its interactions with DA) in regulating effort has been reported (see Salamone, Correa, Farrar, & Mingote, 2007). Accordingly, a tentative speculation is that effects of caffeine on effort-related processes contributed to the present findings.

In line with this idea, a link between effort mechanisms and the present findings has been suggested by Falkenstein et al. (2003), who manipulated effort by presenting cues that instructed participants to invest extra effort on the subsequent trial. These effort trials were associated with a prior increase of a frontocentral CNV, which, according to the authors, reflected activity of a frontal executive process by which additional processing resources can be mobilized on a trial-to-trial basis. This adds to the evidence that slow negativities, in general, are related to effortful executive processes that modulate or change ongoing preparatory processes. It should be noted, though, that the RSME (Zijlstra, 1993), a questionnaire that assessed subjective feelings related to effort investment, failed to show consistent effects of caffeine. Specifically, no effects of caffeine were found on subscales that specifically dealt with the preceived amount of effort allocation.

As yet, it remains to be determined if these energetical mechanisms may play a considerable role in mediating caffeine's actions on cognitive control. In addition, it is unclear at this point whether these factors constitute moderator variables (*influencing* the strength of a relationship between two variables), or should be rather thought of as mediator variables (*explaining* the relationship between two variables; Baron & Kenny, 1986).

6.7 Generalizing the findings to daily-life coffee drinking

An important goal of this type of research is to assess the real-life impact of caffeine and coffee on human thinking and behavior. A couple of remarks will be made concerning the generalization of the present outcomes, as obtained in laboratory experiments, to manifestations of coffee drinking in day-to-day situations.

First, groups of participants were selected according to certain including and excluding criteria (e.g., nonsmoking, habitual coffee drinkers, 18-30 years of age). The rationale behind this approach is to minimize the variability in effects of caffeine and, hence, increase the possibility of finding treatment effects. At the same time, however, these selection criteria limit the generalization of the findings to the general population. By the same logic, if the goal of the researcher is to maximize caffeine's effects, it might be best to

test participants who only occasionally drink coffee and hence should be highly sensitive to caffeine. In other words, occasional consumers may be preferred over regular consumers if the primary goal of the researcher is to maximize effects of caffeine. However, we chose to select regular coffee consumers instead of occasional consumers, because we argued that the former group would be more representative of the normal population of coffee drinkers.

An additional point is that caffeine was always ingested in a single serving of coffee. This differs from regular coffee consumption, which consists of ingesting small doses at successive time points. Interestingly, it has been shown that one single dose and several smaller doses of caffeine had comparable effects on alertness and cognitive performance (Brice & Smith, 2002). These authors therefore suggested that previous findings from studies using a large single dose may be applicable to normal patterns of caffeine consumption. Accordingly, it seems justified to generalize the outcomes of this thesis to real life settings, at least to a certain extent.

Another issue concerns withdrawal. It has been argued that abstinence from caffeine-containing products during the 12 h preceding a session may cause impaired performance in the placebo condition, rather than improvement under caffeine (Juliano & Griffiths, 2004). However, it is unlikely that this "relief from withdrawal" hypothesis can fully explain the present findings. For instance, it has been shown that caffeine withdrawal of the magnitude usually seen in studies does not lead to a marked decrease in psychomotor performance (Richardson et al., 1995). Moreover, beneficial effects of caffeine on cognitive performance have been found even in the abence of withdrawal (e.g., Warburton et al., 2001). Finally, several studies (reviewed by Rogers & Dernoncourt, 1998) indicate a significant increase in subjectively reported negative symptoms after about 12 h abstinence, but at the same time objective performance measures indicative of abstinence are hard to establish. The findings suggest that deprivation periods (of at least 10 h) may impair performance, but that even in such conditions observed caffeine effects cannot be attributed solely to reversal of withdrawal. In conclusion, the current findings appear to mainly reflect caffeine-induced improvements in cognitive functioning, although the relief from withdrawal by caffeine may have contributed to some extent. In this respect, it is noteworthy that the majority of participants were tested in the morning (they drank their "morning cup" in the laboratory) and were therefore required to abstain from caffeine-containing products during the night, which is quite consistent with normal coffee drinking patterns.

Although caffeine has been the focus of this thesis, there is more to coffee drinking than just caffeine. That is, coffee drinking is usually associated with relaxation, sociability, and stress reduction. Surprisingly, only 14% of regular consumers report drinking coffee to be stimulated (Harris Research Centre, 1996). Furthermore, coffee drinking is a habit that is usually learned early in life, and its effects can be conditioned by environmental cues associated with coffee drinking (e.g., time of day, situations in which coffee is drunk, coffee making). In other words, what we see, smell, and taste all contribute to making the coffee drinking an experience where the total effect appears to be far greater than the sum of the component parts. Combined with our previous enjoyment of the drink, and therefore our

expectations, it is not difficult to appreciate why such wide ranging reactions to a similar solution of caffeine are found among people (Meyer, 2001). This is exactly the reason that the coffee drinking "ritual" was mimicked as much as possible in our experiments, within the limits of the laboratory setting. As an example, the coffee was usually prepared in the presence of the participants, since this would expose them to the sight and smell of coffee. Nevertheless, coffee drinking in the laboratory setting differs from regular coffee drinking, and this should be kept in mind when generalizing the outcomes of this thesis and other laboratory studies to normal coffee consumption.

Finally, given that the critical factor manipulated in the present studies was caffeine, the sensory and behavioral cues associated with coffee drinking were kept constant across test sessions. Accordingly, the effects of caffeine were examined in the "context" of drinking a cup of coffee. Future studies may focus on other aspects of coffee drinking in relation to cognitive functioning, for example, manipulating coffee smell or expectations associated with coffee. The complementary findings of these studies, encompassing multiple aspects of coffee drinking, may ultimately lead to a comprehensive understanding of caffeine and its effects on cognition.

6.8 Recommendations for future research

Throughout this thesis, several ideas and hypotheses have been postulated with respect to the neurocognitive mechanisms of caffeine in man. However, these ideas are largely derived from animal studies. Current attempts to investigate the human brain regions affected by caffeine through source modelling techniques were not succesful, since dipole analyses did not yield stable solutions. This is not surprising, considering the fact that neural activation underlying the presently investigated cognitive functions are probably not limited to a few specific brain areas, but rather involve widely distributed networks in the brain.

Clearly, more research on caffeine's effects in the human brain is required. At first glance, functional MRI appears to be a suitable technique for elucidating the loci of caffeine effects in humans. A disadvantage of this technique, however, is that caffeine appears to change the dynamics of the BOLD response due to its vasoconstrictive properties (which causes a decrease in baseline cerebral blood flow; e.g., Mulderink, Gitelman, Mesulam, & Parrish, 2002). The design of any fMRI/caffeine study should therefore be carefully chosen, enabling the disentanglement of the caffeine-induced physical effects on the BOLD response from actual modulations in brain activation as a result of caffeine.

Another issue has to do with the finding that caffeine effects are especially found in situations of lowered arousal or fatigue. If one's goal is to maximize effects of caffeine, it may be preferable to test people who are fatigued or otherwise in a suboptimal arousal state (e.g., during the post-lunch dip or at night), or employ tasks that are lengthy and not intrinsically motivating or challenging to participants. In addition, older adults appear to be especially susceptible to caffeine's effects and consequently benefit more from caffeine than

young subjects (Lorist et al., 1995). Thus, older adults may be well suited as participants in studies on caffeine. In addition, the possibility that cognitive functioning in the elderly may benefit from caffeine is well worth studying in light of the sharp rise in the ageing population. Yet an alternative approach to maximize effects of caffeine is to test subjects who are accustomed to very low doses of caffeine. A related issue concerns the doses used. That is, the absence of dose-dependent effects in the reported studies suggests that future research should rather focus on lower, behaviorally relevant doses (between 0 and 3 mg/kg BW) or employ a repeated-dosing regimen (Denaro, Brown, Jacob, & Benowitz, 1991).

Finally, it seems plausible that inter-individual differences in, for example, personality, susceptibility to caffeine, and arousal level may have caused substantial variability in the present findings, since these factors have all been shown to contribute to the perceived actions of caffeine. Moreover, inter-trial differences in chosen strategy (especially in task-switching studies) may further complicate the picture. Rather than viewing such factors as "confounding" variables, they should instead be the topic of interest. Does caffeine exert its cognitive effects only in subjects who experience suboptimal arousal levels, or do these effects pertain to optimal arousal levels as well? Does caffeine specifically affect the amount of prepared (relative to unprepared) trials during task switching? These are interesting questions, and certainly relevant to the knowledge of caffeine, and it is therefore suggested that future studies place greater emphasis on inter-individual differences and trial-by-trial strategic changes in performance. In sum, the effects of caffeine on human cognition are diverse and there are complex interactions between caffeine's neurocognitive effects and factors such as the nature of task requirements and level of arousal. Clearly, these factors should be taken into account when examining caffeine.

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Nederlandse samenvatting (Dutch summary)

Inleiding

Cafeïne is een bestanddeel van thee, chocolade, frisdranken zoals cola en sommige medicijnen, maar de grootste hoeveelheid cafeïne wordt ingenomen met het drinken van koffie. De eigenschappen die aan cafeïne worden toegeschreven hebben grotendeels te maken met een veronderstelde stimulerende werking op het centraal zenuwstelsel. Zo leeft het idee bij de meesten dat cafeïne alerter en energieker maakt en vermoeidheid wegneemt, en daarnaast zou het de concentratie verhogen. Vanwege het wijdverspreide gebruik van koffie heeft de relatie tussen cafeïne en cognitieve functies (het "denkvermogen") al geruime tijd de interesse van wetenschappers. Het betreffende onderzoek heeft veelvuldig aangetoond dat cafeïne, conform subjectieve waarneming, een mild stimulerende werking heeft die kan resulteren in prestatieverbeteringen. De meest consistente bevinding is dat een hoeveelheid cafeïne die in 2-4 kopjes koffie aanwezig is de reactiesnelheid verbetert en het aantal fouten soms verlaagt (men wordt dus nauwkeuriger). Een te hoge dosering cafeïne kan een trillerig gevoel geven en een verslechtering van de fijne motoriek. Cafeïne wordt echter beschouwd als "zelfregulerend", wat inhoudt dat de meeste mensen weten wanneer ze genoeg koffie hebben gehad en daarom hun inname staken.

De psychoactieve effecten van cafeïne zijn doorgaans subtiel van aard. Daarnaast wordt het onderzoek naar cafeïne gekenmerkt door een grote variabiliteit als gevolg van methodologische factoren zoals dosering, tijd van de dag en de gebruikte cognitieve taak. Andere factoren zijn persoonsafhankelijk waaronder leeftijd, cafeïnegebruik, metabolismesnelheid, stemming en verwachtingen over koffie. De cognitieve effecten van cafeïne worden grotendeels toegeschreven aan diens werking als antagonist van adenosine in de hersenen die een remmende werking heeft op hersenactiviteit. Cafeïne onderdrukt de remmende werking van adenosine receptoren, hetgeen resulteert in een "netto" stimulatie van het centraal zenuwstelsel door veranderingen in verschillende neurotransmittersystemen (o.a. dopamine). De neurochemische werking van cafeïne is echter complex en een helder beeld hiervan behoeft nog veel onderzoek, vooral bij mensen. Al met al kan worden gesteld dat een eenduidig beeld van de neurocognitieve werking van cafeïne vooralsnog ontbreekt.

Effecten van cafeïne zijn gevonden in verschillende domeinen van cognitie. Het meeste onderzoek heeft zich tot op heden toegelegd op gedragsstudies waarbij reactietijden (RTs) en fouten worden gemeten. De laatste jaren is dergelijk onderzoek aangevuld met metingen van hersenpotentialen of *event-related potentials* (ERPs), welke meetbaar zijn aan de schedel met behulp van gevoelige elektroden gemonteerd in een soort badmuts. Deze

ERPs ontstaan door elektrische velden die worden teweeggebracht door de activiteit van de hersenen. Met deze onderzoeksmethode kan de activiteit van de hersenen ten tijde van informatieverwerking online worden gemeten met een hoge tijdsresolutie. De conclusie van een reeks ERP studies, waarbij specifieke stadia van informatieverwerking werden gemanipuleerd, was dat cafeïne voornamelijk inwerkt op basale cognitieve functies, zoals perceptuele en aandachtsprocessen en responsgerelateerde processen. Daarentegen ligt de focus van het huidige proefschrift op effecten van cafeïne op hogere-orde processen, die een hoge mate van *cognitieve controle* vereisen. Cognitieve controlemechanismen stellen ons in staat ons gedrag te organiseren en te coördineren met inachtneming van de continue veranderingen in onze omgeving. Deze controle is onontbeerlijk wanneer een snelle en flexibele aanpassing in gedrag gewenst is, zoals in nieuwe, onbekende situaties. Met andere woorden, cognitieve controleprocessen 'managen' of houden toezicht op meer gespecialiseerde cognitieve processen. Dit mechanisme is essentieel voor doelgericht gedrag en moet worden aangewend bij functies als plannen, redeneren, problemen oplossen, en het uitvoeren van meerdere taken tegelijk. De vraag is óf en hoe dergelijke functies worden beïnvloed door cafeïne. Stel voor, je bent aan het autorijden en bedient tegelijkertijd een mobiele telefoon (wat overigens bij de wet verboden is). Zou cafeïne invloed hebben op de mate waarin je in staat bent om deze handelingen vloeiend naast elkaar of afwisselend uit te voeren? En als het stoplicht op groen springt en je trapt het gaspedaal in, maar plotseling springt er een kind de straat op, wordt de snelheid waarmee de rem wordt ingetrapt beïnvloed door cafeïne? Dergelijke vraagstukken zijn vertaald naar een experimentele setting, en de uitkomsten hiervan worden besproken in dit proefschrift.

Cognitieve controle kan grofweg worden onderverdeeld in *evaluatieve* en *executieve* controle. Executieve of uitvoerende controle behelst cognitieve processen die het gedrag zodanig reguleren dat het efficiënt en doelgericht kan zijn. Voorbeelden hiervan zijn het onderdrukken van reflexmatig of impulsief gedrag, het actief onthouden van context informatie gedurende langere periodes, of het anticiperen op toekomstige gebeurtenissen. Evaluatieve controle verwijst naar een verzameling van basale cognitieve functies voor het toezicht houden op gedrag en omgeving, het herkennen van situaties waarin executieve controle nodig is en het alarmeren van executieve controlemechanismen wanneer deze moeten worden gemobiliseerd. Dergelijke regelfuncties zijn waarschijnlijk noodzakelijk voor het vertonen van intelligent gedrag. Er is dan ook veel onderzoek gedaan naar deze functies en de neurale mechanismen die hieraan ten grondslag liggen. In dit proefschrift is de invloed van cafeïne op zowel evaluatieve controle (hoofdstuk 2) als executieve controle (hoofdstukken 3 tot en met 5) onderzocht.

Het onderzoek

Wat betreft evaluatieve controle gaat Hoofdstuk 2 over *action monitoring*, ofwel het toezicht houden op gedrag en het detecteren van foutief gedrag. Foutdetectie is een van de

alarmsignalen voor het evaluatieve controlesysteem om executieve controle aan te wenden. In een dubbelblind, within-subjects experiment werden aan koffiedrinkers twee doseringen cafeïne (3 en 5 mg/kg lichaamsgewicht; één kopje koffie bevat gemiddeld 85 mg cafeïne, een mok 120 mg) of een placebo toegediend. Zowel de placebo als de cafeïne werd opgelost in een kop cafeïnevrije koffie. Deelnemers mochten 12 uur voor aanvang van elke experimentele sessie geen cafeïnehoudende producten nuttigen. Dit werd gecontroleerd in het speeksel. Nadat de cafeïne was ingewerkt, wat 30-45 minuten duurt, voerden de deelnemers een computertaak uit waarbij gedrag en ERPs werden gemeten. Er werd specifiek gekeken naar de *error-related negativity* (ERN), een hersenpotentiaal die optreedt kort na een foutieve reactie. De ERN wordt gezien als een psychofysiologische index van action monitoring. Deze ERN had een grotere amplitude in cafeïnecondities dan in de placeboconditie. Het evaluatieve controlesignaal werd dus versterkt door cafeïne. Bovendien werd onder invloed van cafeïne ook een tweede foutengerelateerde component, de *error positivity* (Pe), groter. De exacte betekenis van de Pe is echter niet bekend. De conclusie van deze studie is dat cafeïne een gunstig effect heeft op action monitoring, een essentiële component van evaluatieve controle. Dit zou kunnen impliceren dat de veelal gerapporteerde prestatieverbeteringen als gevolg van cafeïne deels kunnen worden toegeschreven aan een verbeterd of versterkt evaluatief controlesysteem.

Het voornaamste deel van dit proefschrift richtte zich op de invloed van cafeïne op executieve controle. Deze invloed wordt in de hoofdstukken 3 en 4 onderzocht aan de hand van *taakswitchen*, het wisselen van taak naar taak. In het alledaagse leven worden vaak verschillende handelingen tegelijk uitgevoerd. Efficiënt switchen (schakelen) tussen de verschillende handelingen is daarbij een vereiste. Als zodanig is taakswitchen een goed voorbeeld van flexibel, doelgericht gedrag. Dit is uitgebreid onderzocht aan de hand van taakswitch paradigma's, waarbij deelnemers snel heen en weer moeten switchen tussen twee of meer simpele reactietijdtaken. In taakswitchparadima's moet de aankomende taak in het werkgeheugen opgehaald worden en actief worden gehouden tot de stimulus verschijnt, maar tegelijk moet de niet-relevante taak worden onderdrukt. Een algemene bevinding is dat het uitvoeren van de taak duurt langer (en foutenpercentage hoger is) wanneer wordt geswitched van taak (switch trial) dan wanneer dezelfde taak wordt herhaald (repetitie trial), en dit verschijnsel wordt de *switch kost* genoemd.

In het experiment zoals beschreven in hoofdstuk 3 wordt een taak gebruikt die is opgebouwd uit *mixed-task blocks*. Hierin moeten de deelnemers bij elke tweede trial alterneren tussen het beoordelen van een letter op diens kleur (rood of blauw) of identiteit (klinker of medeklinker), en *single-task blocks,* waarbij één en dezelfde taak gedurende een heel blok wordt uitgevoerd. Met dit experimentele design kunnen tevens subprocessen van taakswitchen worden geïsoleerd. Zo kan *task-set maintenance*, ofwel de vaardigheid om twee taken actief te houden in het werkgeheugen en bescherming te bieden tegen afleidende informatie, worden onderzocht door het actief houden van twee taken (in mixed-task blocks) te vergelijken met het actief houden van slechts één taak (in single-task blocks). Daarnaast kan *task-set updating*, ofwel het ophalen en activeren van de nieuwe taak in het

werkgeheugen, worden onderzocht door switchtrials te vergelijken met repetitietrials (binnen mixed-task blocks). Beide mechanismen zijn vereist voor succesvol taakswitchen. Ten slotte is de preparatieduur, ofwel de tijd van voorbereiden op de eerstvolgende taak, gevarieerd om eventuele specifieke effecten van cafeïne op anticipatieprocessen aan het licht te brengen. Qua onderzoeksopzet was dit experiment identiek aan de eerste studie. De doses waren 3 en 5 mg/kg lichaamsgewicht cafeïne.

Uit de resultaten bleek allereerst dat switchkosten afnamen onder invloed van cafeïne, wat duidt op een verbetering in de vaardigheid om tussen taken te switchen. Dit effect was het sterkst wanneer de preparatieduur voldoende lang was, wat aangaf dat cafeïne waarschijnlijk op voorbereidende of *anticipatie*processen inwerkt. Voorts bleek dat cafeïne een enigszins gunstig effect had op task-set maintenance. Maar met name task-set updating leek versterkt te worden door cafeïne. Met betrekking tot de ERPs lag de focus op de *slow negativity*, een trage negatieve golf in de ERPs die zichtbaar was tijdens de voorbereidende fase en aanhield totdat de letter werd vertoond. Deze ERP component lijkt anticipatieprocessen te reflecteren. De slow negativity was groter bij de voorbereiding op het switchen tussen taken, dan bij anticipatie op een taakrepetitie. Onder invloed van cafeïne nam dit switchgerelateerde effect in de *slow negativity* verder toe. De conclusie was dat taakswitchen werd verbeterd door cafeïne, voornamelijk door diens versterkende werking op switchgerelateerde anticipatieprocessen. Dit onderzoek laat voor het eerst zien dat cafeïneconsumptie kan leiden tot een verbetering in executieve controlemechanismen die een rol spelen bij taakswitchen.

Ter ondervanging van een aantal methodologische tekortkomingen van de eerste studie werd in een tweede studie gebruik gemaakt van een *gecued* taakswitch paradigma waarbij iedere trial aanvangt met een *cue*, een stimulus die als het ware een seintje geeft welke taak moet worden uitgevoerd. Bovendien beoogden we met deze studie een gedetailleerder inzicht te verkrijgen in de aard van de cafeïne-effecten op taakswitch processen. In het bijzonder werd onderzocht of de eerder aangetoonde switchgerelateerde effecten van cafeïne wel of niet taakspecifiek waren. In het eerste geval (taak-nonspecifiek) heeft cafeïne invloed op meer algemene processen zoals task-set maintenance of *goal-setting*, die dus niet samenhangen met de specifieke eigenschappen van de taak. In het tweede geval (wel taakspecifiek) heeft cafeïne invloed op het ophalen en updaten van specifieke aspecten van de taak. Hiertoe werd het aantal taakaspecten gemanipuleerd. In *single-shift* condities moest één aspect worden geswitched. Dit kon ofwel de *mapping* van een bepaalde stimulus op een respons zijn (bijvoorbeeld een linkerhand respons in het geval van rode letters, en een rechterhand respons bij blauwe letters, of juist omgekeerd), of het kon betrekking hebben op de *response effector* zijnde de vinger waarmee de respons werd gegeven (wijsvinger of middelvinger). In *dual-shift* condities moesten beide aspecten, zowel stimulus-respons mapping als de effector, worden geswitched. De doses waren 3 en 6 mg/kg lichaamsgewicht cafeïne.

De resultaten lieten wederom een prestatieverbetering als gevolg van cafeïne zien. Deze verbetering kwam tot uiting in een afname van de switchkost. Tevens werd in de ERPs

een effect van cafeïne op de slow negativity waargenomen, vergelijkbaar met het effect uit het eerste taakswitch experiment. In tegenstelling tot onze verwachtingen werd echter geen taakspecifiek effect van cafeïne gevonden: de cafeïne-effecten waren in single- en dual-shift condities vergelijkbaar van grootte. Deze bevindingen suggereren dus dat cafeïne een taak-nonspecifiek effect lijkt te hebben op taakswitch processen.

Uit deze twee taakswitchstudies kunnen drie conclusies worden getrokken: a) een hoeveelheid cafeïne (vergelijkbaar met de hoeveelheid cafeïne in twee tot vier kopjes koffie) leidt tot een verbetering in het vermogen tot taakswitchen; b) dit kan vooral worden toegeschreven aan een versterkte cognitieve controle als gevolg van cafeïne; en c) deze effecten van cafeïne lijken taak-nonspecifiek te zijn.

Opvallend is dat er vrijwel geen dosisafhankelijke effecten werden gevonden (in hoofdstuk 4 wordt één dosisspecifiek effect van cafeïne op de cuegerelateerde P3 component beschreven). De lagere dosis cafeïne leverde vergelijkbare effecten op als een hogere dosering. Dit kon niet worden toegeschreven aan de cafeïnemanipulatie, want de verschillende doseringen vonden hun reflectie in cafeïne waarden in het speeksel (deze analyses zijn enkel verricht in de studies zoals beschreven in de hoofdstukken 2 en 3).

Uit eerder onderzoek is bekend dat er een soort *omslagpunt* is met betrekking tot het effect van de hoeveelheid toegediende cafeïne. Een prestatieverbetering bij toenemende doseringen kan omslaan in een stabilisatie of verslechtering van prestaties. Het eerste lijkt op te gaan voor de onderhavige onderzoeken. Bij een 3 mg/kg dosering werd optimaal gepresteerd en hadden de deelnemers geen profijt van de extra *boost* van 5 of 6 mg/kg cafeïne. Een alternatieve verklaring voor het uitblijven van dosisafhankelijke effecten hangt mogelijk samen met de aanzienlijke verschillen tussen deelnemers in dagelijkse cafeïneconsumptie. Mogelijk heeft dit geresulteerd in prestatieverslechtering na de hoogste dosering cafeïne van mensen die slechts weinig cafeïne consumeren, terwijl mensen die aan een hogere dosis cafeïne gewend zijn wel degelijk profiteren van de hoogste dosering.

In hoofdstuk 5 wordt het onderzoek beschreven dat zich richtte op *responsinhibitie*, een mechanisme van executieve controle dat ons in staat stelt ongewenst gedrag te onderdrukken of te remmen. In drie verschillende gedragsexperimenten werd aan de deelnemers één dosering cafeïne (3 mg/kg) en een placebo toegediend. De effecten van cafeïne werden bekeken op drie taken die elk een beroep doen op een ander aspect van respons inhibitie: a) de *Continuous Performance Test* (AX-CPT) die een maat geeft voor inhibitie van een dominante respons; b) de *stopsignaal taak* die een beroep doet op de inhibitie van een reeds in gang gezette respons; en c) de *flanker taak* waarmee de inhibitie van storende, afleidende informatie kan worden onderzocht. Het algemene beeld dat uit de resultaten naar voren kwam is dat responsinhibitie tamelijk ongevoelig is voor de invloed van cafeïne. Een uitzondering hierop is een effect van cafeïne in de AX-CPT, dat duidde op een lichte verbetering in responsinhibitie als gevolg van cafeïne. Dit effect zou echter ook een weerspiegeling kunnen zijn van een cafeïnegeïnduceerde modulatie van andere cognitieve processen dan responsinhibitie, zoals aandachtsprocessen. Dit sluit aan bij het feit dat de algehele prestatie op de drie taken, gereflecteerd in gemiddelde RTs en

foutenpercentages, verbeterde als gevolg van cafeïne terwijl een specifiek effect van cafeïne op responsinhibitie meestal uitbleef.

Een voorbeeld ter verduidelijking: in de stopsignaal taak moet een keuzereactietijdtaak (de primaire taak) worden uitgevoerd, waarbij deelnemers af en toe onverwacht worden geconfronteerd met een *stopsignaal* dat aangeeft dat de reeds in gang gezette reactie op de primaire taak moet worden ingehouden. Omdat bij een ingehouden respons vanzelfsprekend geen gedrag manifest is, wordt de snelheid van het stopproces berekend op basis van andere maten, zoals de reactiesnelheid op de primaire taak en het succes waarmee wordt gestopt tijdens stoptrials. Dit resulteert in de *stopsignaal reactietijd* of *SSRT*, een maat voor de duur van het stopproces. Cafeïne had een algemeen prestatieverbeterend effect, wat tot uiting kwam in snellere reacties, maar tegelijk was er geen effect van cafeïne op de SSRT zichtbaar.

Gezamenlijk laten de bevindingen van deze studie dus zien dat responsinhibitie, in tegenstelling tot taakswitchen, niet erg gevoelig is voor cafeïne.

Conclusies en Discussie

De bevindingen in dit proefschrift suggereren dat bepaalde aspecten van cognitieve controle met cafeïne kunnen worden versterkt of verbeterd. Uit de resultaten blijkt dat dit voornamelijk het geval is voor action monitoring, een aspect van evaluatieve controle, en taakswitchen (vooral anticipatieprocessen), dat een beroep doet op executieve controlemechanismen. Daarentegen is responsinhibitie veel minder gevoelig voor cafeïne. Dit duidt erop dat, van de executieve controle processen, cafeïne met name de anticipatieprocessen en meer bijzonder het vasthouden van doelstellingen in het werkgeheugen (zoals bij taakswitchen) beïnvloedt, terwijl stimulusgedreven, conflictgerelateerde processen (zoals bij responsinhibitie) minder gevoelig zijn voor cafeïne.

Overigens hebben energetische factoren, zoals mentale inspanning of *effort*, mogelijk ook een rol gespeeld bij de totstandkoming van de effecten van cafeïne. Zo is het waarschijnlijk dat deelnemers als gevolg van cafeïne een grotere mentale inspanning wilden of konden leveren tijdens het voorbereiden op een taakswitch, wat kan hebben geresulteerd in de gevonden switchafhankelijke effecten van cafeïne. Hier was het onderzoek in het huidige proefschrift echter niet specifiek op gericht; om deze reden is dit niet verder onderzocht.

Een punt van aandacht in al onze onderzoeken betreft cafeïneontwenning. Sommige onderzoekers menen dat de onthouding van cafeïnehoudende producten leidt tot een prestatieverslechtering in placebocondities, en dat dit ten grondslag ligt aan eventuele verschillen tussen placebo- en cafeïnecondities (in plaats van een prestatieverbetering als gevolg van cafeïne). Toch is de empirische evidentie voor deze *'relief from withdrawal'* hypothese niet erg overtuigend. Zo zijn cafeïne gerelateerde prestatieverbeteringen aangetoond zonder dat er een ontwenningsperiode aan vooraf ging. Ook zijn cafeïne-effecten

gevonden in cafeïnegebruikers én niet-gebruikers, terwijl cafeïneonthouding alleen in de eerstgenoemde groep een rol kon hebben gespeeld. Daarom kan worden gesteld dat cafeïne-onthoudingseffecten, die doorgaans mild van aard zijn, slechts een bescheiden bijdrage kunnen hebben geleverd aan de huidige bevindingen.

Vanuit de cognitieve neurowetenschappen wordt momenteel in hoog tempo kennis vergaard over cognitieve controleprocessen en de onderliggende neurale mechanismen. In de discussie (hoofdstuk 6) wordt een aantal neurocognitieve mechanismen gesuggereerd die aan de hier genoemde effecten van cafeïne ten grondslag zouden kunnen liggen. Zo is het zeer aannemelijk dat de neurotransmitter dopamine (DA) een hoofdrol heeft gespeeld in het tot stand brengen van de huidige effecten. Deze conclusie is gebaseerd op de veronderstelde rol van DA in de psychoactieve effecten van cafeïne en in het reguleren van cognitieve controle. De rol van andere neurotransmitter systemen (zoals noradrenaline) kan echter niet worden uitgesloten.

Het is veelvuldig aangetoond dat de (pre)frontale cortex (PFC) een belangrijke rol speelt bij cognitieve controle. Bij ratten is DA stimulatie in de PFC als gevolg van cafeïne aangetoond, en mogelijk treedt een dergelijk mechanisme ook bij mensen in werking. Ook de basale ganglia, een groep hersenstructuren die nauw samenwerkt met de frontale cortex, hebben mogelijk een rol gespeeld in de verkregen resultaten. De basale ganglia zijn betrokken bij cognitieve en motorische controle processen. Er is evidentie voor DA activititeit in de basale ganglia tijdens taakswitchen. Een aantal van deze structuren is bovendien zeer vatbaar voor de stimulerende werking van cafeïne. Dergelijke suggesties zouden in de toekomst verder kunnen worden onderzocht met behulp van o.a. neuroimaging technieken, zoals fMRI.

Menig lezer zal zich afvragen: wat zegt dit nu eigenlijk over alledaags koffiegebruik? Met andere woorden, in hoeverre kunnen de resultaten worden gegeneraliseerd naar het dagelijks leven? In dit verband dient een aantal punten onder de aandacht van de lezer te worden gebracht. Ten eerste is getracht een tamelijk homogene groep deelnemers te verkrijgen voor de experimenten (niet-rokend, 18-30 jaar, enzovoorts), wat de kans op het vinden van significante effecten van cafeïne verhoogt, maar tegelijk ten koste gaat van de generaliseerbaarheid van die resultaten naar de koffiedrinkende populatie. Ten tweede werd een hoeveelheid cafeïne die gelijk staat aan ongeveer 2 tot 5 kopjes koffie toegediend in één enkele kop koffie. Dit wijkt af van normaal koffiegebruik dat meestal in meerdere kleine hoeveelheden geschiedt. Overigens is er enige empirische evidentie dat de cognitieve effecten van een grote dosering cafeïne en meerder kleinere doseringen cafeïne vergelijkbare resultaten oplevert. Een laatste belangrijk punt is dat cafeïne, niet koffie, de kritieke factor was die werd gemanipuleerd in de studies in dit proefschrift. Cafeïne werd dus onderzocht in een context van koffie. Koffiedrinken is echter meer dan het nuttigen van cafeïne alleen. Koffie bevat vele bestanddelen waarvan de werking nog grotendeels onbekend is. Bovendien zijn het koffieritueel, inclusief de smaak en geur van koffie, de verwachtingen omtrent de effecten van koffie en het sociale aspect van koffie drinken, misschien wel net zo belangrijk als de cafeïne. Met andere woorden, wat we zien, ruiken en

proeven draagt allemaal bij aan de effecten van koffiedrinken. Hoewel in de hier besproken studies is geprobeerd om het koffierituеel zo veel mogelijk na te bootsen binnen de mogelijkheden van een laboratorium, is het overduidelijk dat deze aanpak aanzienlijk verschilde van een "normale" setting. Al deze factoren moeten in het achterhoofd worden gehouden bij het generaliseren van de huidige bevindingen naar het koffiegebruik van alledag.

De bevindingen in dit proefschrift leveren veel aanknopingspunten voor verder empirisch onderzoek. Wat zijn de effecten van lagere doseringen cafeïne (0-3 mg/kg lichaamsgewicht) op cognitieve controlemechanismen? Worden de effecten van cafeïne inderdaad veroorzaakt door dopaminerge veranderingen in de basale ganglia en PFC? Dergelijke vragen zijn vooralsnog onbeantwoord. Daarnaast zouden toekomstige studies zich kunnen richten op het verband tussen cognitieve functies en andere aspecten van koffie zoals koffiegeur en de verwachtingen omtrent koffie. Enig onderzoek hiernaar is gedaan, maar met de huidige technieken (psychofysiologisch en neuroimaging) kan veel nieuwe kennis over koffie aan het licht worden gebracht. Samenvoeging van de bevindingen van al deze studies kan uiteindelijk leiden tot gedetailleerde kennis van de invloed van koffie en cafeïne op het dagelijks functioneren.

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Jasper W., Jasper T., Niels, Dimitri, Gabor en Edwin, die ten tijde van mijn AiO-schap als student zeer waardevolle bijdragen hebben geleverd aan de experimenten. Bedankt!

Marcus, Bert, Geert-Jan en Patrick, voor de technische (en soms mentale) ondersteuning bij mijn onmogelijke experimenten.

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Els en Jan, zo goed als familie, jullie betrokkenheid en steun in de afgelopen jaren wordt zeer gewaardeerd. Evenals het gemoedelijke lunchen in Amsterdam.

Diane, bedankt voor alle gebakjes, voor het kritisch lezen van mijn stukken, en voor onze uitjes om de zinnen even te verzetten. Ik prijs me gelukkig met jou als moeder. Madame en Little One doen het zo slecht niet.

Paranimfen, Robert en Arnoud, het is zó fijn dat er wordt meegedacht en geregeld in de aanloop naar deze promotie toe (effe afpromoveren). Jullie waren er al in de Kanaalstraat, en jullie zijn er nog steeds. Dat vind ik top. *My parabitches rule!*

Arnoud, dank je dat je er voor me was, en bent. "Dús ……"

Tot slot, dank aan alle proefpersonen, die zich zo welwillend hebben opgesteld ten opzichte van cafeïnevrije koffie, dubieuze gel en *creepy caps*. En Brigitte Boits, voor het mooie omslag. Zonder koffie, brandstof voor het schrijven, was dit proefschrift er overigens niet geweest.

Appendix

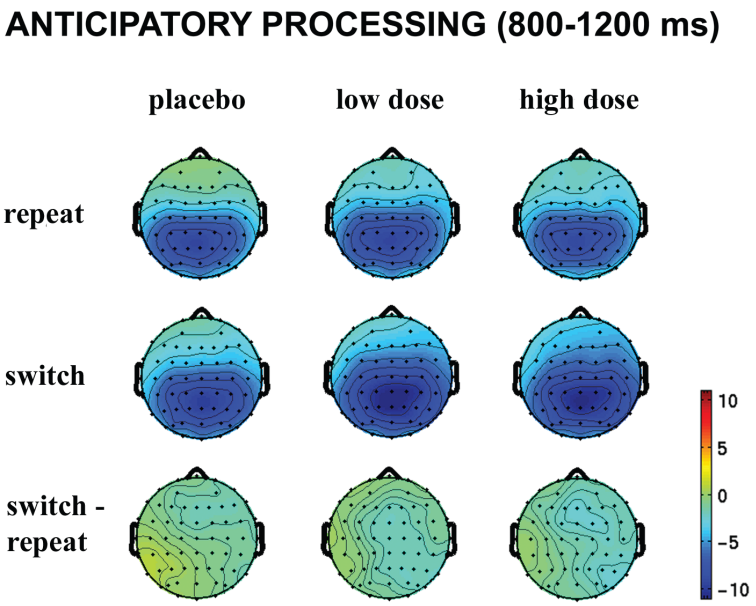

Figure 3 (Chapter 3).

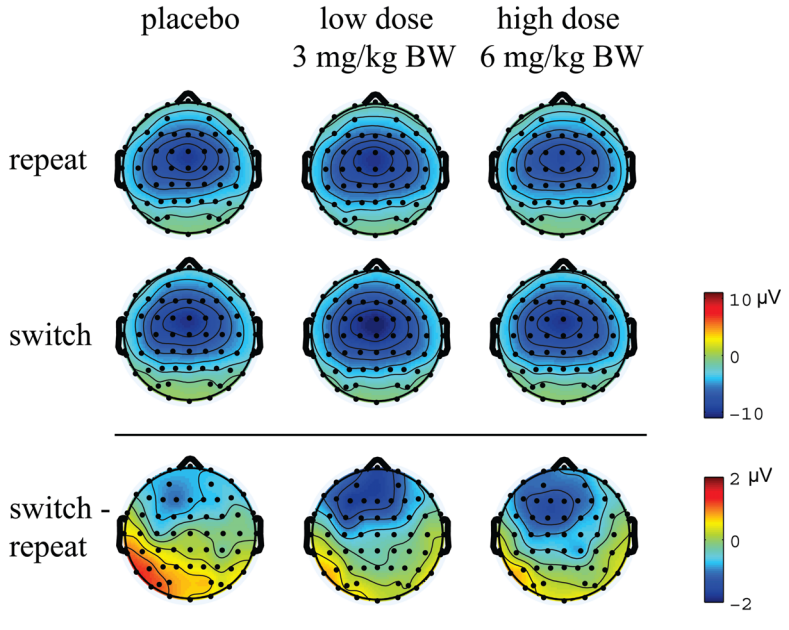

Figure 5 (Chapter 4).