Brain mechanisms of self-control: A neurocognitive investigation of reward-based action control and error awareness

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Chapter 1

Introduction to reward-based action control

The first Chapter introduces reward-based action control. It has three objectives. The first section (1.1) provides a description and definition of cognitive control and introduces cognitive control tasks, among which the task that is at the heart of the studies presented here: the antisaccade task. Section 1.2 discusses the antisaccade task and describes how behavioural and neural research has advanced the knowledge on antisaccade performance. Then, section 1.3. provides an introduction to reward processing and its effect on behavior, and describes the neural reward networks. Section 1.4., introduces an influential model of basal ganglia functional circuits on oculomotor- and limbic function. Furthermore, as few empirical studies have investigated aging from a systems- and individual difference perspective, section 1.5 discusses past and present directions in the field of neurocognitive aging to establish the current approach within a larger framework of related lines of neuroimaging research. Finally, section 1.6 gives an outline to the studies of this thesis.
Introduction to reward-based action control
1.1 What is cognitive control?

Cognitive control involves a set of interrelated mental processes which enable us to plan and initiate goal directed behavior and regulate ongoing behavior by detecting and correcting mistakes (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004).

Cognitive control is essential in situations which one cannot solely resolve by relying on routine or reflexive behavior, but where one needs self-regulation i.e. creating and keeping up a structure oneself. The “self” is herein an important aspect. An individual with intact cognitive control can overrule externally triggered or reflexive actions by those that emanate from internal goals emerging from intentions (Ridderinkhof & Wijnen, 2011) and from goals that service our desires and needs. By describing an action as being “directed” at a goal, it is meant that performance is mediated by knowledge of the contingency between the action and the goal or outcome (Dickinson & Ballaine, 1994).

1.1.1. How to measure cognitive control

Cognitive measurement or testing is a way of assessing the cognitive capabilities of a person. Many different cognitive tests have been designed in neuroscience and health care to assess different areas of cognition. As cognitive control deficits are implicated in a broad range of disorders, such as cognitive developmental disorders, psychotic disorders, affective disorders, conduct disorders, as well as neurodegenerative diseases, ischaemic stroke or other forms of acquired brain injury, the application of cognitive control measurements for clinical applications is broad. The application ranges from the sensitive identification of cognitive deficits, determination of rehabilitation needs based on the measured strengths and weaknesses of the individual, to diagnosis, establishment of direction for treatment plans, treatment monitoring and assistance in patient care.

As previously stated, cognitive control is involved when externally triggered or reflexive actions are to be overruled by those that emanate from internal goals. Therefore cognitive control tasks commonly test deliberate control of automatic reflexes. Measurements of cognitive control come in many forms, and can vary widely on different variables. In fact, “many conventional cognitive control tasks may have as little in common between them as they have in common with other, presumably non-cognitive control tasks” (Nieuwenhuis, 2001). Cognitive control tasks vary for instance in the complexity of the action. The complexity of the action to be controlled can range from “no visible overt action” i.e. the suppression of an inappropriate response in the stop-signal task, fast button presses as in the Simon task, straight eye movements as in the antisaccade task, to complex sketching or building in planning tasks, such as the Behavioural Assessment of the Dysexecutive Syndrome (BADS, Wilson, Alderman, Burgess, Emslie, & Evans, 1996) or the Tower of London (Shallice, 1982), as used frequently in clinical neuropsychological assessment.

Another variable that can vary in cognitive control tasks and in daily life alike is the used effector. An effector is a muscle, gland, or organ capable of responding to a stimulus, such as the eyes, hands, feet, speech etc. We control for instance our eyes, arms, hands, legs and feet in a goal-directed manner when we put on clothes in the morning, make coffee, turn on the
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Radio, use the elevator or overview the agenda. In order to control action within the motor- and language system, we overrule reflexive motor and language responses. When one considers language tasks that demand keeping a goal mind in the presence of a distractor, the Stroop task inevitably comes to mind (Stroop, 1935). In the Stroop task the distractor stimulus provides a competitor for the target, given that the participants must name the colour in which a conflicting word is printed. Other effectors commonly used in cognitive control paradigms are the hands, as in the stop signal or Simon task, or the eyes, as in oculomotor tasks.

This thesis studies cognitive control in tasks with the eyes as primary effectors in an influential cognitive control task, the antisaccade task. The appearance of the antisaccade task reminds of situations in daily life, when we deliberately control externally triggered automatic eye-movements. Eyes are for instance commonly drawn towards movement and abrupt changes in our field of sight. This reflexive behavior is useful when a car suddenly shows up when we are about to cross the road. However, this behavior is less useful when we are driving our car at high speed and we see from the corner of our eyes that our lunch bag falls off the passenger seat. To be able to keep our eyes on the road, we need to suppress the reflexive response and instead direct our eyes to what, to our intrinsic goals, is more important. This demands cognitive control.

1.2. The antisaccade task and the oculomotor network

The following section is organized in three major points, which attempt to first, introduce the antisaccade task and discusses its value for the study of cognitive control in brain and behavior. Second, after briefly addressing the clinical applications of the antisaccade task, the next paragraphs reviews the findings on decline in antisaccade performance with advancing age and Parkinson’s disease, and factors generally known to stabilize performance on this task. Third, a general review of the major findings in non-human primates and human neuroimaging studies on the neural oculomotor network is presented, followed finally by a description of the neural underpinnings of the preparatory phase before the antisaccade response (also named preparatory set). This preparatory phase is particularly relevant to the experiments in part I of this thesis.
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1.2.1. The antisaccade task

In its original form, the participant is instructed to inhibit a reflexive eye movement towards a peripherally presented stimulus (reflexive prosaccade), and instead make a voluntary eye-movement in the direction opposite to that stimulus (deliberate antisaccade) (Hallett, 1978). Therefore the most important requirements for antisaccades are the suppression an automatic response in favour of volitional initiation of a response, the ability to maintain the correct rule/goal in working memory, and (incongruent) stimulus response mapping. The time that is needed to prepare and execute the movement, while suppressing the automatic response, is measured by antisaccade-onset latencies.

Figure 1: Impression of the antisaccade task.

If the eyes move directly in the correct direction, shorter antisaccade-onset latencies have been proposed to reflect better behavioural response preparation (Munoz & Everling, 2004) and less difficulty of overriding the prepotent response (Nieuwenhuis et al., 2004). Reflexive glances toward the visual stimulus (i.e., antisaccade errors) are common. These errors usually take the form of a rapid saccade in the direction of the stimulus followed by a correction saccade away from the stimulus, and some of such antisaccadic errors have been reported to go unnoticed (Nieuwenhuis et al., 2001).

1.2.2. Why the antisaccade task

A number of features make the antisaccade task useful for investigating neural mechanisms of cognitive control.

First, although to date, empirical data on the specific brain networks involved in oculomotor control are largely lacking in humans, the neural oculomotor system is relatively well understood based on literature from single cell recordings in non-human primates (e.g. Johnston & Everling, 2008) and lesion studies in humans (e.g. Pierrot-Deseilligny, Milea, & Muri, 2004). Second, although there are few empirical data available on the role of the subcortical brain structures in human oculomotor control, there is good convergence between work on the cortical oculomotor structures in non-human primates and human functional neuroimaging studies. Third, antisaccades provide a quantifiable behavioural performance with a number of reliable parameters. As such, the study of cognitive control via oculomotor tasks has found diverse applications, extending from investigations of basic oculomotor behavior, modified oculomotor tasks, cognitive neuroscience studies of cognitive control, to studies of cognitive control in neurologic and psychiatric conditions (for a review see Hutton & Ettinger, 2006; McDowell, Dyckman, Austin, & Clementz, 2008). An important advantage of the antisaccade task in this context is that it entails the eyes, rather than hands or speech, as the effector. This feature may be especially relevant when studying cognitive impairments in clinical populations. After stroke and in neurological
syndromes such as aphasia, dementia or Parkinson's disease, hand- or language function may be impaired or even absent. In these cases, the (in) ability of performing an antisaccade task (and its neural correlates), can be used to establish at what level impairments in cognitive control are manifest.

1.2.3. Clinical applications of the antisaccade task

The potential of oculomotor tasks for clinical applications is broad (Everling & Fischer, 1998; Hutton & Ettinger, 2006). The antisaccade task is sensitive to frontal lobe dysfunction in aging, schizophrenia, Huntington disease, and a variety of neurodegenerative dementias (Hillmuth et al., 2012). It aids the diagnosis of Frontotemporal Dementia and Alzheimer Disease (Boxer et al., 2012; Garbutt et al., 2008), Huntington's disease (Lasker & Zee, 1997), Lewy body dementia (Mosimann et al., 2005), the etiological diagnosis of Parkinson syndromes (Pierrot-Deseilligny & Rivaud-Pechoux, 2003), schizophrenia and obsessive compulsive disorder (for a review see Hutton & Ettinger, 2006). It is furthermore a sensitive marker for ischaemic stroke and mild traumatic brain injury (Dong et al., 2012; Suh et al., 2006). After ischaemic stroke ocular motor assessment has been shown to be a sensitive marker for motor and cognitive recovery (Dong et al., 2012).

1.2.4. Antisaccade performance with advancing age

The antisaccade task has been used to assess cognitive control in aging, where it has been mainly, but not solely associated with frontal lobe function (Klein, Foerster, Hartnegg, & Fischer, 2005).

A robust body of research has shown that antisaccade performance decreases with advancing age. This age-related decrease in antisaccade performance has been discussed preferentially with regard to involvement of functions such as working memory and inhibition (Butler & Zacks, 2006; Eenshuistra, Ridderinkhof, & van der Molen, 2004), and goal neglect (Nieuwenhuis, Broerse, Nielen, & de Jong, 2004).

The decreases in antisaccade performance with advancing age are not entirely consistent with regard to which performance measure is more affected by aging, accuracy or latency. Whereas some studies observed decreased accuracy as well as increased anti-saccade onset latencies with advancing age (Nieuwenhuis, Ridderinkhof, de Jong, Kok, & van der Molen, 2000; Olincy, Ross, Youngd, & Freedman, 1997), others report only increased onset latencies (Eenshuistra et al., 2004; Fischer, Biscaldi, & Gezeck, 1997; Munoz, Broughton, Goldring, & Armstrong, 1998). Experimental differences, such as the amount of trials subjects were allowed to practice, have been suggested to account for the divergence in these findings (Abel & Douglas, 2007; Nieuwenhuis et al., 2000). Studies investigating the effect of aging on both prosaccades and antisaccades, generally report disproportionally increased accuracy-rates and onset latencies in antisaccades as compared to prosaccades (e.g. Abel & Douglas, 2007; Butler & Zacks, 2006; Butler, Zacks, & Henderson, 1999).
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1.2.5. Antisaccade performance and Parkinson's disease

Older adults with Parkinson’s disease, generally show more difficulty with self-initiation of movement than with externally guided movement, which is particularly reflected in decreased performance on antisaccades, with equal (or faster) performance on prosaccades (Briand, Hening, Poizner, & Sereno, 2001; Briand, Strallow, Hening, Poizner, & Sereno, 1999) Parkinson's disease is a degenerative disease of the central nervous system, characterized by disturbances of movement, cognitive and emotional problems, resulting from the atrophy of dopamine-generating cells in the substantia nigra. As compared to healthy age-matched controls individuals with Parkinson’s disease display decreased antisaccade onset latencies and more difficulties in suppressing reflexive prosaccades and premature responses (Amador, Hood, Schiess, Izor, & Sereno, 2006).

1.2.6. Stabilizing effects on antisaccade performance

Less extensively studied are conditions or manipulations in the antisaccade task that have been shown to stabilize or improve antisaccade performance with advancing age. Except for the above-mentioned effect of practice on antisaccade accuracy (Smyrnis et al., 2002) manipulations known to generally influence antisaccade performance are for instance the duration of the delay between cue and target (Nieuwenhuis et al., 2000) the use of overlap versus gap paradigms (Munoz & Everling, 2004) and the presentation of specific cues indicating the direction of the upcoming eye movement (Butler & Zacks, 2006).

A shorter duration of the delay between cue and target generally leads to higher error rates and longer latencies (Nieuwenhuis et al., 2004; Smyrnis et al., 2002), due possibly to a less stable fixation before target appearance and less time for preparation processes. In gap conditions the fixation point disappears before the target is presented, whereas overlap conditions have a permanent fixation point. The latter generally helps to inhibit reflexive eye movements, whereas gap conditions usually increase direction errors (Munoz & Everling, 2004). The relation between the “gap-effect” and advancing age and is however not entirely clear as some studies show and enhanced gap effect in aging (Fischer, Gezeck & Hartnegg, 1997), while others don’t (Eenshuistra et al., 2004). The presentation of a specific cue (i.e. an arrow), indicating the direction of the upcoming eye-movement has been shown to improve antisaccade performance in elderly (Butler & Zacks, 2006). This effect has been attributed to improved response preparation processes.
1.2.7. The neural oculomotor network

**Figure 2:** Impression of the oculomotor network with the nucleus caudate in the middle. The figure is drawn after Fig. 1 in Sharma and colleagues (Sharma et al., 2011).

Using the antisaccade task described above, several studies in human and non-human primates have typically found a host of widespread bilateral cortical brain regions and multiple subcortical structures with reciprocal connections active during oculomotor control (for a review see McDowell et al., 2008).

The neural oculomotor network includes specific subcortical structures (caudate nucleus, substantia nigra pars reticulata, thalamus, superior colliculus), and specific cortical oculomotor control structures such as the cortical eye fields (frontal and parietal eye fields), the pre-supplementary motor area, and parts of the dorsolateral prefrontal cortex (Lynch & Tian, 2006; C. Pierrot-Deseilligny et al., 2004; Tian & Lynch, 1997).

1.2.7.1. Findings in non-human primates on the oculomotor network

Previous studies in non-human primates have shown specific interactions between the subcortical and cortical oculomotor control structures. If a stimulus attracts attention and gaze, the cortical oculomotor control structures bias saccades via direct and indirect pathways.

Direct pathways project excitatory input to the oculomotor-executor in the brainstem, the superior colliculus. Indirect pathways project onto the caudate nucleus/substantia nigra pars reticulata, which can render the superior colliculus more receptive for cortical input (Hikosaka, Nakamura, & Nakahara, 2006; Lauwereyns, Watanabe, Coe, & Hikosaka, 2002). The caudate/substantia nigra acts as a gate for saccade generation by inducing gamma-aminobutyric acid (GABA) inhibition on the superior colliculus. Only when the caudate/substantia nigra reduce inhibition of the superior colliculus, do the superior colliculus neurons spike, and is the oculomotor action executed (Hikosaka, Takikawa, & Kawagoe, 2000).
1.2.7.2. Findings in human neuroimaging on the oculomotor network

Functional magnetic resonance imaging (fMRI) usually measures the blood-oxygenation-level-dependent (BOLD) signal. The BOLD signal is an indirect measurement of neuronal activity that depends on several physiological factors such as cerebral blood flow, cerebral blood volume, and cerebral oxygen consumption (Logothetis & Wandell, 2004).

To date, empirical data on the striato-cortical networks involved in oculomotor control are largely lacking in humans, and are not available in human older adults. Several factors complicate the study of the subcortical oculomotor structures in human functional neuroimaging. The specific limitations are dependent on the technique and the structure. In general, subcortical structures can pose a problem in blood-flow based methods because they are small and located close to vasculature (e.g. the caudate and the superior colliculus), making the measurement of BOLD signal more vulnerable to artefacts (Schneider & Kastner, 2005). While functional imaging of subcortical regions is not impossible, such challenges, together with the practical problems of simultaneous acquisition of oculomotor response and fMRI signal, may explain why there are relatively few human neuroimaging studies on the role of subcortical structures in oculomotor control (McDowell et al., 2008).

The studies that do report oculomotor-related findings in subcortical structures describe activation in the striatum, cerebellum, thalamus, and superior colliculus (e.g. Matsuda et al., 2004; Optican, 2005; Sweeney et al., 1996).

Comparing prosaccade and antisaccade tasks, human neuroimaging has shown prosaccades activating the visual cortex, parietal cortex, frontal and supplementary eye fields, basal ganglia, and superior colliculus. Antisaccade generation has been found to activate the same regions as prosaccade generation, albeit to a greater extent, and in addition the dorsolateral prefrontal cortex and anterior cingulate cortex (e.g. Ettinger et al., 2008; McDowell et al., 2008).
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Figure 3. The frontal eye fields have a crucial role in executing voluntary saccades. The supplementary eye fields are important for internally guided decision-making and sequencing of saccades. The dorsolateral prefrontal cortex is involved in executive function, spatial working memory and suppressing automatic, reflexive responses. All of these frontal regions project to the superior colliculus. The frontal and supplementary eye fields and superior colliculus project directly to the paramedian pontine reticular formation to provide the necessary input to the saccadic premotor circuit so that a saccade is initiated or suppressed. Frontal cortical oculomotor areas also project to the caudate nucleus. Neurons in the caudate nucleus project through the direct pathway to the substantia nigra pars reticulata. Neurons in the substantia nigra pars reticulata form the main output of the basal ganglia circuit: they project to the intermediate layers of the superior colliculus and to nuclei in the thalamus that project to the frontal cortex. Cortical inputs to the direct pathway lead to disinhibition of the superior colliculus and thalamus because these signals pass through two inhibitory synapses. There is also an indirect pathway through the basal ganglia, in which a separate set of neurons in the caudate nucleus project to the external segment of the globus pallidus (figure adapted from Munoz & Everling, 2004). Abbreviations: FEF = Frontal eye fields, SEF = supplementary eye fields, DLPPC = Dorsolateral prefrontal cortex, CN = caudate nucleus, GPe = globus pallidus (external segment), SNpr = substantia nigra pars reticulata, LGN = lateral geniculate nucleus, STN = subthalamic nucleus, SNr = substantia nigra pars reticulata, SCi = superior colliculus, SCs = superior colliculus.

1.2.7.3. The preparatory set of antisaccades

Particularly relevant to the current experiments on motivational control have been neural findings on the preparatory phase, that is, before the actual antisaccadic response.

In order to study how motivational incentives (i.e. the anticipation of a reward) affects the preparation of goal directed action, we investigated the period leading up to an antisaccade (i.e. when knowing the instruction to make an antisaccade while awaiting the cue to execute it) separated from the response period (i.e. the presentation of the peripheral stimulus and the execution of the saccadic response).

Single-cell recording studies in non-human primates on the preparatory period suggest that correct performance requires the maintenance and implementation of the proper task set
and/or suppression of saccade neurons in the frontal eye fields and in the superior colliculus before the presentation of the antisaccadic stimulus. (Everling & Johnston, 2013; Everling & Munoz, 2000).

Several brain areas, mainly in the frontal and parietal lobes (Ford, Goltz, Brown, & Everling, 2005; Pierrot-Deseilligny et al., 2003) and basal ganglia (Lasker & Zee, 1997), have been proposed as mediators of this signal in the preparatory period before an antisaccade. This state of readiness and the response is commonly termed the “preparatory set” (e.g. Connolly, Goodale, Menon, & Munoz, 2002). Human neuroimaging studies identified the following oculomotor-network structures for the maintenance of the preparatory set during long periods of antisaccade preparation: frontal and supplementary eye fields and the intraparietal sulcus (Curtis & D’Esposito, 2006).

![Impression of the location of the frontal and supplementary eye fields and the intraparietal sulcus.](image)

Other structures that have been observed to be involved (albeit not exclusively) in the preparation of antisaccades in human neuroimaging, include fronto-parietal areas such as the dorsolateral prefrontal cortex, the anterior cingulate cortex, pre-supplementary motor area, and precuneus (Connolly et al., 2002; Curtis & D’Esposito, 2003). Anterior cingulate cortex has been found to be associated with both better antisaccadic performance and with antisaccadic errors (Ford et al., 2005), suggesting a role of the anterior cingulate cortex in both planning during preparation, as well as antisaccade error monitoring (see for review McDowell and colleagues, 2008).

Taken together, there seems to be consensus that in humans, within the oculomotor circuit, the frontal and supplementary eye fields are specifically important for the preparation and execution of antisaccades. The intraparietal sulcus has been implicated to play a role in antisaccade preparation to a smaller extent than the frontal eye fields. Non-human primate studies suggest furthermore a role of the superior colliculus and the basal ganglia in preparatory set.

Concluding, the oculomotor network includes subcortical structures, cortical eye fields, the pre-supplementary motor area and parts of the dorsolateral prefrontal cortex.
To prepare and improve performance, the cortical oculomotor control structures, especially the frontal eye fields, are active in the preparatory period. Cortical oculomotor structures interact with saccade generators in the superior colliculus directly, as well as indirectly through the caudate, which can render the superior colliculus more receptive for cortical input.

As the research in the current thesis aims to gain more insight into how this neural preparatory period is influenced by reward expectation, the following section will introduce past and current lines of research on reward processing.

1.3. Action and Desire: Reward processes and the neural reward network

In the previous section the neural mechanisms associated with oculomotor responses in the antisaccade task were discussed. As this thesis aims to investigate the correspondence between oculomotor actions and reward processes, the current chapter will introduce the concept of reward and highlight findings on the role of reward in behavior and in brain processes.

1.3.1. How reward influences behaviour

The study of the reward processes controlling simple, goal-directed actions has been neglected over decades (Dickinson & Ballaine, 1994). Although in folk psychology the concepts of reward and motivation are well-grounded, most empirical research on the link between incentive motivation and action control so far has taken place in non-human primates rather than in humans. However, the rise of cognitive behavioural therapy, which among others focuses on changing behavior through rewards; and findings on the role of natural reward systems in addiction (Schultz, 2000), have caused an increasing interest in clinical practice and human neuroscience in the influence of reward on behavior.

Rewards come in many shapes and flavours. Compliments, attention, sweets, juices, money, acclaim and even symbolic tokens such as game points are considered rewards. Generally, rewards are categorized into primary and secondary rewards. Primary rewards satisfy vegetative needs such as needs for food, liquids and sex. Secondary rewards have grown by abstract representations and pertain for instance to money, acclaim and power.

The importance of reward for goal directed behavior can be appreciated by the vast amount of functions reward is postulated to have in behaviour. Among these, the following functions can be highlighted. Reward provides motivation for initiating actions (Matsumoto & Tanaka, 2004), biases decision making (e.g. Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004) increases the frequency of behaviour that results in its achievement, elicits approach and consumption reactions, induces feelings of pleasure (Schultz, 2000, 2006) and makes the control of actions more purposeful and efficient (e.g. Lauwereyns et al., 2002). In a broader context, the vital biological importance of reward for an organism has been postulated to relate to the fact that reward can guide actions towards getting hold of energy supplies, thereby increasing the likelihood to live long and have offspring (Dickinson & Ballaine, 1994); for an extensive review see Schultz (2000, 2006).
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One powerful motivator of goal-directed behavior is the expectation of obtaining a reward. In non-human primates, the expectation of reward is commonly investigated using conditioned reinforcement or pavlovian-to-instrumental transfer paradigms (e.g. Robbins, Cador, Taylor, & Everitt, 1989). In short, these paradigms assess the effects of (pavlovian) cues associated with reward on subsequent (instrumental) responding for reward. The state triggered by external stimuli that have appetitive (rewarding) or aversive (punishing) properties is referred to as incentive motivation. For nonhuman primates (Kawagoe, Takikawa, & Hikosaka, 2004; Lauwereyns et al., 2002) as well as humans (Ramnani & Miall, 2003), it is shown that actions are executed with greater efficiency when a reward is at stake. As people’s behavior is regularly directed at obtaining rewards or preventing punishment, reward expectation is intrinsically linked the planning and preparation of behavior.

1.3.2. The neural reward network

In the brain, reward anticipation increases activation in a complex network including structures of the basal ganglia (nucleus accumbens, putamen and caudate), amygdala, and orbitofrontal cortex (Haber & Knutson, 2010; Knutson & Cooper, 2005). Reward-related processes are prevalent in the entire striatum (nucleus accumbens, caudate, putamen), which receives massive input from the limbic system (e.g. amygdala, orbitofrontal cortex; Fudge, Kunishio, Walsh, Richard, & Haber, 2002). Functionally, the caudate nucleus has been proposed to reinforce plans for complex action (O’Doherty et al., 2004), founded on the valuation of action outcomes offered by the nucleus accumbens.

Figure 5. Impression of the location of the caudate and nucleus accumbens.
Neural evidence on age- and PD-related changes in the reward system is inconsistent. While Samanez-Larkin et al. (2007) observed intact ventral striatal activation (and activation of the medial caudate and anterior insula) during gain anticipation in both younger and older adults, Schott et al. (2007) observed ventral striatal activation during reward anticipation only in the young.

The neural circuitry underlying reward has been defined largely by dopamine projections, which originate in the substantia nigra and ventral tegmental area and project to the prefrontal cortex and basal ganglia. Thalamic relay nuclei transmit basal ganglia output to the prefrontal cortex, forming “closed loops” often referred to as the basal ganglia thalamocortical circuits.

1.3.3. An influential model of the basal ganglia functional loops

In the previous two sections, the behavioural and neural mechanisms behind oculomotor control and reward processes were discussed. In order to provide a framework for the empirical chapters that investigate the correspondence between oculomotor control and reward processes in the basal ganglia, the following section introduces an influential model on basal ganglia function proposed by Alexander and Crutcher (1990).

While best known for their motor functions, the basal ganglia are involved in several aspects of goal-directed behaviours, including not only its expression through the control of movement, but also the processes that lead to movement, including the elements that drive actions, such as motivation, and cognition. Based on physiologic and anatomical studies, an influential model on the function of the basal ganglia was introduced in the 1990s (Alexander & Crutcher, 1990; Alexander, DeLong, & Strick, 1986). This model emphasizes the functional inter-relationships between the cortex and the striatum, and how the various basal ganglia nuclei relate to one another, and to the cortex. It postulated that basal ganglia nuclei, thalamus, and cortex are components of re-entrant and largely closed loops that remain largely segregated from one another, both structurally and functionally. Within this outline of basal ganglia architecture, specific cortical areas project to the basal ganglia and thalamus in non-overlapping regions, and then return to their respective (frontal) areas of origin. The different loops are labelled "motor," oculomotor," "prefrontal," and "limbic" circuit, though these labels do not sufficiently apprehend the complexity of the functions assisted by these circuits. Whereas according to Alexander and Crutcher the putamen is involved in the 'motor circuit', the caudate forms part of the oculomotor, prefrontal and limbic circuits. Reward-related processes are prevalent in the entire striatum (caudate nucleus, putamen, nucleus accumbens), which receives substantial input from other structures of the limbic system (e.g. Fudge et al., 2002). The basal ganglia part of the limbic circuit has been proposed to specifically involve the ventromedial striatum, including the nucleus accumbens, and the rostral, ventral caudate nucleus, and putamen.
**Figure 6:** Schematic figure of the Basal Ganglia Thalamocortical Circuits. The nuclei of the basal ganglia are proposed to be differentially connected to the cortex in segregated corticostriatal loops. The caudate is thought to be involved in the oculomotor-, prefrontal and limbic loop, whereas the putamen is considered to contribute to the motor loop (the figure is drawn after Fig. 3 in Alexander et al., 1986, and Fig. 1 in Wichman & de Long, 2006). Abbreviations: SMA = Supplementary motor area, DLPFC = Dorsolateral prefrontal cortex, (L, M)OFC = (Lateral, medial)Orbitofrontal cortex, GPi = globus pallidus (internal segment), SNr = substantia nigra pars reticulata, VLo = ventrolateral nucleus of thalamus pars oralis, Vlm = ventrolateral nucleus of thalamus pars medialis, FEF = frontal eye fields, SEF = supplementary eye fields, Gpi = globus pallidus (internal segment), SNr = substantia nigra pars reticulata, VAmc = ventral anterior nucleus of thalamus pars magnocellularis, MD = mediodorsal nucleus of the thalamus, DLPFC = dorsolateral prefrontal cortex, ACA = anterior cingulate area, VS = ventral striatum.

Although the ability of this model to account for a large amount of functions may partly explain why it has been, and is still predominating research and clinical practice dealing with conditions related to basal ganglia function and dysfunction (e.g. Wichmann & DeLong, 1996), some questions have nevertheless been raised that contributed to cast doubts on its explanatory power for adaptive behavior (Haber, 2011; Haber & Knutson, 2010). One concern refers to the fact that this parallel model does not provide an answer to the critical question of how the brain organizes its subsystems to support adaptive behavior. A key consideration regards the fact that adaptive behavior requires a combination of reward evaluation, associative learning, the ability develop of appropriate action plans and inhibit inappropriate choices on the basis of earlier experience. Adaptive behavior has therefore been deemed to originate from the interaction of reward signal in limbic circuits and brain regions involved in cognition and (oculo) motor control (Haber, 2011; Haber & Knutson, 2010).
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This concern, accompanied by new empirical findings on cross-talk among circuits in non-human primates, paved the way to a new direction in perspectives on basal ganglia networks: moving beyond a parallel organization toward a dual organization of the basal ganglia networks that permits both parallel and integrative processing. A first step had been achieved when the idea of a motivation-to-movement interface through basal ganglia loops was developed quickly after the identification of the limbic part to the basal ganglia (Nauta & Domesick, 1976). Later on, several studies have addressed the hypothesis of the coexistence of both parallel and integrative networks (see for an overview Haber & Knutson, 2010). One example comes from recent anatomical evidence from primates and from diffusion tensor imaging (DTI) studies, demonstrating that the neural networks within basal ganglia pathways are in a position to move information across functional circuits (Draganski et al., 2008). Another example is research on primate caudate neurons, whose firing patterns correspond to the speed and accuracy of imminent saccades have been observed to also respond to reward cues (Kawagoe et al., 2004).

In human research, although an increasing focus has recently been given to the investigation of large-scale network properties of brain, typically during the resting state, a puzzle yet to be solved concerns the understanding of network properties of a focused set of brain regions during specific task conditions. While reward and action elements recruit many brain regions, it is currently unknown how they pervade inter-region interactions (Kinnison, Padmala, Choi, & Pessoa, 2012).

1.4. Neurocognitive aging

In the previous section, an influential model of basal ganglia function was presented that emphasizes the functional inter-relationships between the cortex and the striatum. Before we turn to the empirical chapters that will investigate the basal ganglia systems during reward-based action control in young and older adults from an individual difference- and systems perspective, the following section provides an introduction to neurocognitive aging. Few empirical studies have investigated neurocognitive aging from a systems- and individual difference perspective.

Therefore, the following section discusses past and present directions in the field of neurocognitive aging to establish the current approach within a larger framework of related lines of research. The paragraphs give merely a summary to sketch the picture, and are not intended as an exhaustive overview.

The section is organized in three major points. It will start with the main directions in behavioural research on cognitive aging, and the predominating explanatory theories put forward to account for the behavioural findings. These explanatory theories have put their mark on neuroimaging approaches to aging, which will be covered in the second part. Third, challenges in neuroimaging studies of aging are discussed to introduce the current approach.
1.4.1. Demographics and neurobiological changes

With respect to the demographics of aging in the Netherlands, the Nationaal Kompas van de Volksgezondheid states that whereas in 1995 13.3% (2,000,000) of the population in the Netherlands was above 65 years, in 2025, 21.2% (3,700,000) of the population is expected to be above 65 years (Nationaal Kompas van de Volksgezondheid, www.rivm.nl).

In order to very briefly outline the neurobiological changes in the aging brain, it may be put that the aging brain is generally characterized by a deregulation of neuroreceptors, non-uniform decreases in the grey matter volume, as well as in the structural integrity of the white matter that connects grey-matter regions (e.g. Head et al., 2004; Moseley, 2002; Park & Reuter-Lorenz, 2009; Sullivan & Pfefferbaum, 2006). Particularly in the frontal and occipital areas, a higher amount of white-matter hyper-intensities has been observed with advancing age (Wen & Sachdev, 2004), as well as deterioration in white-matter diffusivity and anisotropy in measures DTI (Head et al., 2004). In a longitudinal studies over a course of 5 years, Raz and colleagues obtained brain images of older adults, revealing both cross-sectional and longitudinal declines in brain volume. The magnitude of these declines was observed to vary across regions (Raz et al., 2003). They report among others longitudinal shrinkage of the whole striatum (caudate, putamen, and globus pallidus). Furthermore, prefrontal, hippocampal, caudate, and cerebellar regions were found to display the most reductions, whereas the entorhinal and visual regions of the brain were observed to be relatively stable. In selected healthy volunteers, reliable individual differences in change were found in all measured regions except the inferior parietal lobule. The differences were particularly clear in the cerebellum, prefrontal white matter, fusiform gyrus, visual cortex and inferior temporal cortex (Raz et al., 2005).

1.4.2. Behavioural findings of cognitive aging

One of the initial findings with regard to the effects of advancing age on cognition was the observation that aging is associated with selective decline as well as selective preservation of abilities. Cross-sectional aging data from a lifespan sample of adults aged 20–89 suggested that, beginning in young adulthood, age-related decline occurs in behavioural performance on measures of processing speed, working memory and long-term memory. Measures of verbal ability and world knowledge, however, were observed to show some improvement. Longitudinal data demonstrate similar findings for speed of processing, working memory, list recall, and verbal ability, suggesting that the cross-sectional results are not primarily due to cohort effects see for a review (Park & Reuter-Lorenz, 2009). Other cognitive functions which have been observed to decline with age are cognitive flexibility, the efficiency of reasoning processes, inhibition, goal maintenance and goal neglect (Butler & Zacks, 2006; Kray & Eppinger, 2006; S. Nieuwenhuis et al., 2000). Decline on some cognitive functions have been shown to affect other cognitive functions. Working memory function, for instance, along with speed, has been proposed to mediate age-related variance on a broad array of cognitive measures (Park et al., 1996). Working memory function in turn has been proposed to be mediated by declines in cognitive control processes such as inhibition (Hasher & Zacks, 1988), or declines in controlled, but not automatic, processes leading to decreases in explicit memory but relatively good memory for versions of stimuli that are familiar (Jennings & Jacoby, 1993).
1.4.3. In search of a unifying principle

In an initial attempt to common-cause models of cognitive aging, a major aim of cognitive aging scientists has been for long to disentangle a single underlying factor that can explain age-related change on a diverse set of cognitive measures (Span, Ridderinkhof, & van der Molen, 2004). Predominating the aging literature for a long time, the general slowing hypothesis (Salthouse, 1996), the frontal-lobe- and the dopamine hypothesis are examples of leading common-cause models. Based on among others meta-analysis of cross-sectional reaction-time data of elderly in the so-called Brinley plots, the general slowing hypothesis postulates that the increase in reaction times on speeded and non-speeded tasks, reflects a general decline in the speed of information processing within the nervous system regardless of their cognitive function. A key-postulation of the frontal lobe hypothesis is that the specific vulnerability of the frontal lobes to advancing age accounts for many age-related changes (e.g. West, 1996). Likewise, the dopamine hypothesis of aging suggests that a monotonic dopaminergic decline explains many of the changes found in cognitive aging. Notwithstanding that both the frontal lobe and the dopamine hypothesis are well grounded in neurobiological changes, and have both been found to mediate many cognitive impairments that accompany normal aging (e.g. Backman, Nyberg, Lindenberger, Li, & Farde, 2006; Kaasinen & Rinne, 2002), a growing body of evidence suggests that particular caution should nevertheless be taken when attributing age effects exclusively to single factors (for a review see Raz & Rodrigue, 2006). It has been proposed that there is only weak and conflicting evidence that frontal regions are selectively and differentially affected by aging (Greenwood, 2000). Therefore, a network-based theory of cognitive aging has been argued to have advantages over the localizationist approach inherent in the frontal aging hypothesis. At present, age-related cognitive decline is commonly considered as pertaining to a range of mechanisms including speed, working memory, inhibition, and cognitive control that show varying degrees of vulnerability in different individuals. As the spectrum of cognitive changes with advancing age is broad, it has been deemed unlikely that any single process or unitary mechanism can entirely explain age-related decline across all individuals (Park & Reuter-Lorenz, 2009).

1.4.4. Cognitive neuroscience of aging

Research in areas by tradition described as clinical neuropsychology, cognitive neuroscience, and cognitive aging has joined together lately into a new discipline, the cognitive neuroscience of aging (Grady, 2008). A main drive in this development has been the investigations carried out in structural and functional neuroimaging, especially in positron emission tomography (PET), and magnetic resonance imaging (MRI).

1.4.5. Approaches to white matter systems

The majority of this research has so far focused on cerebral grey matter. Yet, about 40-50% of the brain volume comprises white matter (Madden et al., 2009). White matter covers regions with a predominance of axons covered with myelin, which also contribute significantly to efficient cognitive functioning, as initial studies of healthy older adults suggest. Although some cognitive or perceptual functions are modular and localizable, others, such as attention and memory, depend on widely distributed neural systems.
Consequently, changes or disconnections within these systems have significant effects on cognitive functioning and behavior (Catani & Ffytche, 2005; Mesulam, 1990).

However, the relation between white matter fibre pathways and cognition with advancing age has not yet been established clearly (Madden, Bennett, & Song, 2009). The majority of previous research on the relation between white matter and cognition has been conducted in patient populations with a focus on ischemic lesions of white matter (e.g. Rabbitt et al., 2007; Raz, Rodrigue, Kennedy, & Acker, 2007).

It is important to note that the clinical rating of the different locations of white matter lesions often results from combining all lesions into a single score, and by dividing whole-brain white matter into two broad categories such as periventricular white matter (long association fibres between subcortical nuclei and more distant cortical areas) and subcortical white matter (subcortical short looped U-fibres, which connect to adjacent cortical areas, (e.g. de Groot et al., 2001; de Groot et al., 2002), restricting the spatial information on the specific networks involved.

In order to identify specific networks associated with individual differences in motivated behavior among healthy older adults, the study in the current thesis applies DTI (diffusion tensor imaging). DTI is a form of MRI that uses a tensor model to measure both the rate and directionality of the displacement distribution of water molecules across tissue components and as a result can characterize the properties of white matter. We applied probabilistic DTI tractography to a group of healthy older adults. Generally, DTI tractography has been successful in isolating white matter pathways with a high degree of correspondence to post-mortem dissection and histology (Catani, Howard, Pajevic, & Jones, 2002). Probabilistic tractography is specifically valuable for tracking into subcortical regions (Jones, 2008; Nucifora, Verma, Lee, & Melhem, 2007), and for identifying white matter pathways within each participant, rather than the degree to which the individual pathway is shared with the group average (Madden et al., 2009). Characteristically, tractography estimates the most likely structure and projection-site of an individual white matter pathway spreading from a specified source region. Thus, because tractography is conducted in native space of each individual and is specifically sensitive to subcortical regions, it can reveal variability in the spatial structure of the basal ganglia tracts across participants. (For discussions of the value of DTI voor neuroscience, its limitations and its physics the reader is referred to Beaulieu, 2002; Johansen-Berg & Rushworth, 2009).

To date, to the best of our knowledge there has been a paucity of research focusing on healthy aging from a network- and individual difference perspective. Therefore we first establish the current approach within the present directions in the field of the cognitive neuroscience of aging.

1.4.6. Functional neuroimaging approaches

Starting to apply neuroimaging tools to the study of aging in the past decade, neuroscientists have revealed selective changes in the aging brain that reflect neural decline as well as compensatory neural recruitment. Within the realm of the frontal lobe hypothesis, and in another attempt to provide comprehensive explanation of aging effects, neuroscientist aimed to relate age-related changes across a variety of cognitive processes to global patterns of changes in prefrontal lobe activation, proposing several models, among
which the dedifferentiation (Baltes, Staudinger, & Lindenberger, 1999), the neural inefficiency (Morcom, Li, & Rugg, 2007), the compensatory plasticity models HAROLD and PASA (e.g. Cabeza, 2002; Cabeza, Nyberg, & Park, 2005) the Scaffolding Theory of Cognitive Aging (STAC) (Park & Reuter-Lorenz, 2009) and the CRUNCH model (Reuter-Lorenz & Cappell, 2008), as elaborated in more detail below (see for a review Maillet & Rajah, 2013).

1.4.6.1. Models of dedifferentiation and neural inefficiency

The dedifferentiation model (Baltes et al., 1999) posits reduced regional specialization in function (dedifferentiation) owing to a reduced signal-to-noise ratio on the basis of reduced catecholaminergic availability in the PFC. This reduced signal-to-noise ratio renders task-related PFC regions less activated and age-specific PFC regions more activated. Thus, the model predicts an increased overlap in the PFC regions recruited across tasks in older versus younger adults. The dedifferentiation model’s prediction of increased activation in age-specific regions is typically seen as a detrimental process, whereas theoretically, increased activation in age-specific regions may as well be compensatory since it is possible that the reduced specialization in function may facilitate the recruitment of novel PFC regions with age (Maillet & Rajah, 2013).

The neural inefficiency model proposes reduced processing efficiency in the prefrontal cortex with advancing age, possibly due to under-lying reductions in grey- and white matter and/or altered neurochemistry (Morcom et al., 2007), leading to over-recruitment of task-related prefrontal cortex areas in order to compensate for this neural inefficiency. Hence, the model predicts increased activity in task-related prefrontal cortex regions in older as compared to younger adults. It is unclear how this model accounts for over-activations in age-specific prefrontal cortex regions; theoretically they may pertain to attempted or successful compensatory neural plasticity in response to inefficiency in task-related prefrontal cortex-areas.

1.4.6.2. Models of compensatory plasticity

Compensatory plasticity models concentrate explicitly on over-recruitment of age-specific prefrontal cortex regions during various cognitive tasks. Some of these models posit functional reorganization in the aging brain; while others propose that functional organization sustained, and additionally, new neural strategies are implemented via the recruitment of additional neural resources in the prefrontal cortex.

Originating from a group of neuroscientists around Roberto Cabeza (Cabeza, 2002), the compensatory plasticity neural models HAROLD and PASA, propose that the aging brain adapts to reduced neural resources in frontal and posterior brain regions by recruiting additional neural resources. This compensatory process is suggested to take two forms.

First, according to the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) Model, older adults display a more bilateral activation pattern, in contrast with the relatively more lateralized pattern of brain activation usually observed in younger adults. Initially demonstrated in the prefrontal cortex during a verbal memory task, this pattern was discerned during number of other cognitive processes such as working memory, episodic memory encoding and retrieval, semantic memory retrieval, inhibition and perception.
Second, the Posterior-Anterior Shift in Aging (PASA) model (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) proposes an age-related increase in prefrontal cortex linked with a decrease in occipital cortex, which correlates positively with performance.

HAROLD and PASA, propose that the aging brain adapts to reduced neural resources in frontal and posterior brain regions by recruiting additional neural resources. This theory predicts for instance increased bilateral frontal activation. Park and Reuter-Lorenz (2009) proposed that scaffolding does not occur exclusively in aging, but across the entire lifespan, when cognitive function is challenged.

The compensation-related utilization of neural circuits (CRUNCH) model posits limitations on the potential of the aging brain to compensate for neural insults. Although the CRUNCH bears resemblance with the compensatory models described above, it can be said to differ from these in that it makes specific predictions about compensation only occurring at lower task difficulty levels. As task demands increase the CRUNCH argues that a “resource-ceiling” is reached, resulting in decreased activation and cognitive decrements (Reuter-Lorenz & Cappell, 2008).

Although these models certainly provide an incomplete picture of neurocognitive aging, it yet reflects the direction in the past decade of neuroimaging-research on neurocognitive aging has taken.

1.4.6.3. When less is less and more is more: Challenges in the neuroimaging of aging

1.4.6.3.1. Cross-sectional studies

Notwithstanding the advances which have been accomplished in neuroimaging research of neurocognitive aging, it is now time to also think about the limitations of the direction that has been taken so far, and to think of ways to improve approaches to neurocognitive aging.

In daily neuroimaging practice, distinguishing between these competing neural models has proven difficult, especially using functional imaging data (Maillet & Rajah, 2013). At present, for instance, the group of neuroscientist behind the HAROLD and PASA model is working on an extension of their models by implementing changes in functional connectivity, by implementing a CRUNCH-like differentiation between “attempted” and “successful compensation” (Davis, in press), and by testing their assumptions on the causal relationship between increased brain activity and successful performance, with transcranial magnetic stimulation.

Given the variety and heterogeneity of results observed in the study of neurocognitive aging, it is currently deemed unlikely that any of the models can completely explain all the findings. Instead, it has been proposed that dedifferentiation, neural inefficiency and compensatory plasticity may all be at play, and reflect the function of complementary neural processes in the aging brain (Maillet & Rajah, 2013).

Moreover, similar to developmental neuroimaging studies performed in cross-sectional groups of children and adults, one persistent puzzle in studies on neurocognitive aging is that, although consistent findings are reported across studies, these are often limited to the observation that a specific brain area which is important for behavior in young adults, is not
activated to the same level in older adults, or that elderly activate a number of other brain areas that are not observed in young adults (for a review see Crone & Ridderinkhof, 2011). At present the findings in older adults are often interpreted post hoc, based on reverse inference about the function of these unexpectedly activated brain areas in young adults. This post hoc reverse inference based on activations in adults may not be trivial, as cognitive processes are made up of different sub processes that might be differentially affected in older adults. Inhibition tasks for instance may require the maintenance and active representation of a rule of goal, such that elderly may use different strategies when performing the task. Therefore, it is advisable to base neuroimaging investigations of neurocognitive aging on process-specific knowledge from experimental cognitive psychology, and interpret compensatory activation with caution.

1.4.6.3.2. Neurovascular changes

Moreover, in cross-sectional studies, age-related changes in the cerebrovascular system complicate the interpretation of brain activation. As stated previously, fMRI usually measures the BOLD signal, which is an indirect measurement of neuronal activity that depends among others on cerebral blood flow, cerebral blood volume, and cerebral oxygen consumption. Advancing age is related to alterations in the cerebrovascular system, such as reduced elasticity of vessels and increased atherosclerosis. These changes may influence neurovascular coupling and the BOLD response.

Several laboratories investigated the effect of normal ageing on the BOLD response, by studying the spatial and temporal features of the BOLD haemodynamic response function (HRF) during a task that is thought to result in equal neural activity in younger and older adults (D’Esposito, Deouell, & Gazzaley, 2003). The studies converge on the conclusion that there are similarities and differences in the BOLD response between age groups. A frequently observed difference is the decreased signal-to-noise ratio in the BOLD signal of older adults when compared to younger adults (e.g. Huettel, Singerman, & McCarthy, 2001). This decreased signal to noise ratio has been attributed to a higher level of noise in the older adults that led to a decrease in the spatial extent of the BOLD signal (D’Esposito et al., 2003). The amplitude of the HRF has been found to be similar to young adults in visual cortex (Huettel et al., 2001) and decreased when compared to young adults in sensorimotor cortex (Hesselmann et al., 2001). These observed similarities and differences in the amplitudes of the HRF in different areas of the brain with advancing age, have been proposed to mirror the non-uniform distribution of atherosclerosis in the aging brain (D’Esposito et al., 2003).

The above described changes in the BOLD response in older adults indicate that some property of the coupling between neural activity and BOLD signal changes with age. As the BOLD signal is an indirect measure, which depends among others on cerebral blood flow Bangen and colleagues (2009) recently measured both BOLD and cerebral blood flow, while older adults were performing an episodic memory encoding task. They found increased cerebral blood flow, but not BOLD response in older adults during encoding as compared to young adults. The authors concluded that the BOLD contrast can give misleading information about the underlying activity of neurons when interpreting the BOLD response in isolation, especially in the presence of influencing factors such as age, disease, or disease risk (Bangen et al., 2009). As even ‘healthy’ older subjects may have undetected, clinically
silent vascular pathology, it seems critical to assess for cerebrovascular function (e.g. stroke risk) in older adults and to take cautions when designing experiments and interpreting fMRI results (for review see D’Esposito et al., 2003).

The generally observed lower signal to noise ratio in older adults (d’Esposito et al., 2003), combined with the earlier mentioned fact that subcortical structures can pose a problem in blood-flow based methods because they are small and located close to vasculature, rendering the BOLD signal more vulnerable to artefacts (Schneider & Kastner, 2005), lead us to initially record BOLD signal in a group of older adults, but in the end refrain from performing analysis of BOLD functional connectivity on basal ganglia structures in older adults, but to apply probabilistic tractography based on DTI measures. As stated previously, probabilistic tractography has been suggested to be specifically valuable for tracking into subcortical regions (Jones, 2008), and for identifying white matter pathways within each participant, rather than the degree to which the individual pathway is shared with the group average (Madden et al., 2009).

1.4.6.3.3. Individual differences

Moreover, in cross-sectional studies across age groups, the interpretation of brain-behaviour correlations is generally difficult due to many potential confounds among which cohort effects, and the large inter-individual differences in performance (Crone & Ridderinkhof, 2011). This holds especially for the study of the elderly (Hedden & Gabrieli, 2004), whose response times have been associated with global slowing, increased variability; and a relatively higher response time-increase with increasing task difficulty or complexity than in younger adults (Nieuwenhuis, 2001). For an extensive account of these limitations in the context of developmental and aging research, the reader is referred to Span, Ridderinkhof, and Van der Molen (2004) and Crone and Ridderinkhof (2011).

1.4.6.3.4. Concluding

Although common-cause theories of aging may have the merit of providing comprehensive explanation of aging effects, the above-described considerations currently pave the way towards a new direction in the research on cognitive aging, with the following thoughts at the bottom-line:

Various cognitive processes, brain mechanisms and neurotransmitters are at work in neurocognitive aging. Just as cognitive processes are made up of different sub processes that might be differentially affected, brain regions are organized in networks, interconnected by white matter pathways, all of which together underlie cognitive processes. The impact of cognitive aging differs depending on the task and brain region - even within the frontal lobes.

Individual difference approaches to neurocognitive aging may circumvent some of the problems related to cross-sectional neuroimaging studies, and detect adaptive neuronal processes in healthy aging that might be masked in cross-sectional studies.
Introduction to reward-based action control

1.5. Summary

To sum up Chapter 1, the current dissertation studies reward-based action control in an antisaccade paradigm that was developed based research in on non-human primates. We focus on neural circuitry to investigate the correspondence between reward and oculomotor processes. Little is known about the oculomotor circuitry in humans, particularly on the role of the subcortical striatum. Based on research in non-human primates the caudate is conceived as an important player in both oculomotor- and reward processes. Neuroimaging research on neurocognitive aging faces many methodological challenges. Individual difference approaches to neurocognitive aging may circumvent some of the problems, and detect adaptive neuronal processes in healthy aging that might be masked in cross-sectional studies. Neurocognitive research on aging is currently moving from a common-cause approach to methods which are based on process-specific knowledge, and on the understanding that specific cognitive processes are associated with brain regions that are organized in networks.

1.6. Outline of part I of this thesis

This thesis comprises two major parts. The first part investigates reward-based action control. Chapter 2 was motivated by the observation that goal directed actions are executed with greater efficiency when the goals of the actions are rewarded. We investigated the hypothesis, whether the expectation of reward improves performance in an antisaccade task—a task in which age-related declines in performance are typically observed—in a group of older adults and in individuals with Parkinson’s disease. Chapter 2 describes a behavioural study in three groups (young and older adults, and older adults with mild Parkinson disease) and tested predictions with a novel antisaccade-task that we developed based on non-human primate research. The results on the effects of reward anticipation on antisaccade performance in the 2nd Chapter, serve as a foundation for the investigation of the neural systems related to this effect in the subsequent Chapters 3 and 4. Chapters 3 and 4 were motivated by the hypothesis, that the optimizing effect of reward anticipation, if there is any, should be reflected in increased communication between brain systems concerned with reward and oculomotor control. Chapter 3 concerns a study in young adults. We replicate the behavioural results from Chapter 2 in a second experiment, and examine the hypothesis that, during reward anticipation, the basal ganglia, particularly the nucleus caudate increases its inter-region interactions with cortical oculomotor structures. It is explored if individual differences in behavioural benefit from reward anticipation are related to these enhanced striato-cortical interactions. For this purpose oculomotor measures and BOLD measure are concurrently acquired using combined eye-tracking and fMRI. Chapter 4 describes an investigation in older adults. We replicate the behavioural results of Chapter 2. Based on the findings in Chapters 2 and 3, we investigate the hypothesis that individual differences in overt benefit in antisaccade performance from reward anticipation, relate to differences in striato-cortical white matter pathways among older adults. For this purpose we perform a DTI study on the basal ganglia in older adults using probabilistic tractography. We combine the results with individual differences in
Chapter 1

overt eye-tracking measures of antisaccade performance. Chapter 8 summarizes and discusses the empirical results and provides an outlook for possible future research.