Chapter 9

General Discussion, Conclusions & Future Directions
9.1 General Discussion

In this thesis, we were able to elucidate the role of internal and external impacts on parietal-premotor circuitry in cerebral motor control. The experiments described in this thesis were mainly done with fMRI paradigms in healthy volunteers. Based on the findings of the fMRI experiments, subsequent behavioral experiments were conducted in two patient groups with movement disorders, i.e., Parkinson’s disease and degenerative cerebellar disease. All experiments had in common that cerebral motor control beyond basic visuospatial processing was required. This provided the opportunity to investigate cortical circuitry that supports parieto-premotor circuitry in motor control.

9.1.1 Space-referenced Time-processing

Cortical processing beyond the activation of parieto-premotor circuitry, particularly with regard to the dynamic aspects of visuospatial coordination, was demonstrated in chapter 2. The results of the described fMRI experiment showed that the spatial estimations concerning the displayed movements of a ball were restricted to activations in parieto-premotor circuitry whereas the estimation of temporal movement characteristics revealed additional prefrontal, pre-SMA and cerebellar activations. The activation of this additional circuitry shed new light on cerebral processing required for making temporal estimations. Firstly, the finding that the neuronal circuitry underlying temporal processing did include parieto-premotor activation might implicate that the processing of temporal information is space-referenced. The fact that this parieto-premotor activation was not longer present when contrasting the temporal estimation condition with the spatial estimation condition supported this.

With regard to the additional timing-related activations, the involvement of the pre-SMA in time keeping was suggested to reflect the sequential organization of demarcated spatial ‘frames’ provided by parieto-premotor circuitry. Such a role in the sequential organisation of cortical information was already attributed to the (pre) SMA in early functional neuroimaging experiments (Roland et al., 1980, 1982). In those studies, subjects had to execute (Roland et al., 1982) or imagine (Roland et al., 1980) sequential movements. No judgement on sequential aspects of visually presented stimuli was required. The fact that the (pre-) SMA thus appears to be involved in the sequential organization of both motor and perceptual information may be seen as an argument
in favour of a general time keeping mechanism in the brain. This common involvement of the (pre-)SMA in time perception and motor timing has indeed been demonstrated by recent functional brain imaging, which showed that such common involvement also held for other brain structures such as cerebellum, basal ganglia and fronto-parietal regions (Bueti et al., 2008; Ivry and Hazeltine, 1995; Schubotz et al., 2000). Based on both behavioral and neuroimaging results, the concept of a unifying time keeping mechanism has emerged (Bueti et al., 2008; Ivry and Hazeltine, 1995; Keele et al., 1985; Rammsayer, 1989; Schubotz et al., 2000; Treisman et al., 1992).

The contribution of sensorimotor integration in time-keeping mechanisms can already be inferred from observations in lower vertebrates such as the zebrafish larvae, in which neuronal activity in the optic tectum times motor behavior based on the duration of a preceding visual stimulus (Sumbre et al., 2008). Such a ‘adjustable metronome’ that coordinates visuomotor behavior gives evidence for a phylogenetic old coupling between temporal aspects of sensory input on motor output and adds insight in the neuronal basis of the temporal organization of sensorimotor control.

The fMRI experiment of chapter 2 was primarily designed to study the relation between spatial and temporal processing, in which the prediction conditions were optimally balanced. The additional comparison of speed estimation with judging the actual location of the ball’s disappearance showed a distribution of activations that strongly resembled the pattern of activation related to time prediction (contrasted to spatial prediction). This similarity provided support for the idea that after the ‘extraction’ of a spatial component from velocity (expressed in m/s), an indicator of ‘momentary time’ is obtained. This implied a measure of time linked to a minimal interval of spatial change. Indeed, to estimate the velocity of a moving object, i.e. fast, slow and all gradients between them, small intervals of its displacements over time need to be compared with reference to intrinsic cerebral processing time. The fact that the activations related to this ‘momentary time’ assessment also included striatum (caudate) activation, which was not the case in time prediction, further highlighted the involvement of the dopaminergic system in time-keeping. The specificity of the caudate activation in velocity estimation, relative to momentary spatial judgment (Ch. 2) was confirmed by an additional ROI analysis that further showed a significant increase of caudate activation relative to baseline. In chapter 4, the specificity of striatum involvement in velocity estimation and not in temporal prediction was further supported by the subsequent behavioral study in PD patients and patients with degener-
ative cerebellar disease: velocity estimation was exclusively disturbed in PD patients, thus in the condition of striatal deficit.

The estimation of small spatial displacements over time could be based on the processing of ‘minimal’ intervals in CBGTC loops by means of ‘clock-like’ neural circuitry. Interestingly, previous neuropharmacological research in rodents (Maricq et al., 1981; Meck, 1983) also reported involvement of the dopaminergic system related to time keeping. In these studies, drugs stimulating the dopaminergic system (methamphetamine) and drugs inhibiting the dopaminergic system (haloperidol) respectively increased and decreased perceived interval durations (Meck, 1983). Ever since, this relation between clock-like neural circuitry and temporal processing (Gibbon et al., 1984) still exists and has been refined several times and resulted in the Striatal Beat-frequency (SBF) model (Meck, 2005; Meck and Benson, 2002). In that model, timing is based on the coincidental activation of medium spiny neurons of the striatum and cortical neural oscillators.

With regard to the interaction between cortical processing and striatum function, we speculated on a model (Ch. 2, Fig. 2.3) in which general cerebral processing time is essential in the demarcation of minimal (spatial) intervals, thus constructing a measure of time that is closely associated with external stimulus input. In addition, the striatum is proposed to play a role in accumulating cortically dispersed intervals related to initially given stimuli, thus enabling this central integrator to achieve the emission of a regular ‘pulse’. In this way, it serves as a timekeeper for the cerebral cortex, not based on independent signal emission but based on stimulus processing in the cortex itself. The basic scheme of the connections between the cortex and basal ganglia indeed enables the latter to play a role in imposing sequential regularity on the cortex. Such computations not only concern the serial organization of movements but also the serial order in perceiving moving objects. As a consequence of striatum dysfunction, e.g. in PD, the sequential organization of movements may slow down (bradykinesia), while alternating contractions of antagonistic muscles may become inadequately tuned in time (rigidity/tremor). Whether such disruption also causes impairments in perceptual temporal estimations has long remained an issue of debate because the majority of applied paradigms used responses that could not dissociate motor from perceptual timing components (Wearden et al., 2008).

In chapter 4, the striatum contribution to ‘momentary’ time assessment gained further support by the selective impairment of velocity estimation in
PD patients. Moreover, these results could definitely be attributed to a perceptual deficit because motor impairment was circumvented by using dichotomous instead of reaction-time-dependent responses. Additional analysis of these data revealed that the difference between PD and control subjects was almost entirely due to an impaired judgment of fast, and not slow, velocities (Fig. 9.1). This might implicate a decrease of hypothetical internal clock speed in PD, associated with enlargement of the intervals of minimal spatial change that demarcate spatial frames (Ch. 2). Based on the literature concerning the ‘flash-lag’ illusion we speculated that, in healthy subjects, processing time needed for establishing a distinct spatial frame might be in the magnitude of 100 ms. We tested the idea of a distinct unit indicating minimal intervals, as well as its hypothesized change in PD, by asking PD patients and healthy volunteers to assess whether velocity of a moving ball either remained the same or changed after the ball touched and rebounded from the upper side of the screen (Ch. 5). A most intriguing result was that both healthy volunteers and PD patients indicated to perceive a decreased return velocity of the ball when it actually remained unchanged, while the perception of unchanged velocity occurred when the ball actually increased its velocity at the point of return. This shift, i.e. the difference between the duration of the stimulus of perceived similar- and actual similar velocity, concerned 100 ms for the healthy volunteers and 76 ms for the PD patients. This implied that a measure of cerebral processing time inferred from our paradigm indeed corresponded with the previous suggested measure derived from the flash-lag illusion (Eagleman and Sejnowski, 2000; Nijhawan, 1994).

A variant of the flash-lag illusion is the flash-lead illusion which means that a moving object is perceived to be behind a spatially concurrent stationary flash in case the moving object actually disappears together with the flash (Roulston et al., 2006). When the moving dot does not disappear, but proceeds in its trajectory, its position is perceived to be ahead of the spatially concurrent flash, indeed referred to as the classical flash-lag illusion (Eagleman and Sejnowski, 2000; Nijhawan, 1994). In chapter 2, spatial assessments were made at the moment the moving ball disappeared, which may indeed be associated with a position virtually projected backward. In chapter 5, assessments concerned velocity change at the turning point. As the ball moved on after the turning point, a flash-lag phenomenon might occur. In other words, the moving dot is projected ahead to its actual position. A consequence would be that velocity decrease at turning is masked by the preceding higher velocity. In other words, an actual velocity decrease is perceived as unchanged velocity. This is exactly what we found, including the measure of 100 ms. In the concept of a
Figure 9.1: Velocity estimation in the control (con) and Parkinson’s disease (PD) group. Percentage of stimuli (and SD) that were actually slower than average and perceived as such (left, ‘slower’) and vice versa (right, ‘faster’). * = p < 0.05, ns = non significant.

Furthermore, the equal perceived velocity correlated significantly with the amount of bradykinesia patients had. In this, the more bradykinetic patients were, the more positive the perceived equal velocity was (Ch. 5). This correlation was not related to other disease characteristics, e.g. tremor or rigidity. The absence such small-scale feedforward processing in visuomotor control in PD might explain the actual slowing of movements: bradykinesia.

An important conceptual issue raised in the introduction of chapter 2 concerned relative slowness of nerve conduction, which hinders real-time adjustments to environmental changes. To overcome such insufficiency, the brain makes use of predictions in order to anticipate future environmental states.
Cortico-cerebellar networks, with an architecture that adequately fits feed-forward processing, play an important role in such predictions, which was indeed demonstrated in chapter 2. This temporal role of the cerebellum was also described in a recent fMRI experiment that showed considerable resemblance with our study (O’Reilly et al., 2008); see discussion Ch. 2). The specific relation between the cerebellum and feed-forward based temporal predictions was further underscored by the selective impairment in patients with a degenerative cerebellar disease and not in PD patients (Ch. 4).

Making predictions implies the use of preceding information. In chapter 2, this was phrased as the ‘ordering of both past and future spatial states’. In chapter 3 we focussed on cerebral processing related to actually attending to the successive locations of a moving ball, which was the case in the experimental condition that only required indicating the location of its disappearance. By contrasting this condition with conditions in which either the past start location or the estimated future location was indicated, evidence for co-occurring activation in the posterior hippocampus was obtained. The association between the latter and ‘on-line’ registration of spatial change is consistent with the role of the hippocampus in saliency detection. In this respect, an early stage of detecting spatial change may possibly provide early feedback enabling the adjustments of visuospatial predictions based on most recent environmental information.

Taken together, in the first part of this thesis we obtained arguments for the model that cerebral handling of temporal information in a spatial context involves at least four categories of neuronal processing: (i) an initial fragmentation of the spatial information flow into distinct spatial frames, requiring subsequent sequential ordering (Ch. 2), (ii) the computation of spatial change over time with reference to such spatial frames, while minimal intervals of spatial change are defined by intrinsic neuronal processing time (Ch. 2, 4 & 5), (iii) the extrapolation of this information by means of feed-forward based circuitry enabling the preparation of coming action (Ch. 2 & 4) and (iii) the on-line registration of actual unwinding of reality to facilitate early feedback on predictions generated by feed-forward based circuitry (Ch. 3). These ideas gained support by the behavioral experiments performed in patients with PD and degenerative cerebellar disease that showed selective impairments in respectively velocity assessment and temporal prediction (Ch. 4 & 5).
9.1.2 Free Selections

The second major question addressed in this thesis concerned the links between circuitry involved in free movement selection and parieto-premotor circuitry previously implicated in visuomotor tasks based on fixed instructions (Ch. 6). In such previous studies, a dissociation was discerned between parietal motor representations based on respectively environmental spatial locations and body-scheme (de Jong et al., 2001). Now, we were particularly interested whether such parietal dissociation was also present at the level of the PFC when free selections were made. To investigate this, we instructed subjects to freely choose either one of four buttons (target referenced) or one of four fingers (body-scheme referenced) with which they gave a motor response and respectively contrasted this with fixed button and finger responses while fMRI data was obtained. Contrary to other conducted free-selection paradigms (Frith et al., 1991; Lau et al., 2004b; Mueller et al., 2007) we were able to overcome a visual attention bias between the fixed and free selection conditions by presenting the instruction stimuli auditory.

A striking new finding was that increased activation related to free selection, relative to the fixed selection, included the rostral extension of the dorsal pre-motor cortex and the inferior parietal cortex (Color Fig. 8 on page 206). The fact that these activations were so closely linked to parieto-premotor circuitry, and not restricted to the PFC, provided support from human data for recent neurophysiological findings in monkey that early stages of visuomotor processing may already contribute to action selection (Cisek and Kalaska, 2005; Cisek, 2007). These findings add insight in the relation between the role of the rostral PFC (BA 10) and early-stage selection, particularly highlighting the efficiency by which the most appropriate action is finally selected. It would be interesting to further characterize the temporal profile of the BOLD response in the anterior parietal and pre-PMd cortex while free selections are made. This characterization could give more insights in unconscious determinants of free selections that precede both action awareness and execution (Soon et al., 2008) in these regions. The temporal dispersion of the stimuli that were used in our paradigm (once every 3 seconds) made the design less appropriate to conduct these analyses on our current data.

Another important aspect of our data was the absence of pre-SMA activation in the free selection conditions (Color Fig. 5 on page 203). To explain this difference with previous studies that addressed free selection, we emphasized that in our visuomotor experiment instructions were provided auditory, thus
9.1. GENERAL DISCUSSION

avoiding a bias between fixed and free selection with regard to visual cuing. As a consequence response times were not longer in free- than in fixed selection. Such association between free selection and prolonged reaction times was the case in previous studies and introduced a component of working memory that might alternatively explain part of the pre-SMA involvement. This temporal component is also an intrinsic part of choosing the moment when to make an action. Recently, it has indeed become increasingly clear that in studies on free-selection a distinction between ‘what’ and ‘when’ to select can be made (Brass and Haggard, 2008; Mueller et al., 2007). One of the cortical representations of this ‘what’ component was concluded to be the anterior cingulate cortex (ACC) whereas the pre-SMA was particularly involved in the ‘when’ component of action selection (Mueller et al., 2007). This role of the ACC is in line with the specific activation of this area in the free selection of external targets in our data (Ch. 6). Since ACC activation was only present in free button- and not in free finger selection in our experiment, we considered this role to reflect a selective involvement in the selection of externally defined behavioural goals. This implies that the ACC is not specifically implicated in selecting behavioral ‘means’. Observations that the ‘what’ component in decision-making appears to require a more extensive cortical processing than the ‘how’ component, may suggest that the free selection is intrinsically stronger anchored in motor programs than in the representations of (spatially defined) external events. The similarity between free selection of when to perform an action (described in other studies) and accurate timing of a distinct action (Ch. 2) is that they both occur in the relative absence of actual external information. Since both actions involve the pre-SMA and are both disturbed in PD, in which especially the (pre) SMA is affected (Jahanshahi et al., 1995; Jenkins et al., 1992; MacDonald and Halliday, 2002), a slower perception of time (Ch. 4-5) might be the consequence of the same deficit underlying slower initiation of movements (Dick et al., 1989) in PD. Such convergence between neuronal circuitry involved in free selection of the moment for action and timing might implicate that a metric of time is a prerequisite for free selections of time: given the concept of temporal processing described in chapter 2, a choice is made between future ‘spatial frames’.

The dissociation between target-based- and self-referenced free selection (Ch. 6) illustrates that neuronal correlates of freely selected actions are widely embedded in the brain, particularly in those cortical regions that process the information from which can be chosen. When this information concerns either the external environment or body scheme, inferior parietal and rostral premotor areas are involved. When decision-making concerns ÔtimeÔ, neural
circuitry involved in time keeping is involved. In this respect, one may argue that we do not create but select possible behaviour (Kolk, 2008).

9.1.3 Unfamiliar Movements

In the previous section, we investigated free selected finger movements that were either guided by body-scheme information or by external objects. The finger movements that were involved in this paradigm consisted of everyday movements that belonged to the motor repertoire of subjects. When movements do not belong to such repertoire, a reference to a body scheme is not used and parieto-premotor circuitry is not involved in the translation of observed movements into actual movements. The question thus arises whether representations of ‘unknown’ movement exist at all. A consequence of the latter would be that ‘practice-induced’ mapping of movements and their sensory consequences on this parieto-premotor circuitry is crucial for effective motor control. We investigated this by letting subjects imagine, execute and observe a movement they had never made before, and could indeed initially not perform: hallux abduction. The degree to which subjects were able to make such movement correlated with activation in the anterior parietal cortex: the secondary somatosensory cortex (SII).

The dominant involvement of SII generates new research questions. E.g., what is the effect of passive movements on learning the skill of hallux abduction? In this respect, one may wonder whether learning an unfamiliar movement can be realized by only providing kinaesthetic information or that a co-occurrence of premotor activation is required. Comparing the learning curves of hallux abduction following passive movements in two groups, either with- or without simultaneous movement imagining might provide an answer in this. Based on the activations related to motor imagery with peak values in the premotor cortex and no anterior parietal responses in subjects who did not master hallux abduction (Ch. 8), one might predict that co-occurrence of externally induced SII activation and internally generated premotor activation establishes effective hallux abduction by means of hebbian learning (Keysers and Perrett, 2004). A variant on this would be to let subjects watch the hallux abduction movements, either with- or without imagining this movement. Developing these motor-learning techniques might provide an entry to restore motor control after neural injury. In this, hallux abduction might be a powerful tool evaluate and optimize strategies to improve motor skills that can be extrapolated to (neuro) rehabilitation programs.
9.1.4 Cerebral Activation Patterns Over Time

The brain is an adaptive organ that optimizes its efforts to support motor control. This means that the brain is able to adapt future processing based on previously performed sensorimotor transformations (Ch. 3). In Chapter 8 we illustrated that only after actual experience of a previously unfamiliar movement parietal circuitry becomes involved in the execution, imagery and observation of such movement. Next to this, but at a timescale of tens of minutes, i.e. within an fMRI session, such adaptations also occurred in the basal ganglia (Ch. 7) and went along with decreases in reaction times. Contrary to these increases in activation, prolonged exposure to stimuli showed decreased cerebral activation patterns (Ch. 8). This subtle balance with on the one hand decrease of cortical activation and on the other hand the facilitation of (sub) cortical circuitry over time illustrates that only the most appropriate cortical circuitry ‘survives’ during repeating stimulus-response tasks. This might be seen as a functional pendant of neural Darwinism in which the appropriate task-related circuitry is a result of previous exposure, resulting in internalized task requirements, and current task demands.

9.2 Conclusions

Sensorimotor transformations based on information directly and unambiguously provided by external stimuli can be distinguished from sensorimotor transformations that require additional cerebral processing. Sensorimotor transformations that interact in an unequivocal way with external stimuli are processed in parieto-premotor networks whereas additional processing of e.g. temporal information or free selection requires additional (sub) cortical involvement. This involvement of ‘internal processing’ is besides, and not instead of, parieto-premotor involvement in cerebral motor control. For the additional neuronal processing of temporal information, spatial information, encoded in parieto-premotor circuitry, may be sequenced and extrapolated by respectively fronto-striatal and fronto-cerebellar circuitry. Such circuitry involved in sequential measurements of time (fronto-striatal) and anticipations on future events (fronto-cerebellar) might form the core of cerebral time keeping in sensorimotor control. For the additional neuronal processing of free choice based actions, cortical circuitry adjacent, and even in, parieto-premotor circuitry is already involved. Such close interrelation between basic sensorimotor circuitry and circuitry related to free choice based decisions gives support for a widely distributed cortical embedding of free selections instead of an exclusive involvement of the prefrontal cortex. On the other hand, actions, notwithstanding
whether they are made free or according fixed instructions, require both ade-
quate representations of the external scene in which they take place and access
to body scheme information to command the contractions of specific muscle
assemblages. For the latter, the cortical embedding of a particular movement
has a close interrelation with its accompanying proprioceptive feedback that is
processed in the (parietal) secondary somatosensory cortex. Taken together,
additional cortical processing beyond basic sensorimotor control depends on
an actual interplay with parieto-premotor circuitry and is not necessarily an
autonomous process. This implies that cerebral motor control is based on
a continuous interplay between externally provided information and internal
selection, sequential organization and extrapolation of this information.

9.3 Future Directions

The research questions that formed the principles of this thesis (see intro-
duction) arose from previous work from our group. Similar to these original
questions, the findings of the conducted experiments described in this thesis
also give rise to new research questions. In the following paragraphs the most
important future directions that are currently investigated will be described.

9.3.1 Time-keeping in Tourette Syndrome

Contrary to the decrease of overt motor performance in PD, Tourette Syn-
drome (TS) is a disorder characterized by an abundance of overt behavior:
tics. However, TS is not limited to motor-tics. Patients suffering from TS also
experience preliminary or discrete sensations which are described as ‘sensory-
tics’ (Shapiro, 1988) for review see (Prado et al., 2008) from which their motor-
tics may emerge. A possible explanation for the neural basis of both PD and
TS is that the balance between inhibitory and facilitating mechanisms for es-
ablishing efficient goal-directed behavior is disturbed in disfavor of inhibition
in TS and in disfavor of facilitation in PD (Redgrave et al., 1999). The neural
embedding of such inhibition and facilitation is in CBGTC loops (Toxopeus
et al., 2007; Wright et al., 2006). Next to the widely known alteration of this
circuitry related to PD (Leenders et al., 1984), recent neuroimaging, e.g. Diff-
fusion Tensor Imaging (DTI), findings report also report CBGTC deficits in
TS (Makki et al., 2008). It this respect, the functional role of the striatum,
especially the caudate nucleus, in directing goal-directed behavior (for review
see (Grahn et al., 2008) might be affected in an opposing way in PD and TS.
To further investigate this, the behavioral experiment described in Chapter 4
is currently conducted in a TS group. Hypothetically, the CBGTC deficits in
9.3. **FUTURE DIRECTIONS**

TS could lead to decreased striatal inhibition, and lead to an abundant velocity of both perception and action. In fact, this phenomenon has already been observed for a long time. However, these observations mainly concern anecdotic descriptions of TS patients catching flies manually, maneuvering through incredibly small apertures in turning doors and catching objects with amazing velocities.

### 9.3.2 Effects of Optic Flow Modulation on Circuits Implicated in Motor Control

Support for the contribution of the medial prefrontal cortex to internal movements also came from our most recent fMRI experiment (van der Hoorn et al.). In this experiment we visually presented radially expanding optic flow, which generated the illusion of forward self-motion. By disrupting this sensation a shift from circuitry implicated externally driven- to internally driven motor control was expected. Such disruption was evoked by narrowing the field of expanding optic flow stimuli or reversing the direction of flow into contraction. Our hypothesis was confirmed and specified by common activation in the medial prefrontal cortex related to the presentation of reversed and narrowed optic flow, relative to forward optic flow (Color Fig. 16 on page 214). On the contrary, dorsal stream activation was present during the optic flow induced perception of forward self-motion. These two findings provide support for respectively an internal and external support for the motor system.

In PD, such internal support of movements is diminished (Dick et al., 1989; Praamstra et al., 1998), while external stimuli may be difficult to suppress. As medial prefrontal circuitry is especially affected in PD (Jahanshahi et al., 1995; MacDonald and Halliday, 2002), a next question is to see to what extent an activation shift occurs in PD. In this respect, it will be interesting to assess how the elicited activation patterns in motor circuitry correlate with the severity of bradykinesia and Freezing Of Gait (FOG) (Bartels and Leenders, 2008; Snijders et al., 2008) in these patients.

By continuing this line of research, the cortical circuitry underlying cerebral motor control could be further elucidated in both healthy controls and patients with movement disorders. Such understanding is not only a goal on its own, but it also provides the theoretical framework for the development of future treatments to optimally support movements.