Performance monitoring and decision-making: psychophysiological and developmental analyses
Crone, E.A.M.

Citation for published version (APA):
1. General introduction

1.1. Introduction

Cognitive developmental theories have provided important insight into developmental changes in children's hypothetical thought, organized strategies, and the emerging ability to introspect and self-monitor, which underlie age-related improvements in a broad range of intellectual and social behaviors. However, remarkably little is known about cognitive and neurophysiological dimensions of childhood and adolescent maturational processes. This issue, however, is an important drive for recent progress in the field of developmental science. That is, we are now starting to examine developmental changes in cognitive control functions from the perspective of cognitive neuroscience. In this thesis, we describe studies that were inspired by an understanding of neural systems contributing to the development of cognitive control and complex decision-making. This unified approach has the potential to move cognitive developmental theories toward incorporating the effects that neural system interactions have on reasoning, self-monitoring and decision-making. Additionally, this unification may lead to integrating our understanding of normal cognitive functions with disordered processes, observed, for example, in children with impulse control disorders (e.g. Attention-Deficit Hyperactivity-Disorder), and may lead to better characterizations of behavioral deficits found in disordered child populations.

This thesis will argue that the prefrontal cortex is a key brain region contributing to developmental changes in cognitive control and decision-making. The frontal lobes comprise a substantial area of the human brain, and there is evidence that these regions have reached their maximum size in humans compared to other organisms, therefore allowing for a greater complexity in intellectual abilities (Grafman, 1994). Moreover, this region of the brain is proposed to be the latest to fully develop, reaching full maturation only in adolescence (Casey et al., 1997; Dempster, 1993; Van der Molen & Ridderinkhof, 1998; Stuss, 1992).

Recently, many neuroimaging studies have investigated processes that are relevant for cognitive control functions, such as reward processing, guessing, planning, inductive reasoning and manipulating complex information in working memory. These studies emphasize the importance of the prefrontal cortex in higher cognitive processing, and also point out that this region may be fractionated according to separate subprocesses, reflected in distinct neural connectivity between prefrontal and other brain regions. The ventromedial prefrontal cortex, for example, is presumed to be involved in best-guess estimations, and emotional experience associated with gains and losses (Breitner, Aharon, Kahneman, Dale & Shizgal, 2001; Elliott, Rees & Dolan, 1999; Knutson, Westdorp, Kaiser & Hommer, 2000; Rogers, et al., 1999). Studies of humans with ventromedial brain injury and neuroimaging studies indicate that this region is highly relevant for processing many types of reward and punishment, and making rapid changes in behavior to accommodate...
to environmental change. The dorsolateral prefrontal cortex, in contrast, appears to be relevant in manipulating information on-line, considering options, and updating performance outcomes (Fletcher, Frith & Rugg, 1997; Goel & Dolan, 2000; Goldberg, Podell, Harner, Riggio & Lovell, 1994; Robin & Holyoak, 1995). Both the ventromedial and the dorsolateral prefrontal cortex are thought to have close connections with the anterior cingulate cortex, which is involved in conflict processing and outcome relevant processing (Botvinick, Nystrom, Fissell, Carter & Cohen, 1999; Carter et al., 1998).

This fractionation should not be taken to suggest that separate regions carry out functions in isolation, but rather that different areas of the prefrontal cortex appear to be engaged in separable neural systems involved in separable cognitive functions, while interacting with many other brain areas. Within this context, the goal of this thesis is to describe recent advances made in the investigation of developmental changes in subprocesses that rely on the ventromedial prefrontal cortex and the dorsolateral prefrontal cortex. The anatomical segregation between ventromedial and dorsolateral will serve as a reference point for the remainder of this thesis, and will be particularly relevant to the description of developmental patterns in functions such as decision-making, switching attention, and updating performance outcomes.

Before we turn to the introduction of chapters that are most pertinent to these questions, we describe models in the developmental literature that suggest a close relationship between cognitive development and prefrontal brain maturation (section 2). On the basis of these models, it can be concluded that taking into account the different subregions of the prefrontal cortex can potentially specify the general predictions that are derived from the existing literature. For this purpose, we first present a section about the anatomical segregation of separate regions of the prefrontal cortex (section 3). This section covers the regional distinction between ventromedial, dorsolateral, and connection structures. The next section will discuss the functional specificity of these regions on the basis of patient and neuroimaging studies, and describes the interaction between associated brain regions (section 4). In the fifth section, we will present support for the assumption that children activate similar prefrontal regions as adults, providing evidence for the hypothesis that neurological development is mirrored in cognitive performance changes (section 5). This section is followed by an outline of the chapters that are presented in this thesis, which will focus on differential development of functions controlled by the ventromedial and dorsolateral prefrontal areas (section 6).

1.2. Prefrontal maturation
The past quarter century has produced great improvements in the ability to study behavior and cognition even in the youngest children. This progress has been important for understanding both normal development and relevant clinical variations. Though much of the nervous system develops prior to birth, a long period of postnatal development is needed to complete the basic formation of the brain, and significant maturation continues throughout childhood and after adolescence. Concurrent with this brain maturation, children increasingly gain control of their behavior, so that they can exercise a degree of control over their emotions, thoughts and actions (Posner & DiGirolamo, 2000).
1.2.1. The growing human brain

Studies of structural and physiological development of the human brain show a protracted maturation, which spans at least 10 to 15 years (Stuss & Benson, 1986; Van der Molen & Ridderinkhof, 1998). From this perspective, it is important that cortical maturation is complete relatively fast for primary motor and sensory areas, but much slower for secondary and associate regions, including the prefrontal cortex. Although the laminar structure of the prefrontal regions is virtually complete even in the newborn child, the degree of myelination in the prefrontal cortex increases gradually during early and middle childhood (Jernigan, Traumer, Hesselink & Tallal, 1991; Pfefferbaum et al. 1994; Rakic, Bourgeois, Eckenhoff, Zecevic & Goldman-Rakic, 1986; Yakovlev & Lecours 1967). Myelination acts as an insulator to increase neural impulse transmission and plays an important role in formative and regressive changes that take place during the postnatal period. Interestingly, synaptic density in the prefrontal cortex (in layer III of the middle frontal gyrus) peaks by the first year, after which there is a steady elimination of synapses that asymptotes in mid-adolescence (Huttenlocher, 1990). Association areas in frontal, temporal, and parietal regions do not reach mature myelination until the third decade of life (Yakovlev & Lecours, 1967). Myelination has been taken as a possible index for regional brain development, and changes in these neural systems during development could impose important constraints on the development of cognitive abilities (e.g., Case, 1985). Normal development is also associated with changes in a variety of neurotransmitter systems (important for inter-neural communication) that project to the prefrontal cortex; although developmental change in dopaminergic function seems to be the best documented (Diamond, 1996). Dopamine has widespread connections from the midbrain to the limbic system and cerebral cortex—most densely to the prefrontal cortex. The dopaminergic neurotransmitters are largely engaged in the activation of behavior, especially planning and switching between response sets. Beside the level of myelination, the developmental status of the neurotransmitter systems may also impose important constraints on cognitive abilities during development.

1.2.2. Models of prefrontal development

Current theories of development of executive function and brain maturation include those by Dempster (1992; 1993) and Stuss (1992). Dempster (1992; 1993) proposed a theoretical framework assuming a synthesis between developmental research suggesting changes in interference suppression and neuropsychological research indicating that the frontal lobes are critically involved in interference-sensitive tasks. His assumptions were based on the extensive evidence that the frontal lobes are involved in interference suppression (Fuster, 1997), and the difficulties that prefrontal patients experience with interference tasks (e.g., Milner, 1963). Given these relations, Dempster concluded that developmental changes in Piagetian A-not-B tasks (Diamond, 1990) and the Wisconsin Card Sorting Task (Chelune & Bear, 1986) can be ascribed to slow frontal lobe development. Importantly, Dempster argued that inhibition and interference suppression could best be conceptualized in terms of a family of processes. Thus, inhibition may have a variety of operating characteristics that may vary on temporal (proactive, retroactive), formal (motoric, perceptual), and spatial (internal, external) dimensions. These varieties of inhibition were presumed to have
different developmental trajectories, thereby producing a stage-like quality to the child's sensitivity to interference. The different stages of interference sensitivity (e.g., motoric interference, perceptual interference) were all presumed to reflect a common underlying mechanism subserved by the frontal lobes.

Stuss (1992) conceptualized the relation between biological maturation of the frontal lobes and the development of executive cognitive functions in terms of increased efficiency of the supervisory attention system (Norman & Shallice, 1986). The model initially proposed by Norman and Shallice assumes that a supervisory system is invoked whenever the need arises for top-down activation of relevant processing structures and inhibition of inappropriate thought and actions. Under most situations, thought and actions are selected automatically by a 'contention scheduling' system. This system controls the competition of lateral inhibition mechanisms at the lower level of a hierarchy. These routine programs are referred to as 'schemas', which link percepts and thought to actions. Schemas are well learned, and even when complex, they are still standard and routine. However, in case 1) a decision or planning is required, 2) an error needs to be corrected, 3) a novel situation is encountered, 4) a difficult situation arises, or 5) a previously learned response must be overcome, the supervisory system is activated, which functions by top-down activation or inhibition of schemas.

The hierarchical model proposed by Stuss (1992) consists of three processing levels, a sensory-perceptual level, a level for executive control, and a level for self-reflectiveness. These levels are interconnected by feedback and feed-forward loops which allow monitoring and presetting behavior. At the lowest level (sensory perceptual level), operations are routinized and provide a basis for ongoing behavior, selected by the contention scheduling mechanism. Even young children can function well in situations in which particular stimulus inputs trigger specific and appropriate behavioral outputs in a more or less automatic way. At the second level (executive control), ongoing activity at the lowest level is adjusted, allowing conscious direction of the lower level modules towards a selected goal. The highest level (self-reflectiveness), controls all levels including its own. Three main regions anatomically represent these levels: the posterior brain structures (sensory-perceptual modules), the reciprocal connections between multimodal brain structures and the frontal cortex (executive control), and the prefrontal cortex (self-reflectiveness). Stuss (1992) concluded on the basis of a review of pertinent literature that brain maturation research is consistent with a hierarchical model, with the tertiary association areas including the prefrontal cortex maturing last. For example, the control of motor responses improves considerably during early childhood. In contrast, the performance on selective attention tasks matures much later during childhood (Passler, Isaac & Hynd, 1985). Studies examining the development of executive abilities (Welsh & Pennington, 1988, see also Archibald & Kerns, 1999; Luciana & Nelson, 1998; Welsh, Penningston & Goisser, 1991; Zelazo, Fry & Rapus, 1996) show that complex planning and verbal fluency do not reach adult levels until adolescence. Thus, Stuss’ (1992) analysis reveals an interesting parallel between brain maturation and cognitive development with a special focus on the relation with the prefrontal cortex.

To summarize, the two models that have been proposed to describe the relation between cognitive development and brain maturation (Dempster, 1993; Stuss, 1992) share
a common theme. That is, the prefrontal cortex, with the participation of other brain regions in widely distributed circuits, is presumed to subserve many aspects of higher-order cognitive function in which there is robust developmental change during childhood and adolescence. These functions may include working memory, voluntary inhibition of context-inappropriate behavior, and the development of preparatory sets for anticipated action (Goldman-Rakic 1990; Fuster 1997). All of these functions require that cognitive processes be held online to allow for the appropriate binding of environmental cues and behavioral responses over time so that behavior is properly timed and adaptive to specific environmental contexts (Luna & Sweeney, 2001). It is further presumed that measuring functions such as planning, inhibition, and flexibility in children, provides a window on neurological function, specifically the development of the frontal cortex.

One difficulty with the models of Dempster (1993) and Stuss (1992) is that the multistage development of various cognitive functions is ascribed to the frontal lobes in general. Recent evidence suggests, however, that there may be large differences between maturation of different subregions of the frontal lobes. Van der Molen (2000) made an initial attempt to describe functional differences in inhibitory control using a decomposition method of the supervisory attention system (Stuss et al., 1995). Using a psychophysiological analysis, Van der Molen (2000) has successfully applied this model to the study of development of inhibitory control, suggesting that different functions (and possibly regions) of the prefrontal cortex have different developmental trajectories. One of the assumptions of the model proposed by Stuss et al. (1995) is that the supervisory control system cannot be understood in terms of a single, molar process. Rather, the supervisory system includes at least five distinct processes: energizing schemas, inhibiting schemas, monitoring the activity level of schemas, adjusting contention scheduling, and controlling 'if-then' logical processes. Importantly, Stuss et al. (1995) suggest that each of these component processes involved in carrying out attention-demanding tasks is realized by distinct cerebral mechanisms of the prefrontal cortex. For example, patients with dorsolateral lesions are impaired on the Stroop task, whereas patients with orbitofrontal patients are unimpaired. In contrast, patients with orbitofrontal lesions may show poor inhibition of impulses. Damage to the medial parts of the orbitofrontal regions may lead to the inability to maintain normal social constraints on behavior.

The functional specificity of the dorsolateral and medial orbitofrontal cortices is emerging as an important avenue of research in cognitive neuroscience. This distinction is important because it is presumed to reflect the dissociation between cognitive and emotional aspects of self-regulation. More specifically, the functional differentiation between the dorsal and ventral anatomical pathways is presumed to result from dual origins of the frontal cortex in the archicortical and paleocortical divisions of the paralimbic cortex (e.g., Fuster, 1997; Tucker, Luu & Pribram, 1995).

This thesis aims to explore the cognitive control functions that accompany maturational changes in these subregions of the prefrontal cortex. Before we turn to the introduction of chapters that will focus on this issue, we review the regions and functions of the prefrontal cortex in human adults. The review of adult prefrontal functions will serve as a reference point for the study of developmental changes in prefrontal function.
1.3. Regions of the prefrontal cortex and critical connecting structures

1.3.1. Regions of the frontal lobes
The frontal lobes are separated from the parietal lobe by the central sulcus posteriorly, and from the temporal lobe by the sylvian fissure inferiorly (Fuster, 1989). Within the frontal lobes, three main subregions are defined: 1) the motor cortex, which involves most of the precentral gyrus and is positioned anterior to the central sulcus and posterior to the premotor sulcus, 2) the premotor cortex, which is the remaining area of the precentral gyrus, the posterior third of the superior and middle frontal gyri, and 3) the prefrontal region, which involves the remaining area of the frontal lobes. The latter has been found to be especially important for higher cognitive control processes, and is subdivided into several functionally distinct subregions.

The ventromedial prefrontal cortex can best be described as the area that includes both the gyrus rectus and the mesial half of the orbital gyri, as well as the inferior half of the medial prefrontal surface, from its most caudal part to its most rostral part in the frontal pole (Bechara, Tranel & Damasio, 2000). Areas 11, 12, 13, 25, 32, and 10 of Brodmann are included in this sector, as is the white matter subjacent to all these areas. The term orbitofrontal cortex is also widely used, and there is some debate in the literature whether these areas are essentially the same, or if there are subtle distinctions between these areas (Bechara, et al., 2000; Rolls, 1996; 2000). The term orbitofrontal seems to be somewhat broader, because this term applies to the majority of the underside of the prefrontal cortex. The ventromedial prefrontal area applies only to the innermost medial areas of the ventral frontal area, and this distinction may be important, given that recent neuroimaging studies emphasize that the ventromedial area can be separated both regionally and functionally from the ventrolateral area of the prefrontal cortex (Elliott, Dolan & Frith, 2000).

The dorsolateral prefrontal cortex involves the upper and side regions of the frontal lobes, and is comprised of Brodmann's areas 9, which occupies the dorsal region of the lateral prefrontal cortex and extends medially to the paracingulate, and Brodmann 46, which is located at the anterior end of the middle frontal sulcus (Pandya & Yeterian, 1995).

There are three other regions within the prefrontal cortex that may be important for communication with ventromedial and dorsolateral areas. First, the frontopolar prefrontal cortex comprises Brodmann area 10, and is situated above the ventromedial prefrontal cortex and inferior to area 9 and anterior to area 46. Given its junction point between the ventromedial and dorsolateral regions, this area may act as a boundary between these regions, but to date it remains unclear whether the frontopolar cortex has unitary functions of whether it is a heterogeneous area that is comprised of extensions between parts of other frontal regions (but see Christoff & Gabrieli, 2000; Strange, Henson, Friston & Dolan, 2001; for possible functional specificity of frontopolar cortex). Second, the ventrolateral prefrontal cortex occupies Brodmann area 11 and is positioned behind the frontopolar prefrontal cortex. Finally, the anterior cingulate cortex is positioned medially, overlying the corpus callosum.

1.3.2. Important connecting structures
Two additional areas outside the prefrontal cortex seem particularly relevant for its con-
nections with the ventromedial and dorsolateral prefrontal cortex; these are the basal ganglia and the amygdala. The basal ganglia are comprised of the global pallidus, the subthalamic nucleus, and the substantial nigra, and these components are generally involved in the control and execution of motor movement and motor learning, as well as implicit memory (Knowlton, Mangels & Squire, 1997). These structures contain numerous interconnections and are highly connected with the prefrontal regions. Input from the prefrontal regions (and other regions) initially reaches the striatum, which is comprised of the caudate and the putamen. These subregions then project to the global pallidus, which then projects to the midbrain tegmentum, thalamus, and substantia nigra. Some of the thalamic inputs are relayed back to the prefrontal regions, completing a ‘thalamo-cortical loop’ (Cummings, 1995). The subcortical loops which involve the prefrontal cortex and basal ganglia are involved in emotion processing, motivation, and mediating executive control, and are associated with both ventromedial-subcortical circuits as well as dorsolateral prefrontal-subcortical circuits (Cummings, 1995). A second area known for its intimate connections with the prefrontal cortex is the amygdala, which is located subcortically at the anterior end of the temporal lobe. This area is densely connected and receives highly processed visual and auditory information, from several locations in the brain (Rolls, 1999). The amygdala is mostly involved in ventromedial-subcortical connections (Cummings, 1995), and has direct projections to the frontal lobe involved in relaying limbic inputs to these regions.

1.4. Functions of the ventromedial and the dorsolateral prefrontal cortex

The prefrontal cortex is presumed to be the key brain area in many aspects of higher cognitive processing. Evidence for this claim comes in large part from an extensive neurological history of disordered behavior in patients with sustained damage to the prefrontal regions, dating back from the famous case of Phineas Gage. In the following sections, we will present neurological as well as neuroimaging evidence for the functional specificity of ventromedial and dorsolateral prefrontal cortices.

1.4.1. Phineas Gage

Gage was foreman of the construction crew that, in the late summer of 1848, had the responsibility of setting dynamite charges for building a railroad extension. A disastrous accident resulted in Gage being struck by an iron rod, which went through Gage’s skull and brain. Removing the iron rod resulted in two large holes, one where his left cheek had been, and the other from an opening in the top of his head. Nonetheless, Gage lived and had never even lost conscious. Within two months the wounds were healed and Gage was declared cured. Unfortunately, it became apparent that although Gage’s acute effects had subsided, the ‘cure’ was only superficial because his personality had undergone a radical transformation. Previously a hard working, exemplary citizen, Gage had become impatient and rude, and could not follow any coherent plan or action. Friends and family complained that, ‘Gage was no longer Gage’. After Gage’s death 13 years later, his skull and the iron rod were placed in the museum of the Harvard Medical School. Hanna Damasio and colleagues (1994) recently used a modern brain imaging technique to reconstruct Gage’s lesions, and found that the rod had past through the frontal cortex but spared the pre-
motor cortices, accounting for the absence of Gage's motor problems. However, the iron had destroyed the ventromedial parts and the most anterior portions of the prefrontal cortex, in both the left and right hemispheres.

Similar to Gage's case, patients with damage to the prefrontal cortex do not directly show impairment in much of their everyday behavior. Their speech is coherent and they have no difficulties in perceptual abilities. On conventional tests of intelligence these patients also perform normally. Despite these abilities, however, a prominent feature of frontal lobe damage is the inability to carry this intact knowledge into action in day-to-day activities. With more sensitive tests and recent neuroimaging findings, it becomes clear that the frontal lobes have a pronounced role in normal cognition.

1.4.2. Functions of the ventromedial prefrontal cortex

1.4.2.1. Damasio's Somatic Marker Hypothesis

The somatic marker hypothesis of Damasio (1994) was developed to specifically explain the behavior of patients with damage to the ventromedial prefrontal region. Such patients, resembling Gage, have relatively intact intellectual functions, but suffer from poor daily-life decision-making. Emotions play a critical role within this theory, which are defined as 'somatic states', referring to 'the musculoskeletal, visceral, and internal milieu components of the soma' (p.1414, Damasio, 1996). The somatic marker hypothesis suggests that the ventromedial prefrontal cortex plays a critical role in forming relations between somatic responses associated with previously learned outcomes of situations and the reinstatement of these somatic states when a resembling decision has to be made. These associations hold the potential to reactivate an emotion by acting on the appropriate cortical or sub-cortical structures and become highly relevant in situations where future outcomes cannot be easily predicted on the basis of logical cost-benefit comparisons. Given a certain situation, the ventromedial prefrontal cortex establishes a simple linkage between the aspects of the situation and the disposition for the type of emotion that in the past has been associated with the situation. The somatic markers normally help constrain the decision-making space by making that space manageable for logic-based cost-benefit analyses. Such constraints help an individual to decide efficiently in situations in which there is uncertainty about future outcomes. However, in the absence of somatic markers, options and outcomes become virtually equalized and the process of choosing will depend entirely on logic operations over many option-outcome pairs. This strategy is slow and may fail to take into account previous experience, and is often seen in ventromedial patients, who tend to engage in random and impulsive decision-making.

Damasio's theory is motivated by the fact that the frontal lobes, particularly the ventromedial region, are strongly interconnected with limbic structures tied to emotions. These are the pathways through which somatic markers mediate decisions. The hippocampus and amygdala have been linked to memory information. The hippocampus is a general-purpose device for forming associations between stimuli. The amygdala has a narrower memory function. This structure is not essential for forming associations, but provides emotional associations. The connections between these limbic and frontal systems activate somatic markers, through their connections with the somatosensory cortices.
Laboratory tasks examining ventromedial functions along with its interconnections with limbic structures have focused particularly on emotional processing and decision-making. Damasio and colleagues examined these functions in patients with damage to ventromedial regions of the brain as well as control participants, thereby attempting to unravel the specificity of ventromedial regions in these functions. The first task was used to test emotional responses of patients to arousing stimuli. The second, more recent, task is a gambling task developed by Bechara and colleagues, and was used to test real-life decision-making. These researchers utilized the skin conductance response (SCR), a common autonomic response measure. The mechanism generating a skin conductance response is presumed to be intact in patients with ventromedial frontal lobe damage (they display a normal startle response to a loud sound, for example), but they seem to fail to generate a normal SCR to emotionally arousing stimuli or when risky decisions are made.

1.4.2.2. Emotional processing
Traditionally, emotional processing has been examined in a task in which pictures of emotionally arousing stimuli are presented (Gazzaniga, Ivry & Mangun, 1998), and this task may prove especially useful for examining emotional processing in patients with ventromedial damage. Damasio, Tranel and Damasio (1990) examined electrodermal responding in control participants and in patients with bilateral lesions to orbital and lower medial frontal regions, while they were paying attention to negative emotionally arousing pictures (social disasters, mutilation) and neutral control pictures. The participants were either required to passively view the picture (passive condition) or to give a verbal response to the picture (active condition). Damasio and colleagues found that in the active condition, both the patients and the control participants produced SCR when responding to the socially arousing pictures. In the passive condition however, patients failed to produce the normal discriminatory SCRs to target pictures. Damasio and colleagues concluded that the defect in SCR is probably a correlate of the failure to experience a somatic state in response to social situations. Tranel and Damasio (1994) found that, besides ventromedial prefrontal regions, the amygdala also plays a major role in the central mediation of autonomic responses in emotional behavior (Tranel & Damasio, 1987; Tranel & Damasio, 1994). For example, damage to the human amygdala leads to impairments in recognition of facial expression (Adolphs, Tranel, Damasio & Damasio, 1995; Adolphs, Tranel & Damasio, 1998; Adolphs et al., 1999). This may indicate that the human amygdala triggers socially and emotionally relevant information in response to visual stimuli. More specifically, the amygdala is seen as a component of a neural system specialized for triggering physiological states related to stimuli that signal threat or danger. Such physiological states involve both specific sets of behavioral responses and the retrieval of related knowledge.

1.4.2.3. Real-Life Decision-Making: Bechara’s Card Gambling Task
Although laboratory tasks related to emotional processing were relatively easy to apply, decision-making in real life is less applicable for laboratory tasks. This function appears to be compromised, however, based on neurological reports, in patients with ventromedial frontal damage. Bechara, Damasio, Damasio, and Anderson (1994) designed the first neuropsychological test that simulates, in real time, real-life decision-making that incorpora-
tes uncertainty of outcomes, as well as reward and punishment. They hypothesized that patients with ventromedial prefrontal damage would not perform well on this task, because they are insensitive to future outcomes. During the experiment, the participants sit in front of four decks of cards equal in appearance and size, and are given $2000 loan for play money. They are told that the game requires a series of card selections, and the goal of the task is to maximize profit. The participant is free to switch decks anytime as wishes, but is not told in advance how many card selections must be made (100 selections). After turning card A or B the participant receives $100. After turning card C or D the participant receives $50. However after turning some cards from a given deck, the participant receives money, but is also asked to pay a penalty. The ultimate yield of each deck varies, because the penalty amounts are higher in the higher paying decks A and B, and lower in the low-paying decks C and D. Decks A and B are equivalent in overall net loss of trials, but in deck A the punishment is more frequent and of smaller magnitude relative to deck B. Decks C and D are also equivalent in overall net loss, however, in deck C the punishment in more frequent and of a smaller magnitude than the punishment in deck D. More importantly, decks A and B are disadvantageous in the long run, because they cost the most, whereas decks C and D are advantageous in the long run because they result in an overall gain of money. Bechara et al. found that all participants start choosing from all decks. Normal controls eventually make more selections from the good decks C and D, and start avoiding the bad decks A and B. Patients with ventromedial frontal lobe damage however, select fewer from the good decks C and D, and choose more from the bad decks (A and B). The researchers considered three explanations for this finding. (1) Possibly patients with ventromedial prefrontal damage are so sensitive to reward, that the prospect of future punishment is outweighed by that of immediate gain. (2) Possibly these patients are insensitive to punishment, and thus the prospect of reward always prevails. The last explanation was that (3) these patients could be generally insensitive to future consequences, positive or negative, and thus their behavior is always guided by immediate prospects, whatever they may be. This issue was addressed in a follow-up experiment, in which the schedules of reward and punishment were reversed (Bechara, Tranel & Damasio, 2000). In this task punishment was placed upfront and unpredictable reward schedules were used as an unexpected variable. The patients in this task were more influenced by immediate punishment than by delayed reward. This left the researchers to conclude that patients with ventral medial frontal lobe damage are unresponsive to future consequences, whatever they are, and thus are more controlled by immediate prospects.

In a follow-up experiment, Bechara and colleagues (Bechara, Tranel, Damasio & Damasio, 1996; Bechara, Damasio, Tranel & Damasio, 1997) used autonomic activity during the card gambling task as an index of somatic marker activity. The researchers were specifically interested in the following questions. They argued that patients with ventromedial prefrontal damage can access knowledge necessary to conjure up options and actions and scenarios of future outcomes, like normal controls, but their defect seems to be at the stage in the reasoning process at which they must act on such knowledge. Bechara et al. considered several explanations for this defect. Possibly, defects in basic processes such as attention and temporal integration preclude effective utilization of knowledge representation required for effective reasoning. Another possibility is that these knowled-
arge representations can be evoked but are unstable (for example not held in working memory long enough for reason strategies to be applied). The third possibility they considered was that the representations of future outcomes would be properly attended, temporally integrated, and held in working memory, but they would not be marked with negative or positive value. This possibility invokes the somatic marker theory. A final possibility they considered combined features of the previous ones: perhaps somatic markers would not help drive and maintain attention and working memory, and also would fail to mark and bias the representation of certain outcomes.

With a card gambling task combined with autonomic measures, the researchers aimed to distinguish among these accounts. They hypothesized that if somatic state activation is necessary for the distinction between good and bad choices then participants performing the gambling task should show evidence of such activation when they attempt to choose between the good and bad cards. The card gambling task was a similar version of the task described in the previous study of Bechara et al. (1994). The SCR generated during the task was divided into three categories: (1) reward SCR (those generated after turning cards for which there was a reward and no penalty), (2) punishment SCR (those generated after turning a card for which there was a reward followed by immediate penalty), (3) anticipatory SCR (generated prior to turning a card from any given deck, during the time the participant pondered from which deck to choose).

Bechara et al. found that both patients and control participants generated SCR in reaction to reward and punishment. However as controls became experienced with the task, they began to generate an anticipatory SCR prior to the selection of disadvantageous cards. Interestingly, control participants started showing autonomic responsiveness before being consciously aware what the most advantageous strategy was (Bechara et al., 1997). Patients with ventromedial damage, however, failed to generate this anticipatory SCR. The conclusion was that the absence of anticipatory SCR in patients is an indication that these patients were unable to change somatic states in response to imagined scenario. The failure to enact a somatic state appropriate to the consequences of a response is a correlate of their inability to choose advantageously. The somatic markers are proposed to assist decision-making in that they help inhibit normal tendencies to approach immediate reward and enhance and hold representations of future negative scenarios in working memory. The somatic marker related to the representation of future negative scenarios operates as an alarm signal, that signals that an option that causes immediate gain but future loss would be best avoided. Patients with ventromedial frontal damage fail to generate anticipatory SCR because they are supposed to have lost the critical system, which normally connects knowledge about categorization of previous experiences to different profiles of biological response including those that are part of an emotional response. Furthermore, this critical system has the ability to inhibit or activate the response appropriate to a given situation, by activating central bioregulatory structures such as the amygdala and the hypothalamus. This activity could be dissociated from the impairments in working memory as seen in patients with dorsolateral prefrontal damage (Bechara, Damasio, Tranel & Anderson, 1998), suggesting that working memory is not dependent on intact decision-making. On the other hand, decision-making seemed to be somewhat influenced by the impaired working memory.
The performance pattern of ventromedial prefrontal patients could also be distinguished from amygdala patients. Although both groups performed disadvantageously and showed no significant difference in amplitude between anticipatory SCR from good and bad decks, control participants and ventromedial patients generated reward and punishment SCRs in the normal range. In contrast, all amygdala patients were impaired severely in the generation of either reward or punishment SCRs, although these same patients were able to generate SCRs in response to a loud sound (see also Tranel & Damasio, 1989). This finding suggests that amygdala and ventromedial damage exert distinct effects on the ability to generate SCRs after reward or punishment is received. Bechara et al. suggest that the mechanism underlying decision-making impairment associated with ventromedial damage is more complex than that of the amygdala. After somatic states of reward and punishment are evoked with individual cards, each deck becomes associated with numerous and conflicting states of reward and punishment. The role of the ventromedial cortex comes into play when participants sort out this conflict and decide whether to seek or avoid a given deck. The poor decision-making associated with ventromedial damage is related to an inability to integrate effectively all of the somatic state information triggered by the amygdala as well as other somatic effectors such as the hypothalamus and brain stem nuclei. The ventromedial prefrontal cortex has indeed extensive bi-directional connections with the amygdala. The amygdala activity reconstitutes a somatic state that integrates numerous conflicting instances of reward and punishment encountered by individual card draws from that deck. If, in the end, the negative somatic states outweigh the positive ones, an overall negative state is enacted and is indexed by the anticipatory SCR that is observed before the selection of cards from the disadvantageous decks.

1.4.2.4. Testing the Somatic Marker Hypothesis in real-life situations

Several other studies examined real-life decision-making in prefrontal patients from a related perspective. Goel, Grafman, Tajik, Gana, and Danto (1997) argued that personal real-life decision-making, supposedly impaired in patients with ventromedial damage, is poorly measured with existing laboratory tasks and designed a task in a similar spirit as Bechara's card gambling task. Patients with prefrontal damage were asked to help a young couple balance their budget. The household domain was chosen because it is a real life domain, provides good examples of planning, and requires knowledge of the world. The financial information was such that participants were required to manipulate income and expenses, and restructure assets and liabilities to achieve the required goals. Video fragments were coded by specific coding categories. Satisfaction of the goals required the discovery and manipulation of three solution factors: decreasing expenses, increasing income and restructuring assets and liabilities. Control participants were more successful than patients in utilizing these strategies. Normal participants were found to structure the problem space relatively quickly and then spend the majority of their time solving the problem. Patients with frontal lobe damage, on the other hand, took much longer structuring and less time problem solving. According to the authors, this is indicative that these patients have certain difficulties with real-world planning problems. Likewise, Channon and Crawford (1999) examined everyday problem solving in patients with anterior and posterior brain damage. They assessed multiple aspects of problem solving in these
patients and examined the relationships between performance on the problem-solving test and performance on more abstract neurological tests of executive functions. It was hypothesized that lesions involving frontal lobes (anterior patients) would produce greater impairment than lesions not involving the frontal lobes (posterior patients). The test consisted of a series of brief videotapes and stories of an everyday awkward situation, intended to assess the individual’s ability to generate possible solutions and solve them in socially appropriate ways. Dependent measures were fluency, optimal generated solution, and personal generated solution. As predicted, patients with anterior lesions showed more extensive impairment in problem solving than patients with posterior lesions.

In an attempt to test Damasio’s somatic marker hypothesis in a normal population, Batson, Engel and Fridell (1999) recently studied reliance on somatic markers in college students who listened to two audiotapes, each introducing a value being considered as the theme for a new campus-wide campaign. The first tape concerned freedom, the second equality. The value in question was being threatened or violated. Participants received false physiological feedback while listening to the tape. In the low-arousal condition, participants received feedback indicating moderate arousal to the freedom and low arousal to the equality tape. Those in the high-arousal condition received feedback indicating moderate arousal to the freedom tape and high arousal to the equality tape. Damasio’s model suggests that there are distinct cognitive and emotional routes utilized in making value judgments; the cognitive route is most likely to be followed when recalling and expressing beliefs about values, whereas the emotional route is likely to be followed when making concrete value-relevant decisions. Participants in the high-arousal condition were expected to express more preference for equality relative to freedom as a theme than were participants in the low-arousal condition. False feedback appeared on the GSR monitor in front of the participant. This feedback was used to manipulate perceptions of physiological arousal while hearing these value threatening situations. Batson et al. found that participants presented with false GSR feedback while listening to a specific theme showed preferences for these themes. For example, when participants saw high amplitude GSR responses while listening to the equality tape (and assumed that they were generating these GSR responses themselves), they showed preference for the equality theme. According to the authors this finding supports Damasio’s claim that normal individuals can and do rely on perceived somatic makers to guide value-related decisions.

1.4.2.5. Critics of the Somatic Marker Hypothesis

Criticism of the somatic marker hypothesis suggests that somatic marker activity may be overly elaborate in explaining results. For example, Rolls (1999) suggested that the lack of forming appropriate stimulus-response associations, an orbitofrontal function at a simpler level, without re-invoking somatic states, may be sufficient to explain reversal learning difficulties as seen in the card gambling task. Rolls suggested that emotions are responses that occur simply as a result of reward and punishment, and the hypothesis that a bodily signal is sent to somatosensory cortex causing emotional biasing does not fit this interpretation. Following Rolls, in the case of decision-making, the orbitofrontal cortex and amygdala are directly involved in experiencing emotion as a reaction, rather than anticipation to stimuli, and these systems are connected with the basal ganglia for invoking a response.
The somatic marker hypothesis is also criticized for being inefficient, because somatic markers would require a large amount of interpretation by the brain in order to resolve potentially great amounts of somatic input. It is not yet clear if a simpler association deficit in ventromedial/orbitofrontal cortex would yield the same result as a lack of somatic marker. Following Rolls’ position, it remains unclear what the lack of anticipatory autonomic activity prior to bad deck selection indicates. Besides these differences, the theories share many similarities, and Rolls’ interpretation may be well explained by Damasio’s as-if body loop. This system describes re-activation of emotional signals in which the body is bypassed; instead, the signals are directly conveyed to the somatosensory structures, which then adopt the appropriate pattern. The somatic marker theory predicts that from evolutionary and ontogenetic perspective, the body loop is the original mechanism, but has been superseded by the as-if body loop and is possibly used less frequently. In any case, the results of either body-loop or as-if body-loop are simultaneously evoked and displayed by facts pertinent to the situation.

In line with the studies performed by Rolls (1996; 1999; 2000), a related line of research focused on the broader orbitofrontal regions, and showed that this region is critically involved in reward processing. For example, cell recordings in non-human primates have been valuable for understanding the functions of the prefrontal cortex, and these studies typically reveal that the orbitofrontal cortex is involved in motivational behavior, affect and reward processing (Cavada, Company, Tejedor, Cruz-Rizzolo & Reinoso-Suarez, 2000; Hikosaka & Watanabe, 2000). Similarly, following damage to the orbitofrontal cortex, animals have been shown to have difficulties with reward related tasks for primary reinforcers (such as taste and olfaction) (Rolls, 1999). The orbitofrontal cortex has also been shown to be critical in some types of learning, as damage to this region severely disrupts performance on associative tasks (Butter, 1969; Rolls, 2000), suggesting that this area provides essential representations necessary to form stimulus-reward associations. Importantly, Dias, Robbins, and Roberts (1996) found that performance of reward reversal learning was impaired in monkeys that received orbitofrontal lesions, whereas dorsolateral prefrontal lesioned monkeys were unable to properly focus selective attention, providing further evidence that these two regions of the prefrontal cortex can be separated functionally. Neuroimaging studies that have examined reward processing in humans have found that activation of pleasant taste was localized to bilateral areas of the insular cortex and areas of the orbitofrontal cortex (Berns, McClure, Pagnoni & Montague, 2001; Francis, et al., 1999). Regions of the amygdala and cingulate cortex were also active in taste reward. Thus, attempts to maximize gains and avoid losses in making decisions, as seen in the gambling task, may have similarities at the neural level to the phenomenon of attaining a physical reward.

Neuroimaging studies that examine areas involved in processing gains and losses have also shed light on locations of brain activity associated with abstract rewards. These studies show increased involvement of the orbitofrontal and associated brain areas that are thought to play a role in a generalized dopaminergic reward processing system with striatal connections. For example, Elliott, Friston and Dolan (2000), and Zalla, et al. (1999), despite some differences in experimental procedures, both found that the orbitofrontal cortex, basal ganglia, and limbic cortex were activated in tasks involving wins and losses.
Elliot et al. (2000) further suggested that the medial orbitofrontal cortex plays a role in maintaining reward information, while the lateral orbitofrontal regions were mostly involved in inhibiting responses to previous rewards. A recent study by O'Doherty, Kringelback, Rolls, Hornak and Andrews (2001) reports significant orbitofrontal activation in a reversal-learning task including monetary reward and loss following correct and incorrect decisions. The authors emphasize the emotional involvement of this brain area for the representation of magnitudes of abstract reward and punishments. Given that the orbitofrontal cortex has key interactions with the basal ganglia in reward learning, some researchers have suggested that reward processing is associated with a neural circuit that involves the striatal dopamine system (e.g., Schultz & Monague, 1997). Using fMRI, Berns et al. (2001) studied the influence of predictability of a pleasant tasting liquid on orbitofrontal activation, and found that activity in this region was increased when rewards were unpredictable. The authors therefore suggested that the dopaminergic reward system is most active when environmental reward contingencies are uncertain, an interpretation which is consistent with the orbitofrontal cortex role in providing signals relevant to making adaptive choices in a changing environment.

1.4.3. Functions of the dorsolateral prefrontal cortex

1.4.3.1. Set switching, rule maintaining and updating
The role of the dorsolateral prefrontal cortex has been well captured in a numerous theoretical frameworks proposed by Baddeley (1996), Dempster (1991; 1992), Fuster (1989), Kane and Engle (2002), Miller and Cohen (2001) and Stuss, Shallice, Alexander & Picton (1995). All models seem to agree that this area of the prefrontal cortex is one of the most important regions responsible for maintaining and manipulating information in working memory (see also, D'Esposito, Detre, Alsop & Shin, 1995; Goldman-Rakic, 1992; Prabhakaran, Narayan, Zhao & Gabrieli, 2000; Shimamura, 2000). Maintaining information in a highly active, accessible state may be particularly important in the presence of interference. Besides working memory, the dorsolateral prefrontal cortex has also been implicated in different forms of inductive reasoning (Goel & Grafman, 2000; Smith, Patalano & Jonides, 1998) and in the categorization of novel stimuli (Alexander, Porjesz, Bauer & Kuperman, 1995). Davidson and Irwin (1999) argue that, whereas the ventromedial sector of the prefrontal cortex is probably involved in the representation of elementary positive and negative states in the absence of immediate incentives, the dorsolateral PFC may be most directly involved in the representation of the goal states toward which these elementary positive and negative states are directed. Thus, the functions of the dorsolateral prefrontal cortex may be summed as ‘executive attention’, referring to the capability whereby memory representations are maintained in a highly active state in the presence of interference, and these representations may reflect action plans, goal states, or task-relevant stimuli in the environment (cf. Kane & Engle, 2002), or retaining context information in an active state (cf. Miller & Cohen, 2001).

1.4.3.2. Stroop Task and Wisconsin Card Sorting Task
Initially, the importance of the dorsolateral prefrontal cortex in terms of executive atten-
tion was anticipated by the research and case reports of Luria and colleagues (e.g. Luria, 1966; Luria, Karpov & Yarbus, 1966). These reports demonstrated that patients with prefrontal cortex damage had difficulty maintaining a preparatory set during a novel task, particularly if the task conflicted with habitual responses. They also failed to disengage attention from previously relevant stimuli. When one considers tasks that demand novel responses, action plans, and keeping information active in the presence of interference, the Stroop task and the Wisconsin Card Sorting Task inevitably come to mind. In the Stroop (1935) task, the distractor stimulus provides a truly competitor for the target, given that participants must name the color in which a conflicting word is printed. Patients with dorsolateral prefrontal damage show exaggerated Stroop effects in error rates on this task (Vendrell et al., 1995). FMRI data confirm this association, given that the dorsolateral prefrontal cortex is active when Stroop interference must be suppressed (MacDonald, Cohen, Stenger & Carter, 2000).

Set shifting represents a further class of interference wherein prepotent response tendencies must be overcome in order for the participant to act according to goals or intentions. A classical set-shifting task that has been associated with dorsolateral prefrontal functioning is the Wisconsin Card Sorting Task (WCST). In its original form, the WCST uses stimulus cards and response cards that display varying forms (crosses, circles, squares, triangles), colors (red, green, blue, yellow) and numbers (one, two, three, four). Four cards with different combinations of the described characteristics are placed before the participant. The participant is handed a deck of response cards and instructed to place each consecutive card from that deck in front of one of the four stimulus cards, wherever the participant thinks it should go. The participant is informed only whether each response is right or wrong, and is not told the correct sorting principle. Once the participant has made a specified number of consecutive sorts according to the specific sorting principle, the criterion principle is changed without warning. The test proceeds through a specified number of shifts of the three sorting principles (Heaton, 1981). The most important requirements of this task are therefore; (1) the ability to use feedback information to find the correct sorting rule, i.e., efficient use of environmental cues, (2) the ability to maintain the correct sorting rule in working memory, and (3), the ability to inhibit responses to the previously correct sorting rule.

Initial patient reports confirmed the assumption that this task depends on intactness of the dorsolateral prefrontal cortex (Milner, 1963), but this claim has also been called into question (Anderson, Damasio, Jones & Tranel, 1991; Axelrod et al., 1996). For example, Anderson et al. (1991) emphasized that the WCST alone should not be used to group brain damaged participants into frontal and non-frontal groups. Likewise, Axelrod et al. (1996) reported a consistent discrimination between patient and non-patient groups using the WCST, but consistent with Anderson's study, a strong sensitivity of the WCST to brain dysfunction directly involving the frontal lobes was not demonstrated. Lombardi, et al. (1999) explained some of this controversy; they examined whether frontal lobe brain damaged patients perform poorly on the WCST and additionally raised the issue whether subcortical structures like the basal ganglia are involved in performance of this test. The PET data obtained in their study demonstrated that a relationship exists between the functional integrity of fronto-striatal circuits and perseverative responding on the WCST. A strong
correlation was found between perseverative responding on the WCST and glucose metabolism in structures of the right dorsolateral frontal-subcortical circuit. This relationship was assessed with the effects of WAIS-R IQ and nonperseverative errors on the WCST removed. Therefore these researchers argue that a failure to find a relationship between perseveration on the WCST and frontal damage may occur whenever imaged structural lesions do not provide a good indication of the functional status of regions of the frontal lobes. Inclusion of PET metabolism data might demonstrate functional abnormality of the frontal lobes in many individuals who show impairment in perseverative responses on the WCST in the absence of frontal structural lesion. This study also emphasizes the importance of considering the DLPFC as part of a larger network of interconnected brain areas. Both the right DLPFC and the right caudate were found to account for a significant proportion of variance on the WCST. Since the dorsolateral circuit connects the DLPFC with the caudate nucleus as well as other areas of the basal ganglia and the thalamus, these structures form part of an interconnected circuit. Based on these findings, it might be more accurate to consider the entire dorsolateral frontal subcortical circuit, rather than the DLFPC alone, as contributing to perseveration on the WCST. More insight into the circuits involved in WCST performance comes from neuroimaging studies. Despite some difference in experimental procedures, a large number of studies report dorsolateral prefrontal cortex involvement when switching between rules in WCST-analogue tasks (Berman et al., 1995; Nagahama et al., 1996; 1998; Osman Zigun, Suchy & Blint, 1996; Raglan et al., 1997). This activation has been interpreted in terms of a role of the dorsolateral prefrontal cortex in maintaining spatial information on-line over brief delays, rule learning, and shifting sets. Besides the dorsolateral involvement, some authors reported that certain parts of the orbital polar frontal cortex were also increased above control task levels (Berman et al., 1995; Nagahama et al., 1996; 1998). The involvement of these areas may be related to maintaining sets (Nagahama et al., 1996) or information processing in stimulus-reward association (Nagahama et al., 1998).

Set-shifting tasks that are similar to, but less complex than the WCST also produce deficits specific to dorsolateral prefrontal damage (Owen et al., 1993; Owen, Roberts, Polkey, Sahakian & Robbins, 1991). These set-shifts are particularly difficult for frontal patients when the previously reinforced dimension becomes non-reinforced and the reinforced dimension is entirely new. Thus, taken together, recent research with the WCST and its analogues indicates a strong link between shifting attentional sets and the dorsolateral prefrontal cortex. This interest is mirrored in cognitive psychology, where task switching is utilized as a means of exploring the executive control of behavior (Allport, Styles & Hsieh, 1994; Meiran, 1996). Only limited fMRI work has been done with such switching tasks, but recent studies indicate greater activation in bilateral prefrontal cortex (especially areas 9, 6, 44, and 45) on response-switch trials (Dove, Pollmann, Schubert, Wiggings & Von Cramon, 2000; see also, Dreher & Berman, 2002; Sylvester et al., 2003).

1.4.4. Contributions of the Anterior Cingulate Cortex

The anterior cingulate cortex has been presumed to have close functional connections with both ventromedial and dorsolateral prefrontal regions (e.g., Cummings, 1995). Recent neuroimaging studies indicate that the anterior cingulate cortex plays a key role in proces-
singing of situations in which there are conflicting options and high likelihood of making an error (Carter et al., 1998). This interpretation has recently been incorporated in a theoretical framework proposed by Botvinick, Braver, Barch, Carter, and Cohen (2001) that associates anterior cingulate activity with conflict monitoring. For example, Barch et al. (1997) showed that on a variant of the continuous performance test, increased activity in the anterior cingulate was observed under conditions in which decisions had to be made among competing responses. Similarly, using the flanker paradigm, in which individuals are required to respond to a central arrow, which could be flanked by similar, or competing arrows, Botvinick et al. (1999) revealed that anterior cingulate activity was greater in case arrows pointed in the opposite direction from the target arrow, that is, when conflict between response options was greatest.

The anterior cingulate has also been associated with processing outcomes in a gambling situation similar to the type thought to rely on ventromedial prefrontal cortex. Gehring and Willoughby (2002) conducted a study investigating neural responses to monetary outcome using event-related potentials, measured from the scalp. Participants in the study were required to choose between two response alternatives, which could result in large or small gain, but also in large or small loss. Following their choice, the outcome was presented on a computer screen and the gain or loss was added to or reduced their total amount of money. The researchers found a negative brain potential after the participants were informed of loss outcome, and this potential was found to originate from a location in or near the anterior cingulate. Thus, anterior cingulate activation may be related to situations in which selection is guided by internal cognitive representations of conflict, as well as in the evaluation of emotion-related aspects of choice outcome. Recently, researchers have suggested that this differentiation may be related to anterior versus posterior region of the anterior cingulate cortex. The anterior part is characterized as ‘executive’ in function, whereas the posterior part is characterized as ‘evaluative’ (Bush, Luu & Posner, 2000). The dorsal-cognitive division and the rostral-ventral division subserve distinct functions. Specifically, functions ascribed to the dorsal-cognitive circuit include modulation of attention or executive functions by influencing sensory or response selection; monitoring competition, complex motor control, motivation, novelty, error detection and working memory, and anticipation of cognitively demanding tasks. In contrast, the rostral-ventral circuit is primarily involved in assessing the salience of emotional and motivational information and the regulation of emotional responses. On the basis of convergent data from lesion and electrophysiology studies (and a limited number of neuroimaging studies), it has been observed that these sub-divisions are separable (Bush et al., 2000). However, this does not mean that these areas do not interact in many important ways; for example, it has been observed that Stroop interference can be modulated by positive affect (Kuhl & Kazen, 1999).

1.5. Window into the developing brain

Because extensive evaluations of brain-damaged children have not been made, the hypotheses concerning anatomical substrates remain speculative. However, important progress has been made in the field of psychophysiological analysis of the developing brain. It should be noted that this line of research is still in its infancy.
Approaches that were previously applicable only to adults have begun to be available for the study of how brain development and behavior change with growth and experience. Using functional MRI, researchers have become able to trace behavior-related changes in cortical areas (Casey, 2002). By integrating new noninvasive methods of functional Magnetic Resonance Imaging (fMRI) with techniques of developmental cognitive neuroscience, it is now possible to begin systematic research programs to directly test hypotheses of neurodevelopment. An overview of the limited set of studies that are currently available is presented in the following section. The studies described provide a strong argument in favor of the presumed relation between prefrontal development and cognitive development.

Importantly, developmental neuroimaging studies suggest that similar brain circuitry is recruited in children and adults during performance of attention and memory tasks, but the magnitude of activity is typically greater and more diffuse in children relative to adults (see Casey, Giedd & Thomas, 2000; Casey, Davidson & Rosen, 2002, for overviews). More specifically, in a non-spatial working memory task, activation in the inferior and middle frontal gyri was observed when participants performed a memory task relative to a comparison task (Casey et al., 1995). Likewise, studies by Thomas et al. (1999) and Nelson et al. (2000) showed that during a spatial working memory task, children activate similar brain regions as adults, including the middle and superior frontal gyrus or dorsolateral prefrontal region. A recent study by Kwon, Reiss and Menon (2002) revealed changes in the functional distribution of brain regions from childhood through adolescence during performance of a visuospatial working memory task. Like Thomas et al. and Nelson et al., these researchers found increases in brain activation in focal regions of the left and right dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, left premotor cortex, and posterior parietal cortex during a working memory condition. Importantly, age was found to be a significant predictor of activation in these brain regions, suggesting protracted functional maturation of bilateral fronto-parietal neural networks involved in visuospatial working memory development.

Similar studies on inhibition and interference suppression also found activation in similar areas as in adults, but more diffuse patterns for children. Casey et al. (1997) performed one of the first studies examining development of inhibitory control using fMRI. They found that inhibitory processes on a go/no go task were associated with increased activation that was distributed across both dorsolateral and orbitofrontal cortices, and the volume of activation was significantly greater for children relative to adults. Similarly, Tamm, Menon, and Reiss (2002) found that performance on a go/no go task was positively associated with age in the left inferior frontal gyrus, insula, orbitofrontal gyrus, and negatively in the left middle/superior frontal gyri. These results suggest that children activate discrete regions of the prefrontal cortex more extensively than adults, whereas adults show increased focal activation in specific regions associated with response inhibition. Using an oculomotor response-suppression task, Luna et al. (2001) reported increased activation in frontal, parietal, striatal and thalamic regions when inhibition was required, and prefrontal activation was more active in adolescents than in children or adults. These results were interpreted suggesting that efficient modulation of reflective acts might not be fully developed until adulthood. Two recent studies combined response inhibition tasks
with interference tasks, and both found age-differences in involvement of the ventral fronto-striatal circuitry (Bunge et al., 2002; Durston et al., 2002). Finally, Adleman et al. (2002) report a positive correlation between age and Stroop-related interference activation in the left lateral prefrontal cortex, the left anterior cingulate, and the left parietal and parieto-occipital cortices.

The neurobiological underpinnings of developmental changes in affective processing or affect regulation have not yet been studied using fMRI. An exception is a study by Thomas et al. (2001), who examined developmental specificity of amygdala response to fearful facial expression in children and adults. Previous developmental behavioral studies have suggested that the ability to discriminate between discrete facial expressions continues to develop throughout childhood and early adolescence (Kolb et al., 1992). Thomas et al. found increased activity in the amygdala, extending into the substantia innominata during the presentation of fearful faces in adults. This pattern was not observed in children, who showed more amygdala activity in response to neutral faces than in response to fearful faces. Given that amygdala activity is associated with the extent to which contingencies between a stimulus and a negative outcome are altered or unpredictable, it may be that a neutral face for children produced activation consistent with continued attempts to interpret.

Despite some differences in design and experimental procedures, the small number of developmental fMRI studies converges on the conclusion that in general, children activate similar regions associated with cognitive demands as adults. The studies point toward more dorsolateral prefrontal activation when the task requires storage or manipulation of information in working memory, whereas response inhibition seems to activate both dorsal and ventral prefrontal regions, and interference suppression is associated with activation in the ventrolateral prefrontal regions. A preliminary study on affective processing shows that children activate an affective pathway differently than adults, suggesting developmental changes not only in cognitive, but also in the affective components of goal-directed behavior.

1.6. Outline of this thesis
The focus of this chapter has been mostly on functions of prefrontal subregions in adults. Additionally, we have presented supporting evidence for the assumption that children activate similar regions, although this activation is more diffuse. By presenting a behavioral and psychophysiological analysis of children's performance on tasks known to rely on different regions of the prefrontal cortex, we try to examine differential developmental trajectories of ventromedial versus dorsolateral prefrontal function.

The use of psychophysiological measures, heart rate and skin conductance, is seen as an important addition to the behavioral measures (choice preferences, reaction times, errors). The advantage of psychophysiological measures is that they may provide access to processes that cannot be observed via overt behavior (Van der Molen & Molenaar, 1994).

 Chapters 2, 3 and 4 focus on decision-making, and we propose a task that is applicable to study decision-making skills in children, the Hungry Donkey Task (HDT). In chapter 2, we report a study including normal healthy adults that performed the HDT while heart rate and skin conductance were measured. A special focus of this chapter was to
examine the relation between affective responses to reward and punishment, somatic arousal preceding risky choices, and its relation to performance strategy. In chapter 3, we examine the hypothesis that real-life decision-making is subject to developmental change, under the assumption that the ventromedial prefrontal cortex matures slowly. Chapter 4 describes a study in which we examine the relation between decision-making and individual differences in decision-making, with a special focus on cognitive disinhibition.

Chapters 5, 6, 7, and 8 focus on performance monitoring and set switching. In chapter 5, we examine young adults' heart rate changes in response to performance feedback that differed in informative value, providing a fuller account of the strategies that are used when processing performance outcomes. This rationale is applied to examine developmental changes in outcome processing in chapter 6. Chapter 7 describes a study in which we examined children's set maintaining and set shifting skills on an analogue of the WCST. Chapter 8 tries to further understand age-related changes in the ability to shift between task sets.

Finally, in chapter 9 we describe a study in which we examined the relation between cognitive and motivational factors as a method to describe behavior and autonomic responsiveness in children with Attention-Deficit/Hyperactivity Disorder (ADHD), thereby trying to provide a more extensive account of inhibitory deficits in children with ADHD.

All empirical chapters are published in, or submitted to international journals. To acknowledge the important contributions of the co-authors, below a list of references is presented:


Crone, E. A., Jennings, J. R., Van Beek, B. & Van der Molen, M. W. Developmental changes in feedback processing as reflected by phasic heart rate changes. Manuscript submitted for publication. (Chapter 6)
