Lateralisation of Parkinson symptoms and visuomotor control in gait

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CONTENT

CHAPTER 1	General introduction	9
CHAPTER 2	Handedness and dominant side of symptoms in Parkinson's disease *Published as: Parkinsonism and Related Disorders 2011; 17: 58-60*	25
CHAPTER 3	Handedness correlated with the dominant Parkinson side: a systematic review and meta-analysis *Published as: Movement Disorders 2012; 27: 206-210*	33
CHAPTER 4	Interruption of visually perceived forward motion in depth evokes a cortical activation shift from spatial to intentional motor regions *Published as: Brain Research 2010; 1358: 160-171*	45
CHAPTER 5	Narrowing wide-field flow affects treadmill gait in left-sided Parkinson's disease *Adapted from: Movement disorders 2012; 27: 580-581*	69
CHAPTER 6	Parkinson changes of activation in visuomotor brain regions during perceived forward self-motion *Submitted*	85
CHAPTER 7	Transcallosal connections of the opposite dorsal premotor regions support a lateralised specialisation for action and perception *Submitted*	117
CHAPTER 8	General discussion	131
CHAPTER 9	References	145
CHAPTER 10	Summary/ Samenvatting	183
LIST OF ABBREVIATIONS		195
DANKWOORD		199
RESUME/ CURRICULUM VITAE		205
LIST OF PUBLICATIONS		209

CHAPTER 1

General introduction

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Movements are controlled by the cerebral cortex in such a way that the right limbs are predominantly guided by the left motor cortex, while the opposite motor cortex controls the limbs of the left side. Fine-tuning of e.g. precision movements of the hand is not achieved by an isolated cortex, but results from additional support from other brain structures including the basal ganglia contralateral to the moving hand and ipsilateral cerebellum. Almost all people exhibit an increased ability to make fine-tuned movements of one hand above the other. In most people (±90 percent) the right hand performs better than the left, thus demonstrating a lateralised motor performance in favour of the left cerebral hemisphere. The left hand outperforms the right in a small subset of the population (±10 percent), displaying an oppositely lateralised motor control. This means a difference between right and left in favour of the left side. Movements are executed in a subject's surrounding environment, requiring continuous input from that environment. In this respect, particularly visual information plays an important role. Locating environmental objects and reaching for them implies processing of spatial information concerning such objects as well as providing spatial parameters for goal-directed movement. In this way, adequate visuomotor transformations make it possible that movements are adjusted to or initiated by visual information. Regardless whether objects are located on the right or left side of space, spatial processing and visuomotor transformations are predominantly processed in the right hemisphere (Ben-Yishay et al., 1971; Callaert et al., 2011; Corballis 2003; de Jong et al., 1999; Thiebaut de Schotten et al., 2011; Woolley et al., 2010), thus pointing at a right lateralised motor function additional to the left-hemisphere dominance in skilled precision movements.

Lateralised cerebral functions and the way they interact with the brain as a whole are still poorly understood. This similarly holds for symptoms that emerge from impairment of such functions. Parkinson's disease is a disorder showing movements that are more disturbed on one side than the other side of the body. In this thesis we aimed to gain more insight in various aspects of lateralisation in Parkinson’s disease. To that end, we first looked for a relation between the dominant side of extrapyramidal symptoms and a pre-existing cerebral asymmetry as indicated by handedness. Next, we employed the specific visual stimulus pattern of radially expanding optic flow to study the effect on movement related parameters in Parkinson patients and healthy subjects. These were obtained from both behavioural measurements on treadmill gait and regional cerebral activations identified by functional magnetic resonance imaging (fMRI). In this way, we addressed a higher-order visuomotor function for which a dominant right-hemisphere involvement has been suggested. It thus provided the opportunity to look for an association between

dysfunction and left-symptom dominance in Parkinson's disease (Bartels et al., 2006; de Jong et al., 1999). Aside from the issue of cerebral lateralisation, manipulating optic flow mimicking circumstances during freezing of gait due to a narrow passage, was expected to provide basic insight in the neuronal mechanisms underlying this characteristic Parkinson symptom (Azulay et al., 1999; Suteerawattananon et al., 2004).

To put the spectrum of topics treated in this thesis into a wider context, in the following paragraphs a general outline will be given of (1) cerebral motor control with emphasis on the distinction between externally cued and internally driven action, (2) lateralisation, (3) Parkinson's disease including some aspects of lateralisation, (4) freezing of gait in Parkinson's disease, including the specific relation between optic flow and forward locomotion, and (6) the technical backgrounds of fMRI and diffusion tensor imaging (DTI).

MOTOR CONTROL

As indicated above, movements of one side of the body are controlled by the contralateral cerebral cortex. This statement is an oversimplification as movements are actually organised by a network involving many areas. Dynamics in the contributions of essential nodes participating in such networks are still incompletely understood. While much knowledge about this functional anatomy originated from non-human primate research (Passingham 1993), new functional imaging methods of the human brain generated a wealth of new data in the past two decades.

Movements are predominantly encoded by the contralateral primary motor cortex. At that stage of movement preparation and execution, both the specification of muscle groups and more general target associated parameters such as movement direction and even stereotypic movements are represented (Davidson et al., 2007; Georgopoulos and Stefanis 2007; Graziano 2006; Schieber 2001). The primary motor cortex projects to the spinal cord via the pyramidal tract, which in part also contains projections from premotor areas (Dum and Strick 1991; He et al., 1995; Lemon 2008; Wise 1996). The information received by the primary motor cortex from other areas is particularly transmitted via lateral and medial premotor areas. The premotor areas are strongly connected with the parietal cortex (primary and secondary somatosensory areas), prefrontal cortex and ventral thalamus (Ghosh et al., 1987; Jones et al., 1978; Leichnetz 1986; Passingham 1993). The basal ganglia and cerebellum both project to the ventral thalamus. The posterior subdivision of the ventral thalamus is an important target for cerebellum projections, while output of the basal ganglia is mainly to the anterior subdivision of the ventral thalamus (Macchi and

Jones 1997). As the ventral thalamus projects both to premotor and primary motor areas, the basal ganglia and cerebellum are able to influence movements. The cerebellum, contralateral to the thalamus it projects to, aids in the fine-tuned coordination of muscle groups to accomplish smooth performance of movements. The (temporal) adjustments implicated in such coordination may be both in feedback and feedforward modes, using actual sensory information and predicted sensory consequences of movement respectively (Manto et al., 2012; Nowak et al., 2007; Wolpert et al., 1998). To do so, the cerebellum receives information from the spinal cord as well as various cortical brain areas (Fine et al., 2002). The basal ganglia receive information from prefrontal areas and parietal areas of the ipsilateral hemisphere, and play an inhibitory role, suppressing unwanted movements thus selecting the intended movement (Chakravarthy et al., 2010; Mink 2003). In Parkinson's disease, basal ganglia dysfunction results from dopamine depletion. Aside from increased muscle co-activations in motor actions (Toxopeus et al., 2011), one of the consequences is that the intention to move is disturbed.

The intention to make voluntary movements can both be internally and externally driven. Externally driven movements are particularly movements made in response to environmental factors (i.e. external stimuli). When such environmental factors do not contain an explicit cue, goal-directed movements are characterised as internally driven. In humans, this distinction between internal and external movement generation goes along with a functional segregation between networks centred around medial and lateral premotor areas respectively (Debaere et al., 2003; Deiber et al., 1999; Mueller et al., 2007).

The dorsolateral network is specifically important in providing external information for movement preparation. The dorsolateral network includes the premotor cortex (cytoarchitecturally defined as Brodmann area 6), which can be divided in the dorsal premotor cortex and ventral premotor cortex (Rizzolatti and Matelli 2003). The dorsal premotor cortex is strongly connected with posterior superior parietal areas such as the medial inferior parietal lobule, V6A and even directly with visual area V6, particularly organising the spatial direction of movements (Galletti et al., 1999; Galletti et al., 2001; Matelli et al., 1998; Shipp et al., 1998; Wise et al., 1997). The ventral premotor cortex acts together with the antero-inferior parietal cortex to integrate object shape and finger positions to enable adequate object manipulation (Matelli et al., 1998; Sakata et al., 1997; Shipp et al., 1998). These parietal areas are thus involved in the preparation of purposeful movements, which implies interaction with a dynamic extrapersonal space requiring continuous updates by visual motion information. The (dorsal) parietal connections with

striate and extrastriate visual cortex indeed particularly include the visual motion area V5 (also referred to as middle temporal area, MT) (Galletti et al., 2001; Tootell et al., 1995; Zeki et al., 1991). A distinct V5 satellite (area MST in monkey) is particularly involved in the analysis of regular patterns of motion flow, including radially expanding flow (de Jong et al., 1994; Morrone et al., 2000; Wurtz et al., 1993). Homology between the subdivisions of the human posterior parietal cortex and that in monkey has become evident (Bremmer et al., 2001) and is consistent with symptoms such as optic ataxia that arise from human parietal lesions. In optic ataxia, visual guided movement is impaired in such a way that external spatial information is not adequately integrated in assembling the appropriate movement commands for directing hand and eyes to the observed target (Rossetti et al., 2003). To sum up, specific visual and parietal cortical areas, particularly implicated in the analysis of visual motion and visuospatial information, provide a source of externally driven movements. This information runs through superior parietal areas to the dorsolateral premotor cortex. It may be clear that for gait control, equivalent to reaching, spatial information is of more importance that the details of object features, which are particularly required for precise grasping and manipulation.

The organisation of internally generated movements is associated with the medial premotor cortex (Deiber et al., 1999; Lau et al., 2004; Mushiake et al., 1991). This also holds for switching from external to internal movements (Isoda and Hikosaka 2007). The medial premotor cortex is divided in the supplementary motor area (SMA) and pre-SMA, both cytoarchitecturally defined as Brodmann area 6 and separated from each other by the vertical line through the anterior commissure (VCA) (Mayka et al., 2006). The pre-SMA is particularly connected with the prefrontal cortex (Geyer et al., 2000). The medial premotor areas are strongly connected with the basal ganglia (Akkal et al., 2007; Sakai et al., 1999; Sakai et al., 2000). The latter are specifically affected in Parkinson's disease (Weintraub et al., 2008). However, cortical areas including the medial premotor cortex are also involved in Parkinson's disease (Braak et al., 2004; Cunnington et al., 1997; Gerschlager et al., 1999).

LATERALISATION

The brain consists of two hemispheres. Although they look largely identical to each other at first sight, closer examination reveals subtle differences between the two in the macroscopic aspects of gyri and sulci (Strauss et al., 1983). This macroscopic lateralisation corresponds with asymmetries at the microscopic cytoarchitectural level (Galaburda et al., 1990; Strauss et al., 1983).

The anatomical lateralisation is consistent with the fact that many brain functions are lateralised as well. In this respect, functional specialisation of each of the two hemispheres is known as complementary specialisation. This may imply that one hemisphere is unable to perform a task (for example fine finger movements of the ipsilateral hand), although it mostly means that one hemisphere is better than the other in doing a task (for example navigating to a place).

While language is particularly dominant in the left hemisphere, as stated earlier, a specific function of the right hemisphere is spatial processing and visuomotor transformations of which many examples exist (Ben-Yishay et al., 1971; Callaert et al., 2011; Corballis 2003; de Jong et al., 1999; Thiebaut de Schotten et al., 2011; Woolley et al., 2010). An often used test for neuropsychological assessment of right hemisphere (dys)function is e.g. a block design test, which requires aligning blocks according to a picture as in the block design task (Ben-Yishay et al., 1971; Wechsler 2005; Wilde et al., 2000). In split brain patients, this right hemisphere advantage becomes obvious in superior left-hand performance in producing a pattern of coloured blocks, compared to 'dominant' right-hand action (Bogen and Gazzangia 1965; Gazzaniga et al., 1962; Gazzaniga et al., 1965). Split brain patients provide further support for right hemisphere dominance concerning visuomotor performance as they were better at recognizing two-dimensional and three-dimensional geometrical objects with the left compared to the right hand (Franco and Sperry 1977). One of the consequences of right posterior parietal damage in stroke patients is spatial hemi-neglect for the left side (Halligan et al., 2003; Vallar and Perani 1986). Patients with such neglect also show deviation of the walking trajectory (Huitema et al., 2006), which is consistent with results of functional brain imaging showing right hemisphere dominance for estimating heading (Peuskens et al., 2001). To conclude, right hemisphere specialisation is clearly shown by visuomotor and spatial tasks.

For the left hemisphere, classical examples of specialisation are handedness and language. About 90 percent of the population is right-handed, while approximately the remainding 10 percent is left-handed. Right-handedness is driven by the left hemisphere. In right-handed persons, language is usually controlled by the left hemisphere as well. This was first observed in lesion studies by Broca, but has been confirmed later on by functional imaging (Knecht et al., 2000). Left-handers use the right hemisphere for handedness, but are more heterogeneous for other asymmetric functions including language (Galaburda et al., 1990; Knecht et al., 2000). This correlation between handedness and language establishes that, to a large extent, direction of hand dominance reflects direction of cerebral dominance.

Further support is present as it has been shown that the overall cerebral asymmetry strongly correlates with handedness (Liu et al., 2009). Thus, in other words, the direction of cerebral lateralisation depends on the hand preference of a person. For that reason, handedness could be used as simplified indicator for cerebral asymmetry. We will use this in the studies investigating the cerebral asymmetry in relation to the asymmetry of Parkinson symptoms **(chapter 2-3)**. We finally studied transcallosal hemisphere connections to assess the existence of a lateralised dorsal premotor dominance in recruiting information from both hemispheres **(chapter 7)**.

The above, however, does not mean that handedness causes cerebral lateralisation. Handedness is thought to be the result of a mixture of genetic and environmental factors (Levy 1976). Factors underlying handedness might possibly also underlie cerebral lateralisation. Furthermore, it should be noticed that, despite brain lateralisation is well-known for many decades, the actual origin of the lateralisation including handedness remains unknown.

PARKINSON'S DISEASE

Parkinson's disease is a movement disorder primarily affecting dopaminergic neurons in the substantia nigra. The latter projects to the striatum, thus leading to dopaminergic denervation of the striatum (nucleus caudatus and putamen). Parkinson's disease not only affects the basal ganglia; pathological changes include the cerebral cortex (Braak et al., 2004) including the medial premotor cortex (Braak et al., 2004; Cunnington et al., 1997; Gerschlager et al., 1999). Furthermore, cortical functions are affected as a result of impaired basal ganglia function, leading to a disruption of cortico-basal ganglia-thalamo-cortical loops (Alexander et al., 1986; Parent and Hazrati 1995). Although the clinical presentation of Parkinson's disease may vary between patients, some cardinal features of Parkinson's disease are rather consistently present. These include rest tremor, rigidity and bradykinesia. Bradykinesia, slowness of movements, and rigidity can be seen as a lack of internal generation of movements due to the affected cortico-basal ganglia-thalamo-cortical loop.

The asymmetric cerebral involvement in Parkinson's disease is revealed by the typical asymmetrical onset of symptoms. Patients become bilaterally affected with disease progression, but the most affected side remains the same (Pirker 2003). The most affected side is contralateral to the most extensive affected side of the brain (Pirker 2003). The asymmetry in Parkinson's disease was recognised early and used in the early Parkinson

classification of Hoehn and Yahr (1967). Although this intriguing aspect of asymmetry is even included in the diagnostic definition, it has remained an enigma (Djaldetti et al., 2006). In this thesis we aimed to elucidate some of this mystery. To start, we addressed the controversy whether the asymmetrical symptoms in Parkinson's disease is related with the general cerebral asymmetry indicated by hand preference **(Chapter 2-3)**. This provided a solid starting point for hypotheses concerning a causal relation between the two **(chapter 8)**.

Next to the cardinal symptoms listed above, complex manifestations of disease may emerge in cognitive domains. With regard to sensorimotor integration, impairment may result in the phenomenon that external stimuli may have either an enhanced strengthening or an obstructing effect on the execution of motor tasks. As such, sensorimotor transformations are particularly associated with right hemisphere functions, impairment would logically be associated with left-sided Parkinson symptoms. Although a disturbed sensorimotor integration also includes for example auditory stimuli (Freeman et al., 1993), visual stimuli have the strongest impact showing a disturbed visuomotor control in Parkinson's disease. This has been shown for upper-limb drawing (de Jong et al., 1999), but is particularly invalidating in gait when disrupting the cyclic pattern of walking is provoked by the transition to narrow spaces like a corridor or doorway, resulting in freezing of gait (Cowie et al., 2010; Giladi et al., 1992; Giladi et al., 2001a; Hallett 2008; Okuma 2006). Given the asymmetric distribution of Parkinson symptoms, an association of freezing of gait and left-sided symptom dominance is a tempting hypothesis.

Freezing of gait

Freezing of gait is a most disabling problem for Parkinson patients (Giladi et al., 2001a) affecting the independence of patients (Tan et al., 2012). Freezing of gait is defined as the inability to initiate or maintain the cyclic pattern of walking. In other words, despite major effort, patients are unable to put one foot ahead to the other. Mostly, this becomes manifest as trembling of the legs in one spot (Schaafsma et al., 2003). It lasts for less than ten seconds most of the time (Jankovic 2008; Schaafsma et al., 2003). As freezing of gait is likely to disturb balance, falls easily occur (Bloem et al., 2004; Grimbergen et al., 2004). This leads to an increased risk of a collar head fracture, associated with a high morbidity and mortality in Parkinson's disease (Bloem et al., 2004). Furthermore, patients experience an increased fear of falling, adding to the social isolation (Thomas et al., 2010). The prevalence of freezing of gait increases with disease duration and progression of disease severity. In patients with advanced Parkinson's disease, it is around 50 percent with a

range from 20 till almost 70 percent depending on the Hoehn and Yahr stage (Giladi et al., 2001b; Shoulson et al., 2002).

Despite this heavy impact of freezing of gait, the underlying mechanism is still poorly understood (Heremans et al., 2013; Nutt et al., 2011). Some arguments point at a right hemisphere interference of implicated visuomotor and somatosensory-motor transformations. Somatosensory involvement is shown by a right lateralised parieto-premotor network involved in general limb-independent antiphase movements (de Jong et al., 2002), while a disturbed visuomotor interaction in freezing of gait in patients with Parkinson's disease is supported (Bartels et al., 2006; de Jong et al., 1999). Furthermore, disrupted visuomotor interactions in freezing of gait are also demonstrated by the visual cues that are often employed by patients to overcome freezing of gait (Azulay et al., 1999; Brichetto et al., 2006; Morris et al., 1996; Nieuwboer 2008; Suteerawattananon et al., 2004). This is particularly seen with optic flow, the radially expanding visual motion pattern elicited during forward locomotion.

During forward locomotion, the environment is projected on the retina. Distant objects are located near the centre of the visual field and move slowly away from it, while nearby objects are projected in the peripheral field and move further in eccentric direction with increasing speed as they come closer (Wurtz et al., 1993). This phenomenon of radial movement is called radial optic flow. In the case of walking forward, we coined it 'forward' optic flow. In contrast, 'reversed' optic flow happens for example when looking through the rear window of a driving car.

Walking or driving ahead through a natural environment, which implies that objects are placed on the environmental surface, generates 'forward' optic flow in the lower visual field. Such optic flow provides an extra support for gait in healthy subjects (Warren et al., 2001) and Parkinson patients (Azulay et al., 1999; Schubert et al., 2005). This 'forward motion in depth' can be mimicked by presenting a pattern of radial optic flow expanding in the lower part of a static screen (Duffy 1998; Gibson 1954; Kovács et al., 2008). Now, the visual display generates the illusionary perception of forward self-motion in the absence of actual locomotion (Gibson 1954; Kovács et al., 2008). This quality points at a close relation between this specific visual motion stimulus and gait, thus providing a promising opportunity to study the effect of optic flow manipulations. In this way, we expected to gain insight in basic visuomotor interactions involved in gait control, complementing virtual reality paradigms. These experiments were performed in both healthy subjects and

Parkinson patients **(chapter 4-6)**. With regard to the use of optic flow in the functional magnetic resonance imaging (fMRI) studies, wide-field optic flow, providing external support for virtual locomotion, was hypothesised to activate the dorsal premotor cortex of predominantly the right hemisphere. Interruptions of optic flow by either narrowing or decelerating the flow field was thought to put load on the cerebral circuitry implicated in the internal generation of movement, in particular the (pre-)SMA.

TECHNIQUES

To image the brain in Parkinson patients and healthy controls, different techniques were applied. Functional magnetic resonance imaging (fMRI) as well as diffusion tensor imaging (DTI) were used. Studies using fMRI followed positron emission tomography (PET) studies that had shown that regional increase of cerebral blood flow accompanies and even exceeds increased oxygen metabolism (Herscovitch et al., 1983; Raichle et al., 1983). Due to the short halftime of 15-oxygen, repeated perfusion measurements could be made allowing the statistical assessment of task related increases compared to control conditions. Activation studies of fMRI are based on this same principle of measuring increased regional cerebral blood flow reflecting local neuronal activity. I will explain both fMRI and DTI below.

Functional magnetic resonance imaging

The first fMRI image was made in 1992 by Kwong et al (1992). It was, and still is, a wonderful technique as it is possible to show cerebral function in vivo. The quality and knowledge has grown rapidly since the first fMRI scan and it is a frequently used method nowadays.

The technique of fMRI shows a regional distribution of cerebral function in vivo. Such cerebral function is encoded in neuronal activity and can be measured indirectly. Increased neural activity results in enhanced oxygen utilisation. To meet this oxygen demand, neuron-glia mediated signalling to local blood vessels induces an excess perfusion of oxygenated blood. The core principle underlying fMRI is that the resulting increase of oxygenated versus deoxygenated haemoglobin provides a detectable signal. This blood-oxygenated-level-dependent response (BOLD-response) is based on the fact that oxygenated and deoxygenated haemoglobin have different magnetic properties (Ogawa and Lee 1990; Ogawa et al., 1990). A locally increased BOLD-response thus reflects increased activation in that specific brain region. However, the exact mechanism underlying neurovascular coupling is complex and still incompletely understood

(Handwerker and Bandettini 2011; Nair 2005; Silva 2012).

These magnetic differences in oxygenation, the BOLD response, can by picked up by an MRI scanner if the right settings are selected, a T2*-weighted MRI sequence. For fMRI activation studies, the brain is scanned during a specific task or condition, for example looking at different pictures. Since the task evoked BOLD-response is small, just a few percentages, the true task signal can easily be lost in the multitude of natural activity fluctuations that act as disturbing noise.

To improve the signal-to-noise ratio in fMRI experiments, multiple repeats of the same task are required. The task related signal will be consistently present in all repetitions. In contrast, the random task-unrelated fluctuations differ during such repetitions. Accumulation of the signals from the repetitions pops-up the task related signal, while the 'noise' is averaged out (Haller and Bartsch 2009). The number of repetitions used depends on the experimental task. In our designs, each stimulus was repeated at least 36 times in an fMRI experiment **(chapter 4 and 6)**.

The signal-to-noise ratio is not the only aspect to take into account for a well suited design. The repetition of a stimulus can introduce its own pitfalls. When repeating conditions in the same order throughout scanning, a learning effect will be stronger for the second relative to the first condition, thus introducing a new variable that cannot be dissociated from the experimental variables, making the results inconclusive. Such fixed order may further induce the risk of a subjects anticipation to the stimulus. Anticipation is a cognitive activity that can alter neuronal activation (Simmons et al., 2006). To overcome anticipation and to dissociate learning effects from the experimental conditions, stimuli are repeated in a pseudorandom order, meaning that each condition is random but equally spread across the experiment. Another way to avoid anticipation is a design with stimuli of varying durations. The BOLD signal is also modulated by attention and in a reversed way by fatigue (Moradi et al., 2012; Munneke et al., 2012; Ress et al., 2000). Attention increases the signal, while fatigue decreases it. To prevent the latter, an experiment should be kept as short as possible. The equal spread of a condition through the experiments further prevents confounding factors.

The resultant of fMRI acquisition is a three-dimensional image of the brains activation. This image is split in boxes (voxels) mostly sized about three squared millimetres. This allows to distinguish different locations in the brain, the spatial resolution. Neuronal activation in

absolute term is not well suited to assess with fMRI. Instead, fMRI assess task-induced signals relative to rest or other task signals (Haller and Bartsch 2009). By splitting the signal in time dependent on the task, different tasks can be compared. The data, however, needs several preprocessing steps before tasks actually can be compared. This is, however, beyond the scope of this introduction although also there, crucial choices are made that may affect the results.

Next to comparing the activations between tasks, the BOLD signal can be used for connectivity analyses. The psychophysiological interaction method (PPI) is frequently used, which assesses the psychological dependent temporal correlation of one region with others above what can be explained by the main effect of the tasks (Friston et al., 1997). This interaction term thus represents the task dependent synchrony of signal fluctuations of one cerebral region compared with others. A synchronised signal for different regions reflects a functional coupling, connection between those regions, which can be mediated by mono- and polysynaptic connections, which by themselves are not visualised.

Diffusion tensor imaging

DTI is an MRI technique that visualises white matter tracts in the brain by means of detecting the direction of water diffusion. Unrestricted diffusion occurs in a glass of water, or in the ventricles in the brain. This diffusion with random direction, isotropy, occurs in the absence of barriers. White matter tracts introduce a mechanical barrier in one direction. This makes it easier for water to diffuse along instead of perpendicular to the axons. Directional diffusion, anisotropy, thereby, is an indirect method to show the direction of white matter tracts. This only works for white matter tracts as the tracts are organised and aligned along each other. Grey matter, in contrast, cannot show an aligned direction of diffusion as it is not organised in such aligned way. The anisotropic diffusion along white matter tract was first reported in 1990 (Moseley et al.). A translation to DTI images of the human brain quickly followed (Basser et al., 1994; Douek et al., 1991; Pierpaoli et al., 1996). A simple form of diffusion MRI is diffusion weighted imaging (DWI). DWI lacks the directional component and displays only the magnitude of diffusion for all places, while DTI images include the direction of diffusion.

DTI is, like fMRI, a T2*-weighted MRI sequence. The brain is scanned repeatedly, each scan representing a different direction. Nowadays, up to 60 directions are frequently scanned in research settings. The direction per voxel, three-dimensionally displayed, can be quite precisely calculated by combining the 60 directions. The thee-dimensionally displayed

direction is called the tensor. The tensor is used to track from one brain region to another.

The direction is split in several vectors used to trace tracts from one region to another. Tracking can be done by a deterministic or probabilistic method. The former is most likely to encounter problems of crossing fibbers. For this reason, we used probabilistic tracking in our study **(chapter 7)**. In this case, each voxel of a start (seed) region tracks thousands of times (default 5000 times) to find out the most likely tract. It is possible to count how often a target region has been hit during tracking. A higher number thus indicates more hits and more aligned white matter tracts between the seed and target region. The same can be done for all voxels separately showing a whole-brain connectivity distribution of a seed region. If handled with care, statistical analysis can be done on these numbers. Handling with care also includes earlier aspects, for example, a thorough check whether tensors are calculated correctly and correspond with known anatomy knowledge (for example at the level of the corpus callosum and pyramidal tract). The same holds for tracking results from one region to others.

Moreover, it is important to realise that tractography results are highly dependent on the size of the starting (seed) region as the total number of generated tracts for each voxel in the seed region is summed (Behrens et al., 2007). If comparing two regions within a subject, it is important to evaluate a possible bias of the seed region size toward one region. When testing differences of connectivity distributions of a distinct region of interest in two groups or even when testing connectivity distribution differences within the same hemisphere of the same subject, it also should be taken into account that calculated distributions in areas depend on the distance from the seed region. For example comparing the contribution of the right primary visual cortex or the right primary sensory cortex with the right superior parietal lobule will be biased toward a higher contribution for the right primary sensory area as it is adjacent and thus closer to the superior parietal lobule. Comparing one region in two groups (a healthy and patient group) might face less such difficulties as the compared regions between the groups are at the same distance from the seed region averaging out a distance effect. Further, a disease group (e.g. neurodegenerative diseases) might only have some increased atrophy of grey and white matter placing cortical regions minimally different to each other. Comparing a region in the right with a similar region in the left hemisphere does not face the problem of distance bias, while the presence of the seed region size problem is less likely to occur.

OUTLINE OF THE THESIS

The thesis' basic theme concerns lateralisation aspects in Parkinson's disease. We aimed to (1) clarify whether lateralisation of symptoms of Parkinson's disease is related to general cerebral asymmetry (indicated by handedness) and (2) to examine a possible relation between right hemisphere dysfunction and disturbed visuomotor control in freezing of gait.

To that end, we first started with a retrospective study to assess the presence of a possible association between the dominant side of symptoms in Parkinson patients and handedness as indicator of cerebral asymmetry **(chapter 2)**. As many studies that previously addressed this topic showed contradicting results, we continued with a meta-analysis of all known studies to finally establish whether a relation between handedness and symptom side in Parkinson patients is indeed present or not **(chapter 3)**.

We proposed that freezing of gait might occur more frequently in left symptom dominant Parkinson patients, reflecting more pronounced right hemisphere visuomotor dysfunction as cyclic antiphase movements, the pattern used by the legs and arms in gait, are related to a right dominant parieto-premotor network (de Jong et al., 2002), while freezing of gait has been suggested to be associated with right hemisphere dysfunction (Bartels et al., 2006; de Jong et al., 1999). We therefore investigated whether freezing of gait indeed occurs more frequently in left symptomatic Parkinson patients **(chapter 2)**. To get more insight in functional changes in the brain related to visuomotor dysfunction in freezing of gait, we employed the basic visual motion stimulus ‘optic flow’ to investigate mechanisms underlying freezing of gait in Parkinson patients. We assessed motor-circuitry activations by an optic flow manipulation that mimicked the approach of a narrow passage, a circumstance that provokes freezing of gait. Narrowing wide-field optic flow was expected to induce a shift from external movement stimulation to the internal generation of virtual movement, mediated through the lateral and medial premotor areas respectively. To that end, we started with an fMRI study in young healthy subjects **(chapter 4)**. To behaviourally test our paradigm, we compared Parkinson patients with (elderly) age-matched healthy subjects during treadmill gait **(chapter 5)**. Treadmill gait provided the opportunity to manipulate optic flow during walking and to test whether Parkinson patients were more affected in the ability of internal movement generation during interruptions of wide forward flow. As involved visuomotor transformations are mainly a right dominant hemisphere function, gait disturbances were correlated with results from a right-hemisphere specific block design task. Next, we performed the fMRI experiment in which

we explored differences in cerebral activations during optic flow manipulations in Parkinson patients with and without freezing of gait compared to elderly healthy subjects **(chapter 6)**. The final experiment concerned a DTI study on transcallosal hemisphere connections to assess the existence of a lateralised dorsal premotor dominance in recruiting information from both hemispheres **(chapter 7)**. In the general discussion of this thesis, the findings of chapter 2 till 7 will be integrated and treated in a wider perspective **(chapter 8)**.

CHAPTER 2

Handedness and dominant side of symptoms in Parkinson's disease

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ABSTRACT

The aim of this retrospective study was to assess the presence of a possible association between handedness and the side of symptom dominance in 963 patients with Parkinson's disease. In only 287 patients the hand dominance was registered. Out of 254 right-handed patients, 158 (62%) had a right-side dominance of Parkinson symptoms, while 96 patients (38%) had left-lateralised symptom dominance ($p < 0.001$). For the 33 left-handed subjects, 18 (55%) had left- and 15 (45%) had right-sided symptom dominance ($p = 0.602$). Right-handedness thus appeared to be associated with right-sided dominance of Parkinson symptoms, while the group of left-handed patients was too small to draw conclusions from. Possible explanations are discussed.

INTRODUCTION

Parkinson's disease is characterised by asymmetry of symptoms at the onset of disease which is generally maintained during disease progression. Assessment with positron emission tomography (PET) has demonstrated a consistent relation between symptom asymmetry and lateralised cerebral function, in such a way that the dominant side of symptoms significantly correlated with reduced dopamine transporter uptake in the contralateral hemisphere. The cause of symptom lateralisation in Parkinson's disease, however, remains to be elucidated (Djaldetti et al., 2006). A well-known lateralised function in normal conditions is hand dominance, which is related to asymmetry across brain systems (Liu et al., 2009). One might speculate whether such brain asymmetry could provide a clue for a possible explanation for lateralisation of Parkinson symptoms. In that case a relation between handedness and such symptom lateralisation might be expected. This issue has been addressed in a few previous studies, with varying results. Although these studies generally concerned small groups, a relation between hand dominance was suggested in some studies (Reynolds and Locke 1971; Uitti et al., 2005; Yust-Katz et al., 2008) but not in all (Klawans 1972; Štochl et al., 2009; van Rooden et al., 2009). The aim of the present retrospective study was to identify a possible association of handedness with the side of symptom dominance in Parkinson's disease. Moreover, we looked whether a relation could be found between gait associated disease characteristics and the side of symptom dominance.

METHODS

Study population

Parkinson patients were retrospectively identified from a database of the Movement Disorders unit from the neurology department of the university medical centre Groningen. This database contained a total of 1120 patients with the diagnosis Parkinson's disease, seen over a period of about nine years. After assessment of the patient files, 157 patients were excluded for reasons such as uncertainty about the diagnosis Parkinson's disease, adjustment of the diagnosis, too many missing data or bilateral disease onset. A group of 963 subjects thus remained. Approval by the local ethical committee was not required for this study as it concerned retrospective analysis of patient files only. The dominant side of symptoms was based on documented clinical examination, which remained the same over time. Handedness was defined as the reported hand used for writing. To provide support for the correctness of the documented handedness, handedness was also assessed by phone in a small group of patients. In all these interviewed Parkinson patients, of which 26 were documented right-handed and 4 were documented left-handed, the documented

Table 1 | Handedness distribution with symptom dominance in Parkinson's disease

	PD right-sided symptom dominance	PD left-sided symptom dominance	Summed number
Right-handedness	158 (62%)*	96 (38%)*	254
Left-handedness	15 (45%)	18 (55%)	33
Unknown handedness	330 (49%)	346 (51%)	676
All known and unknown handedness	503 (52.2%)	460 (47.8%)	963
Only known handedness	173 (60.3%)	114 (39.7%)	287

The frequency distribution of the dominant side of symptoms in the right- and left-handed patients with Parkinson's disease (PD). * $p < 0.001$ for difference in the side of symptom dominance in right-handed patients (Chi-square test, compared to equal left-right symptom distribution).

handedness was identical to the handedness assessed by phone. The documented handedness was thus inferred to represent a reliable value. In addition we investigated whether gait profiles were different, associated with the side of symptom dominance. This assessment was motivation by previous suggestions that freezing of gait was related to asymmetric motor performance, in such a way that right hemisphere dysfunction might easily cause freezing (Bartels et al., 2006). The following variables were therefore assessed. The time of onset of Parkinson's disease was defined as the first Parkinson's disease attributed sign noticed by the patient, a relative or a care provider. Next, we applied similar criteria to determine the intervals between the time of initial complaint and reduced arm swing, the start of bilateral disease and the onset of freezing of gait, respectively. Information on these variables was documented by the treating clinician. To reduce a selection bias for recording of handedness, we additionally analysed differences between the Parkinson's disease group of known handedness and the Parkinson's disease group of unknown handedness. The parameters for this analysis were sex, age of first symptom, age at diagnosis, disease duration unilateral reduced arm swing, disease duration bilateral involvement and disease duration freezing respectively. No statistically significant difference was found between the groups with known and unknown handedness for these parameters, making a selection bias unlikely.

Statistical analysis

The frequency distribution of the dominant side of symptoms in the right- and left-handed patients was analysed with the Chi-square test, which implied a comparison of this distribution with an equal (chance-based) distribution of left and right-sided symptoms. Differences between patients with right and left dominant symptoms were analysed with the t-test for continuous variables. Effect sizes were described by the Cohen's d, calculated by the differences divided with the pooled standard deviation.

RESULTS

The study population consisted of 561 (58.3%) males and 402 (41.7%) females. A total of 503 patients (52%) were characterised by right-sided symptom dominance while in 460 patients (48%) symptoms were dominant on the left side. The handedness was reported to be right-sided in 254 patients (26%) and left-sided in 33 (3.4%), while this parameter was unknown in 676 (70%). Right-handed Parkinson patients had significantly more often symptoms on the right than on the left side ($p < 0.001$) (Table 1). Although left-handed

Table 2 | Disease characteristics in relation to side of symptom dominance in Parkinson's disease

Disease characteristics	Right symp.	Left symp.			
	Mean (SD) N	Mean (SD) N	Diff (95% CI)	*p*-value	Effect size
Age of first symptom (y)	58.3 (12.6) 437	57.6 (12.3) 383	-0.773 (-2.482 to 0.936)	0.375	-0.062
Age at diagnosis (y)	61.8 (11.9) 334	61.0 (12.2) 317	-0.742 (-2.600 to 1.116)	0.433	-0.062
Disease duration unilateral reduced arm swing (y)	3.5 (3.6) 204	4.1 (4.4) 138	0.592 (-0.265 to 1.450)	0.175	0.150
Disease duration bilateral involvement (y)	3.1 (3.6) 217	3.1 (3.6) 171	-0.062 (-0.778 to 0.653)	0.864	-0.018
Disease duration freezing (y)	9.7 (5.6) 101	10.5 (6.2) 83	0.771 (-0.945 to 2.488)	0.377	0.133

A difference of disease characteristics with a positive value indicates a higher value for patients with left- compared right-sided symptoms. Disease duration concerned the interval between initial complaint and the indicated symptom. N = number; y = year(s); CI = confidence interval; SD = standard deviation; symp. = symptomatic.

patients showed a small excess of left dominant symptoms, this result did not reach statistical significance (p = 0.602). The distribution of side of symptom dominance in relation to handedness was similar between males and females. We did not find significant associations between gait associated disease characteristics and the side of symptom dominance (Table 2). Such association was not seen in the group of only right-handed Parkinson patients either.

DISCUSSION

Our results showed a significant excess of right-sided symptom dominance in right-handed patients with Parkinson's disease, while in the smaller group of left-handed patients no significant preference of left-sided symptoms was seen. These results provide support for previous studies that have reported such association (Uitti et al., 2005; Yust-Katz et al., 2008; Reynolds and Locke 1971), which remained a conflicting issue in the literature because absence of this association has been published too (Klawans 1972; van Rooden et al., 2009; Štochl et al., 2009). The small number of left-handed subjects in our study is consistent with the distribution of handedness found in previous Parkinson research (Yust-Katz et al., 2008; Uitti et al., 2005; van Rooden et al., 2009; Štochl et al., 2009) as well as the distribution of about 10% left-handedness in the general population (Perelle and Ehrman 2005). An ascertainment bias for right-handedness seems therefore unlikely. As our study concerned a retrospective assessment, registration of handedness was according ordinary clinical convention. It appeared that in 30% of the examined Parkinson patient files, handedness was documented. The resulting group of 287 patients can nevertheless be considered as appropriate in size to draw conclusions from. In this respect, it may be relevant to notice that in earlier studies no association was found in groups of, respectively 85, 187 and 472 patients (Klawans 1972; van Rooden et al., 2009; Štochl et al., 2009), while positive associations were found in idiopathic Parkinson's disease populations of 46, 307 and 1277 patients, respectively (Uitti et al., 2005; Yust-Katz et al., 2008; Reynolds and Locke 1971). The different methods that were previously used for assessing handedness might be an additional reason for the above listed differences. Only using recall for determining the side of disease onset, which increases the risk of error, might have been a reason that no association was found in a previously studied group of 472 Parkinson patients (Bartels et al., 2006). Identifying the onset side by a chart review reduces errors (Klawans 1972; van Rooden et al., 2009; Štochl et al., 2009). This method is even more robust after excluding patients with a shifted and thus uncertain side of symptom dominance. The latter has been applied in the present study.

A clear explanation for the association between right-handedness and right-sided dominance of Parkinson symptoms has not been given in previous publications. The idea that the association between side of initial symptoms and hand preference might be due to an attention bias for the dominant hand (Uitti et al., 2005) seems not valid because unilateral distribution of symptoms remains during disease progression. As handedness reflects brain asymmetry (Liu et al., 2009), one wonders whether such asymmetry could be a factor influencing the lateralisation of Parkinson symptoms. Is increased movement complexity, enabled by the most skilled hand, a risk factor for dopamine cell loss in the dominant hemisphere? In this respect, an excitotoxic effect of glutaminergic innervation of the substantia nigra might be considered (Gale et al., 2008). In animal studies, however, the opposite seemed to be the case; forced exercise might be protective (Tillerson et al., 2001). Asymmetry in Parkinson's disease has been phrased to be a mystery. The association of such asymmetry with right-handedness further ads to this mystery but, on the other hand, provides a challenge to further elaborate on this clue. Prospective research on Parkinson's disease should therefore include quantitative assessment of pre-existing handedness.

CHAPTER 3

Handedness correlated with the dominant Parkinson side: a systematic review and meta-analysis

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ABSTRACT

Parkinson's disease characteristically presents with asymmetrical symptoms, contralateral to the side of the most extensive cerebral affection. This intriguing asymmetry, even included in the definition for diagnosing Parkinson's disease, however, is still part of a mystery. The relation with handedness as a common indicator of cerebral asymmetry might provide a clue in the search for causal factors of asymmetrical symptom onset in Parkinson's disease. This possible relationship, however, is still under debate. The objective of this study was to establish whether a relation between handedness and dominant Parkinson side exists. We searched for cross-sectional or cohort studies that registered handedness and onset side in Parkinson patients in PubMed, EMBASE, and Web of Science from their first record until 14 February 2011. Data about handedness and dominant Parkinson side was extracted. Authors who registered both but not described their relation were contacted for further information. Odds ratios (ORs) were analysed with a fixed effect Mantel-Haenszel model. Heterogeneity and indications of publication bias were limited. Our electronic search identified 10 studies involving 4405 asymmetric Parkinson patients. Of the right-handed patients, 2413 (59.5%) had right dominant and 1644 (40.5%) had left dominant Parkinson symptoms. For the left-handed patients this relation was reversed, with 142 (40.8%) right dominant and 206 (59.2%) left dominant Parkinson symptoms. Overall OR was 2.13 (95% confidence interval, 1.71–2.66). Handedness and symptom dominance in Parkinson's disease are firmly related with each other in such a way that the Parkinson symptoms emerge more often on the dominant hand side. Possible causal factors are discussed.

INTRODUCTION

Parkinson's disease characteristically presents with asymmetrical symptoms, contralateral to the most extensive affected side of the brain (Pirker 2003). Although this intriguing aspect of Parkinson's disease is even included in the diagnostic definition, it still remains part of a mystery (Djaldetti et al., 2006). As handedness is an established indicator of normal cerebral asymmetry (Liu et al., 2009), a possible association between the two might provide a clue in the search for causal factors contributing to the onset of this movement disorder. The possible relation between handedness and the dominant side of Parkinson symptoms has been investigated as early as in 1971 (Reynolds and Locke 1971), while the first support for such relation came in 1972 (Klawans 1972). This association, however, remained an issue of debate as it was replicated (Barrett et al., 2011; Uitti et al., 2005; Yust-Katz et al., 2008; van der Hoorn et al., 2011) as well as rejected (Štochl et al., 2009; van Rooden et al., 2009; Reynolds and Locke 1971). This standing controversy prompted us to conduct a meta-analysis of the relation between handedness and side of symptoms dominance in Parkinson patients using cohort and cross-sectional studies. We hypothesised that handedness is related to the side of onset in such a way that right-handed patients more often have right dominant Parkinson symptoms, while left-handed patients more often have left dominant Parkinson symptoms.

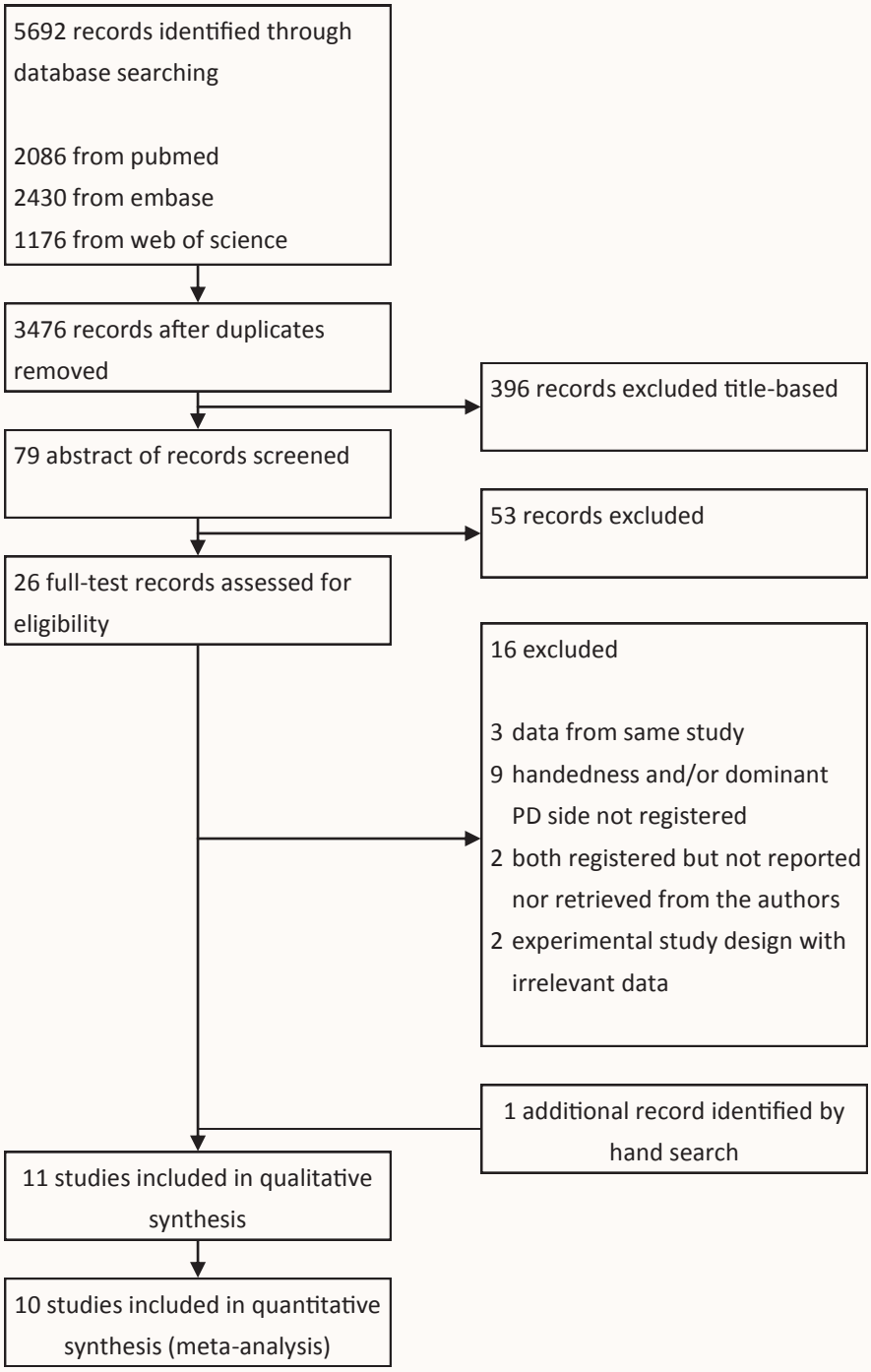
METHODS

Our systematic review was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria (Stroup et al., 2000), the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009) and the AMSTAR guidelines (Shea et al., 2009). No additional review protocol was used.

Search Strategy and Selection Criteria

We searched for cross-sectional or cohort studies that registered handedness as well as dominant side of Parkinson symptoms in the general idiopathic Parkinson population. PubMed, EMBASE, and Web of Science were searched by a researcher (A.H.) and a neurologist/researcher (B.J.) in separate sessions using the search strategy ''handedness OR hand OR handed OR handers'' AND ''Parkinson.'' Databases were searched from their first records with the latest search on 14 February 2011. No language restriction was applied. Possible inclusion was assessed first based upon title and secondly upon the abstract. The full text was assessed for eligibility if the abstract suggested relevance. References of identified studies and conference abstracts were further hand-searched. We extracted binary data on right- and left-handedness, dominant Parkinson side, Parkinson

Figure 1 | Flow chart of literature searches

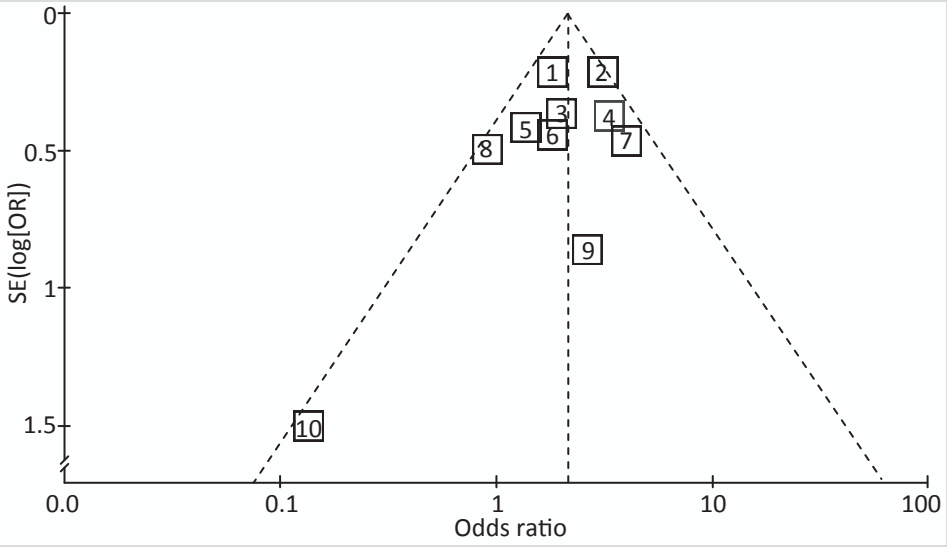


duration, and age of Parkinson's disease onset. Onset side and worst affected side were both accepted as dominant Parkinson side because onset side is known to generally remain the worst affected side during disease progression (Pirker 2003). Subjects with mixed-handedness and Parkinson patients with symmetrical affection were not included in registration. We contacted authors of studies that stated their measurement of handedness and dominant Parkinson side, but had not described their relation.

Statistical Analysis

Potential publication bias was assessed by funnel plot. Heterogeneity of the odds ratios was evaluated using the chi-square test and the I^2 index. Based on guidelines of the Cochrane Collaboration, we regarded heterogeneity as possibly unimportant when the I^2 value was less than 40% and considerable when more than 75%. We used the standard Mantel-Haenszel fixed effect method to calculate pooled odds ratios of handedness in relation to the dominant side of Parkinson's disease. A random effects model was considered in case of heterogeneity. Statistical analysis was done with RevMan 5.1 (Cochrane collaboration). Significance level was set at a two-sided $p < 0.05$.

Figure 2 | Funnel plot



Numbers indicate references; 1 = Barrett et al., 2011; 2 = Uitti et al., 2005; 3 = van der Hoorn et al., 2011; 4 = Sarwar and Lai 2010; 5 = van Rooden et al., 2009; 6 = Yust-Katz et al., 2008; 7 = Munhoz et al., 2010; 8 = Stewart et al., 2009; 9 = Štochl et al., 2009; 10 = Reynolds and Locke 1971.

Table 1 | Characteristics of included and excluded studies

	N	Study type	Dominant PD side; criteria	Handedness; criteria	% M	PD ons	PD dur
Included studies							
Akerman	166	X-sect.	Onset and dominant side; patients recall	Current handedness	-	-	-
Barret	1015	X-sect.	Onset side; chart review	Handedness; chart review	61	57	7
Reynolds	83	X-sect.	Onset side; chart review	Handedness; chart review	74	-	-
Sawar	245	X-sect.	Onset side; chart review	Pre-morbid handedness; chart review	-	-	-
Stewart	425	X-sect.	Onset side; patient recall	Handedness; -	64	58	8
Štochl	392	X-sect.	Onset side; patients recall	Pre-morbid write-hand; patients recall	59	56	10
Uitti	1274	Cohort	Onset side; expert exam	Handedness; expert exam	66	63	7
Van der Hoorn	287	X-sect.	Dominant side; chart review	Pre-morbid write-hand; chart review	58	57	9
Van Rooden	258	X-sect.	Onset side; chart review	Patients recall pre-morbid AHI ≤ -9 L-handed, ≥ 9 R-handed	66	49	12
Yust-Katz	260	X-sect.	Onset side; recall and UPDRS III R-L diff > 4, chart review	Write-hand patients recall	59	30	7
Excluded studies							
Klawans	46	X-sect.	Onset side; chart review	Handedness; -	-	-	-
Munhoz	270	X-sect.	Onset side; -	Handedness; -	53	53	12
Torres	302	X-sect.	Onset side; expert exam	Handedness; expert exam	58	58	6

AHI = Annett handedness inventory; diff = difference; dur = duration; L = left; N = number; ons = onset; PD = Parkinson's disease; R = right; UPDRS = unified Parkinson's disease rating scale; X-sect = cross-sectional. Onset and duration are in years.

RESULTS

Description of Studies

Our electronic search revealed a total of 3476 unduplicated references, of which 10 studies (Reynolds and Locke 1971; Barrett et al., 2011; Uitti et al., 2005; van der Hoorn et al., 2011; Yust-Katz et al., 2008; Štochl et al., 2009; van Rooden et al., 2009; Akerman et al., 2008; Stewart et al., 2009; Sarwar and Lai 2010) were eligible for inclusion in the meta-analysis (Figure 1). Three studies of the initial thirteen included studies were excluded later on. In one case we were unable to contact the author of a small study from 1972 (Klawans 1972). Furthermore, two studies were excluded because the authors were unable to provide the requested information (Munhoz et al., 2010; Torres et al., 2010). Characteristics of these ten included and three excluded studies are described in Table 1. The ten included studies concerned 4405 asymmetric Parkinson patients, of whom 2555 (58%) patients were characterised by right-sided symptom dominance while 1850 (42%) patients were dominant on the left side. Handedness was right in 4057 (92.1%) and left in 348 patients (7.9%).

Main Analysis

Pooled results from the fixed effect Mantel-Haenszel model showed that Parkinson patients in general have more often Parkinson symptoms on their dominant hand side. Of the right-handed patients, 2413 (59.5%) had right and 1644 (40.5%) left dominant Parkinson symptoms. For the left-handed patients this relation was reversed with 142 (40.8%) right and 206 (59.2%) left dominant Parkinson symptoms. The overall odds radio showed a marked and statistically significant association (2.13; 95% confidence interval, 1.71-2.66; $p < 0.0001$).

Publication Bias and Heterogeneity

The funnel plot did not reveal indications of a publication bias, as no major asymmetry was shown except the single outlier constituted by a small negative study (Reynolds and Locke, 1971) (Figure 2). Neither was a significant heterogeneity present, based upon study characteristics, the forest plot (Figure 3) and statistical analysis ($p < 0.12$; $I^2 = 36\%$). Again, the study by Reynolds and Locke (1971) showed an opposite relationship but the confidence interval was large and included 1.00.

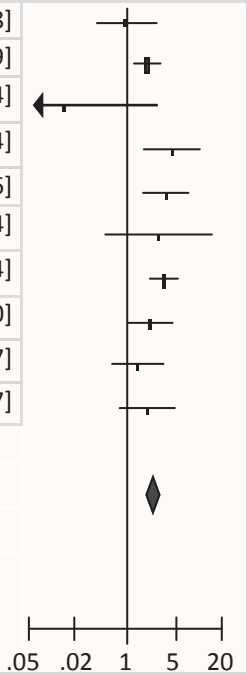
DISCUSSION

By using the statistical strategy of a systematic meta-analysis, we were able to demonstrate a substantial and statistically significant association between the dominant

Figure 3 | Forrest plot

Author	R-handed PDR	R-handed PDL	L-handed PDR	L-handed PDL	Weight	Odds ratio M-H, Fixed, 95% CI
Akerman	78	70	10	8	3.3%	0.89 [0.33-2.38]
Barrett	524	403	37	51	23.3%	1.79 [1.15-2.79]
Reynolds	43	36	4	0	0.2%	0.13 [0.01-2.54]
Sawar	154	69	8	14	7.8%	3.91 [1.57-9.74]
Stewart	238	153	11	23	11.4%	3.25 [1.54-6.86]
Štochl	218	168	2	4	2.0%	2.60 [0.47-14.34]
Uitti	739	439	34	62	31.8%	3.07 [1.99-4.74]
van der Hoorn	158	96	15	18	8.8%	1.98 [0.95-4.10]
van Rooden	129	104	12	13	5.7%	1.34 [0.59-3.07]
Yust-Katz	132	106	9	13	5.8%	1.80 [0.74-4.37]
Total (95%CI)	**2413**	**1644**	**142**	**206**	**100%**	**2.13 [1.71-2.66]**
Percentage %	**59.5**	**40.5**	**40.8**	**59.2**		

Odds ratio M-H, Fixed, 95% CI



Heterogeneity: $Chi^2 = 14.06$, df = 9 ($p = 0.12$); $I^2 = 36\%$

Test for overall effects: $Z = 6.66$ ($p < 0.0001$)

Authors correspond with references of figure 2.

side of Parkinson symptoms and hand dominance. Right-handed patients showed a significant excess of right dominant Parkinson symptoms, while the reverse was true for the left-handed patients with a significant excess of left-sided symptoms. The existence of this relation has been controversial as few previous studies have reported this relation (Klawans 1972; Barrett et al., 2011; Uitti et al., 2005; Yust-Katz et al., 2008; van der Hoorn et al., 2011), whereas others failed to demonstrate it (Reynolds and Locke 1971; Štochl et al., 2009; van Rooden et al., 2009). No studies, however, reported an inverse relation; i.e., an association between dominant hand and the non dominant side of symptoms. This fact in itself already suggested a non-chance relation. The present meta-analysis resolved methodological issues that may have caused the discrepancy between studies. The small number of left-handed patients in previous studies appeared to have been a major reason for the reported absence of a relation between handedness and lateralised symptom dominance. In the overall population about 10% is estimated to be left-handed (Perelle and Ehrman 2005), which is consistent with the 8% left-handed patients revealed by our meta-

analysis. When comparing the odds of right- and left-handed patients, the OR of previous studies is highly influenced by the small and less precise group of left-handed patients. These small numbers resulted in a lack of statistical power. Pooling of results in the present meta-analysis resolved these issues.

The methodological quality of included studies was similar. Small differences may have arisen by differences in assessing lateralisation of Parkinson symptoms and handedness. The latter was determined either by the patient's recall of premorbid handedness or by chart review. Description of the dominant Parkinson side was most often based on the reported side of onset, while in one study (van der Hoorn et al., 2011) it was inferred from the consistently reported worst affected side. The two variables highly correlate with each other, which have been shown by the fact that the onset side generally remains the worst affected side during disease progression (Pirker 2003). Moreover, this is an argument against the tentative assumption that patients may notice Parkinson symptoms earlier when using the dominant hand because it is stronger implicated in task related movement.
As the dominant hemisphere thus appears to be more prone for Parkinson's disease, identification of distinct causal factors becomes a challenging topic. Although lateralisation of symptoms may presently remain part of a mystery, the actual association with handedness provides a strong motivation to formulate hypotheses concerning possible causal relations. In this respect one may consider two general consequences of lateralised motor control implicated in handedness: (1) hand preference implies an increased metabolic demand with possible negative consequences of oxidative stress in the corresponding (contralateral) hemisphere (Jenner 2003), while (2) underlying cortical-basal ganglia-thalamic circuitry has an extensive distribution within the dominant hemisphere and runs highly parallel with language networks (Johnson-Frey 2004; Potgieser and de Jong 2011; Binkofski and Buccino 2004).

With regard to the biochemical characteristics, enhanced oxidative stress may contribute to neurotoxicity inflicted by excitatory neurotransmitters (Atlante et al., 2001; Choi 1988) as well as dopamine metabolites (Jenner 2003). Circuitry involved in the referred dominant hemisphere functions comprises particularly ventral parietal-premotor and superior temporal regions (Ramayya et al., 2010), while each of such regions has additional striatum projection (Kemp and Powell 1970). Coherent cortical functioning is facilitated by the cortico-basal ganglia interactions maintained by these projections. The latter give rise to segregated channels through the basal ganglia (Alexander and Crutcher 1990) while strongly interconnected cortical fields have more common striatum projection (Yeterian

and Van Hoesen 1978). Enhanced basal ganglia activity in the dominant hemisphere may thus logically result from the wider extension of functional networks in this hemisphere. Corticostriatal projections are excitatory, which also holds for subthalamic nucleus projections to the substantia nigra (DeLong and Wichmann 2007; Obeso et al., 2008). As a consequence, the excitatory drive associated with more widely extended corticostriatal projections and possibly stronger excitatory load converging onto the substantia nigra might lead to excitotoxic effects in the long run of life. This might result in a stronger dopaminergic defect in the dominant compared to the non dominant hemisphere, although the subthalamic nucleus innervation of the substantia nigra particularly concerns the pars reticulare and not the pars compacta from which the striatum efferents originate. The primary assumption that normal motor lateralisation is associated with an increased level nigrostriatal dopamine turnover in the dominant hemisphere finds support by human in vivo measurements with positron emission tomography (PET) (de la Fuente-Fernández et al., 2000). One might, in this respect, even speculate to find asymmetric dopamine cell count.

CONCLUSIONS

To conclude, the demonstrated association between handedness and lateralisation of Parkinson symptoms is a fact that provides a new challenge to identify causal factors contributing to the onset of Parkinson's disease.

CHAPTER 4

Interruption of visually perceived forward motion in depth evokes a cortical activation shift from spatial to intentional motor regions

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ABSTRACT

Forward locomotion generates a radially expanding flow of visual motion which supports goal-directed walking. In stationary mode, wide-field visual presentation of optic flow stimuli evokes the illusion of forward self-motion. These effects illustrate an intimate relation between visual and motor processing. In the present fMRI study, we applied optic flow to identify distinct interfaces between circuitries implicated in vision and movement. The dorsal premotor cortex was expected to contribute to wide-field forward motion flow, reflecting a pathway for externally triggered motor control. Medial prefrontal activation was expected to follow interrupted optic flow urging internally generated action. Data of fifteen healthy subjects were analysed with statistical parametric mapping and confirmed this hypothesis. Right dorsal premotor activation was seen in wide forward flow, together with activations of posterior parietal cortex, ventral V5, and the right fusiform gyrus. Conjunction analysis of the transition from wide to narrow forward flow and reversed wide-field flow revealed selective dorsal medial prefrontal activation. These findings point at equivalent visuomotor transformations in locomotion and goal-directed hand movement, in which parietal-premotor circuitry is crucially implicated. Possible implications of an activation shift from spatial to intentional motor regions for understanding freezing of gait in Parkinson's disease are discussed; impaired medial prefrontal function in Parkinson's disease may reflect an insufficient internal motor drive when visual support from optic flow is reduced at the entrance of a narrow corridor.

INTRODUCTION

Forward locomotion generates a characteristic streaming motion of environmental features through the visual field. This 'optic flow' implies a radial expansion from the central point on the horizon ahead, provided that the observer does not fixate a specific object (Gibson 1954; Wurtz et al., 1993). Distant objects are located near the centre of the visual field and move slowly from it, while nearby objects are in the peripheral field and move further in eccentric direction with increasing speed. In stationary condition, a similar sensation of forward self-motion can be evoked by presenting a pattern of expanding radial optic flow in the lower part of the visual field (Kovács et al., 2008). This visual effect is in line with the finding that humans make use of optic flow to walk to a goal (Warren et al., 2001). The latter suggests visuomotor coordination equivalent to the support of visual information to accomplish adequate reaching movements (Johnson et al., 1996; Sakata et al., 1997). In Parkinson's disease, which is predominantly characterised by motor symptoms such as rigidity and bradykinesia, support of sensory cues on walking is illustrated by gait improvement that has been demonstrated by the presentation of parallel traverse lines on the walking surface (Azulay et al., 1999; Suteerawattananon et al., 2004). Suppression of this gait improvement by stroboscopic light further demonstrated that perceived motion of the stripes, induced by the patient's walking, was an essential aspect of gait support and favoured the involvement of visuomotor circuitry responsive to rapidly moving targets (Azulay et al., 1999). In contrast to the supportive effects of sensory cues, incompatible stimuli may obstruct intended movements in Parkinson patients and may even result in deviant movement patterns aligned to these external cues (Freeman et al., 1993; de Jong et al., 1999). With regard to gait, such motor blocking occurs at the transition to narrow spaces (Giladi et al., 1992; Okuma 2006). Given the impact of optic flow on gait, both in normal conditions and in Parkinson's disease, we employed functional magnetic resonance imaging (fMRI) to gain further insight in the interconnection between pathways involved in processing optic flow and circuitry implicated in motor control.

Functional imaging of the human brain has demonstrated that visual motion processing strongly involved activation of extrastriate visual area V5 (Watson et al., 1993; Tootell et al., 1995), while the specific perception of forward motion in depth was related with activations distributed over extrastriate visual regions ventral to V5 (the fusiform gyrus), dorsal V3, and the dorsolateral precuneus of the superior parietal lobe (de Jong et al., 1994; Morrone et al., 2000; Kovács et al., 2008). Particularly, the parietal involvement was proposed to reflect the ability to play a central role in visuomotor coordination, i.e., control of locomotion, integrated with temporal cortex processing associated with the perception

of the environmental scene. Widely described functional interconnection between posterosuperior parietal areas and dorsolateral premotor regions in visuomotor coordination underscores that external stimuli indeed efficiently influence motor control (Wise et al., 1997; Clavagnier et al., 2007). Prefrontal cortical regions, on the other hand, may exert an inhibitory effect on such external triggers, complementing the internal generation of movements (de Jong and Paans 2007; Koechlin and Hyafil 2007). With regard to internal movement generation, particularly medial frontal regions such as (pre-) supplementary motor area and medial prefrontal cortex have been reported to play a prominent role (Brass and Haggard 2008; Lau et al., 2004; Rushworth 2008). These frontal regions are major output targets of the basal ganglia, reached via the thalamus (Middleton and Strick 2000). Dysfunction of such projections in Parkinson's disease leads to a disturbed balance between external and internal impacts on the cerebral organisation of movement, with increased vulnerability to external cues (Hallett 2008; Praamstra and Plat 2001) that may either enhance or obstruct intended movements. In the present study on healthy subjects, we aimed to explore how visual stimulation might influence cerebral circuitry implicated in gait control. To that end, we presented wide-field radially expanding optic flow, mimicking the perception of forward motion in depth, followed by a transition to a narrow flow field. We hypothesised to find activations evoked by wide-field forward flow in the parietal and dorsal premotor cortex, while such activations were expected to stop at the transition to the narrow flow field. At this transition, medial prefrontal activation was expected to occur, reflecting a functional shift between circuitries implicated in respectively externally enhanced and internally generated motor control. Given the fact that motor related cortical circuitry maintains a level of intrinsic activation in resting state without a specific motor task (Xiong et al., 1999), we assumed it plausible that specific visual stimulus conditions might indeed interact with such functional circuitry. To deal with the bias related to the size of the visual field, a condition with reversed wide-field flow was included. Compared to forward flow, less biological significance with regard to locomotion has been attributed to such reversed flow (Ptito et al., 2001; Wunderlich et al., 2002).

METHODS

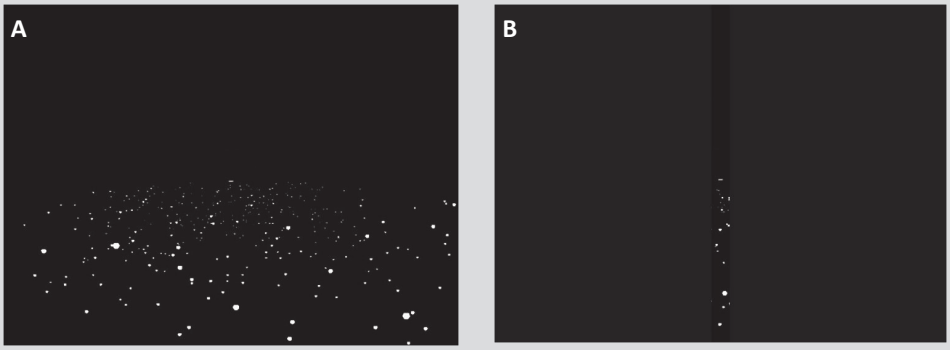
Fifteen healthy right-handed subjects, mean age 23 year (SD ± 4.2), 8 females, successfully participated in this study. None of the subjects had neurological, ophthalmologic, or upper extremity disorders. They signed an informed consent to a protocol approved by the medical ethics committee of the university medical centre Groningen. Procedures and task instructions were explained minimally one week before scanning as well as immediately

before the experiment.

Task design

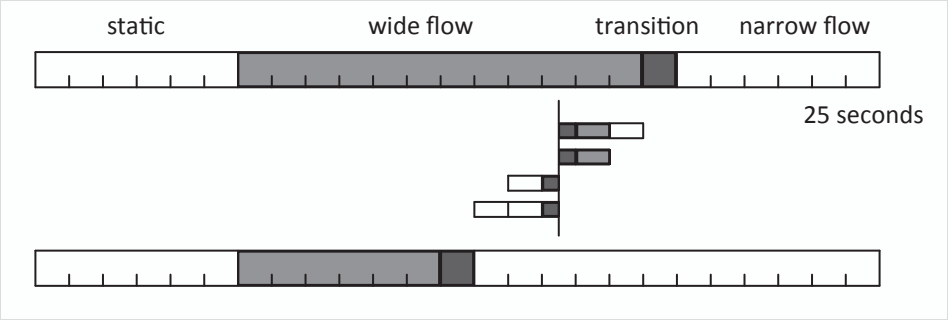
During scanning, subjects watched the stimuli on a screen of 44 by 34 centimetre, comprising 25.5° by 32.7° of the visual field. This screen was visible trough a mirror placed 11 centimetre in front of the face and 64 centimetre from the display screen. A beamer with a monitor refresh rate of 30 hertz and a resolution of 1024×768 pixels (Barco, Belgium) projected the computer-generated stimuli on the screen. The experimental conditions were presented in a pseudo-randomised order using the "Presentation" program (Neurobehavioral Systems, Inc. Albany, CA, USA). All conditions consisted of white dots in the lower half of the monitor screen, on a black background (Figure 1A). At the middle of the virtual horizon, a short horizontal line was placed for gaze fixation. A few observations outside the MR scanner confirmed that subjects easily maintained fixation at this central marker, from which one might infer similar levels of attention. Moving stimuli consisted of 25 frames in a second. The mean density of the dots was approximately 340 over the lower half of the display, while each dot was moving with a linear acceleration from the centre to the periphery in two seconds. The mean speed of each dot was 4.9° in

Figure 1 | Display of the stimulus presentation



Distribution of dots displayed in the lower field of the monitor screen. The wide stimulus field is depicted on the left (A) and the narrow field on the right (B). The transition from wide to narrow fields was established by surfaces (in dark gray tone) that expanded in one second from the horizon in both upward and downward direction. In 'forward flow', enlarging dots moved radial from the centre of the virtual horizon with increasing speed in the lower part of the screen. In 'reversed' flow, visual motion was in opposite direction during which the dots became smaller in size. Further details are explained in the methods section.

Figure 2 | Arrangement of conditions in single trials



The visual stimulus conditions were presented in six blocks, each containing twelve trials. The upper and lower rows illustrate the fixed sequence of conditions in such trials, i.e., stationary control, wide-field flow, transition, and narrow flow. In each block, six trials had a radially expanding flow pattern ('forward flow') and six trails had contracting pattern ('reversed flow'), while in trials with the same flow direction, the transition from wide to narrow occurred respectively 6, 7, 8, 10, 11, or 12 seconds after the onset of wide flow (illustrated by the six horizontal bars).

the first second and 7.9° in the last second, reaching a maximum of 26° per second just before the dot leaves the screen. In condition 1 ('forward wide flow') (FW), dots moved radial from the centre of the virtual horizon with increasing speed in the lower part of the monitor. During this acceleration, the dots proportionally enlarged. In condition 2 ('reversed wide flow') (RW), direction of the moving dots was reversed. Now, dots moved from the periphery of the lower part of the monitor with decreasing speed to the centre of the virtual horizon. The gradual transitions from a wide to a narrow field of stimuli (Figure 1B) was established by surfaces (in dark grey tone) that expanded in one second from the horizon in both upward and downward directions, leaving a central vertical of 4 percent (1.3°) in the visual field. This transition occurred in both forward wide flow (condition 3; FtN) and in reversed wide flow (condition 4; RtN). Although the occluding surfaces expanded from the horizon in both upward and downward directions, the transition was particularly perceived as a loss of the presented dots in the lower visual field. The present design thus provided the illusion of entrance in a narrow corridor of which the specific characteristics remained undefined (condition 3; FtN). The absence of distinct objects in the approaching 'scene' is a difference with the recent study of (Wolbers et al., 2008). In conditions 5 and 6, the narrow optic flow field was presented in respectively 'forward' and 'reversed' directions. Condition 7 served as control condition in which the dots were presented in stationary mode (SW). Subjects were in the scanner for about 40 minutes. The

stimuli were presented in a block design with six different blocks, equally divided over two runs. Each block contained twelve trials consisting of a fixed sequence of conditions, i.e., stationary control, wide-field flow, transition, and narrow flow. Six of such trials had flow in forward mode while it was in reversed mode in the other six trials. In this way, each of the condition 1-6 was repeated 36 times. The order of trials regarding forward or reversed flow was randomised and balanced. The transition from the wide to narrow field of flow lasted one second (and was demarcated as a distinct condition). The onset of this transition varied in time to prevent stimulus anticipation. As a consequence, a wide flow field lasted either 6, 7, 8, 10, 11, or 12 seconds, complemented by a successive narrow field of respectively 12 to 6 seconds. As the initial stationary control condition lasted 6 seconds, each trail lasted 25 seconds (Figure 2). Wide-field stimuli were always presented before the narrow field. This bias in the sequence of conditions was an intrinsic element of the design because, regarding transitions, our research question only concerned cerebral activations related to the transition from wide to narrow forward flow.

MRI characteristics

Data acquisition was performed using a 3 Tesla Philips MR system (Philips medical systems, Best, the Netherlands) with a standard 6-channel SENSE head coil. Functional images were acquired with a gradient-echo T2* blood oxygen level dependent (BOLD) contrast technique using the following scanning parameters: TR = 2000 ms, TE = 28 ms, 39 slices, isotropic voxels 3.5 × 3.5 × 3.5 mm^3, 5° axial orientation. Two runs of 460 volumes each were obtained. A T1-weighted 3D anatomical scan was acquired to obtain high resolution anatomical information.

Analysis of fMRI data

Image processing and statistical analysis (voxel-based, whole brain) were conducted with Statistical Parameter Mapping (Friston et al., 1995), version 5 (2005, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). All volumes obtained were used for data analysis. Preprocessing with SPM included realignment, coregistration, and spatial normalisation (template of Montreal neurological institute, MNI). After this, a Gaussian filter of eight millimetre full-width at half-maximum was applied to smooth the data spatially. Cerebral activations were rendered either onto T1 brain slices or on the surface of a standard MNI brain. For the statistical analysis of regional differences in cerebral activation, all conditions were modelled in a block design at subject level. To identify distributions of activations related to characteristics of visual motion processing in conditions 1-4, each of these conditions was implicitly contrasted to

the stationary condition 7 at subject level. This allowed the confirmation of expected visual cortex activations, and further provided an initial assessment of the responses in the dorsal premotor and medial prefrontal cortex. Thereafter, each contrast was separately analysed at group level using one-sample t-tests. Differences between conditions were analysed (at second level) with a one-way ANOVA for repeated measures (random effect analysis). The contrasts of conditions 1-4 were used in the ANOVA using direction and transition as factors, both with the possibilities forward and reversed. Conditions were assumed to be dependent, equally variant with regard to flow direction and unequal for visual field width, whereas subjects were assumed to be independent and equally variant. Contrasts between the experimental conditions were primarily made to compare FW with RW (condition 1 > 2). In addition to the comparison of FtN with stationary control (condition 3 > 7), from which we expected to find medial prefrontal activation associated with internally driven motor control following reduced visual support, we contrasted both FtN and RW (conditions 3 and 2) with FW (condition 1). To identify overlap in the resulting activation increases, we performed a conjunction analysis (inclusive masking) of conditions 3 > 1 and 2 > 1. This analysis thus provided the opportunity to optimally assess activations related internal motor generation, with a balanced presentation of stimuli within the visual field. The resulting set of voxel values for the indicated contrasts constituted the associated SPM of the t-statistics (SPM<T>) and were thresholded at initial voxel response height $p < 0.001$ with extent threshold k = 8 voxels. Resulting clusters of increased activation were considered statistically significant at cluster-level $p < 0.05$, corrected for the entire brain volume. As we had specific hypotheses for effects in the dorsolateral premotor cortex and the medial prefrontal cortex (including the pre-supplementary motor area), the data were additionally explored at a relaxed threshold of $p < 0.05$ (voxel-level, uncorrected). In addition, profiles of the BOLD response in the resulting voxel clusters at these two locations were assessed by region of interest (ROI) analyses using MarsBar in the SPM toolbox. In this, condition specific values for FW, FtN, RW, and RtN were expressed as a percentage of the overall error term and were corrected to a mean of zero. Differences between these four conditions regarding BOLD profiles in the concerning clusters were analysed by using SPSS version 16.0. Homogeneity of variance was tested with Levene's test for equality of variance. The variance was equal between (1) FW and RW and (2) FtN and RtN but differed between these two pairs. As it has been shown that the F-test is still quite robust by inequality of variance, an ANOVA could be used. Correction for multiple comparisons implied that the threshold for statistical significance was set at $p < 0.0125$ for the post-hoc tests.

Assessment of the illusion of self-motion

All subjects reported the illusion of forward self-motion during FW in the MR scanner. This was not formally tested. A few weeks after the fMRI study, we obtained quantitative assessments from ten of fifteen subjects who participated in the study. The criterion for this subject selection was based on the travel distance to Groningen. Subjects were instructed to rate the strength of the illusion of self-motion on a scale that ranged from 0 (no motion illusion) to 10 (very strong illusion). Stimuli were presented on a computer monitor (VAIO laptop, Sony, Japan) in the same visual field of view as during fMRI. The following stimulus conditions were presented five times each; SW, FW, RW, and a narrow field of forward motion flow. They were ordered in five blocks, of which each block contained the four conditions in random order. Paired t-tests were used for the statistical analysis of differences in ratings that were given to the four conditions. As a total of six paired t-tests were performed, including Bonferroni correction, statistical significance was set at $p < 0.008$.

RESULTS

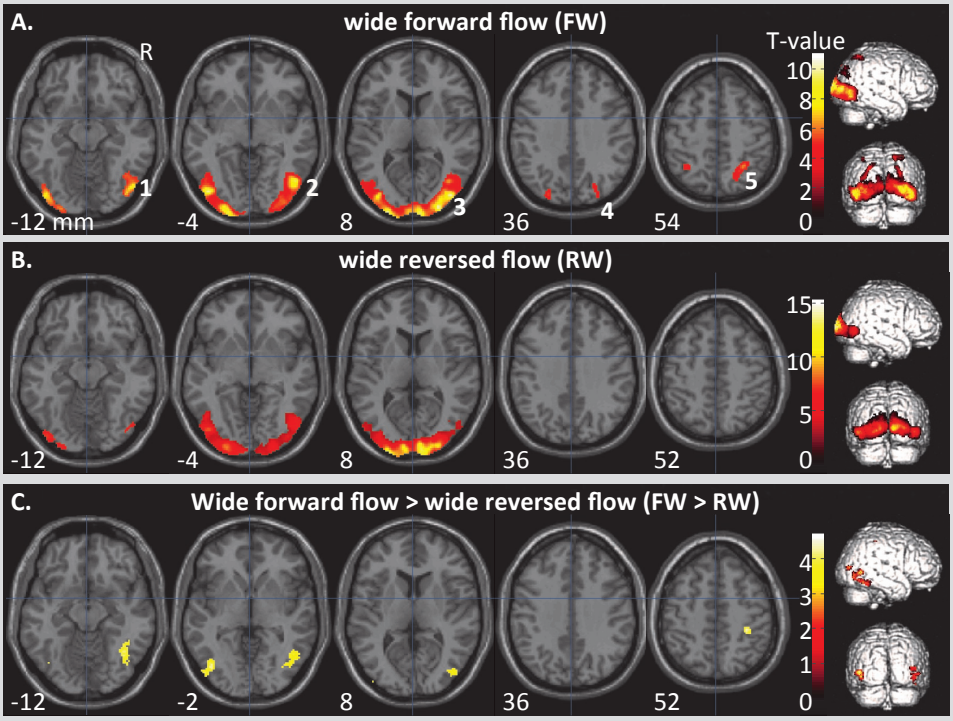
The illusion of self-motion

The control static stimulus display (SW) did not evoke any sensation of self-motion and was rated 0 ± 0.1 (mean ± SD). The scores for wide forward flow (FW), wide reversed flow (RW), and narrow-field forward flow were 6.8 (± 2.4), 6.3 (± 2.7) and 3.0 (± 1.9), respectively. Ratings for these visual motion conditions were significantly different from the score attributed to SW ($p < 0.001$). The illusion of self-motion evoked by each of the two wide-field optic flow conditions was significantly stronger than the sensation evoked by the narrow flow field ($p < 0.001$). No significant difference was found between ratings for this illusion in FW and RW. One might consider that although FW mimics the most natural circumstance of perceived forward self-motion, reversed flow is a visual experience which became particularly familiar in modern life, e.g., during travelling in a train seated backwards.

Forward wide flow

Cerebral activations related to the perception of forward self-motion were identified by contrasting FW to SW (condition1 > 7). Significant increases were distributed around the posterior part of calcarine sulcus, including the fovea representation in the primary visual cortex (V1) and over the lateral extrastriate visual cortex (with putative area V3) extending into the visual motion area V5 (Figure 3). Particularly on the right side, the cluster that included V5 spread ventrally. In dorsal direction, significant increases were bilaterally

Figure 3 | Cerebral activations evoked by wide-field optic flow



Increases in activation (SPM<T>; group of 15 subjects) related to wide-field forward flow (FW) (A) and wide-field reversed flow (RW) (B), each compared to the stationary control condition ($p < 0.05$, corrected for the entire brain volume). The lower row (C) shows the increases of activation related to FW contrasted to RW ($p < 0.001$, voxel-level uncorrected; extent k = 20). Increased activations are projected on transverse anatomical sections of a standard brain volume (Montreal neurological institute, SPM 2005). At the right end of each row of transverse sections, the same activation clusters are rendered onto the surface of a standard anatomical brain volume (right lateral and posterior views). Coordinates of the significant clusters are reported in Table 1. The hair-cross in the transverse sections indicates the cerebral midline and the VCA. The distance to the plane traversing the anterior and posterior commissures (ac-pc) is indicated by the z coordinate (below; in millimetres; mm). R = right side of the brain, 1 = fusiform gyrus; 2 = (ventral) V5; 3 = lateral occipital region; 4 = posterior intraparietal sulcus; 5 = superior parietal cortex.

found at the junction of the occipital and parietal cortex around the posterior part of the intraparietal sulcus and in the superior parietal cortex at more anterolateral locations

Table 1 | Cerebral activations related to the direction of radial optic flow

Brain region (BA)	Left				Right			
	x, y, z	Z	Ext.	p_{corr}	x, y, z	Z	Ext.	p_{corr}
Forward wide flow versus stationary control [FW > SW]								
Foveal V1V2 (17/18)	-26,-102, 6	5.46	6155	0.000	28, -96, 8	5.42	sc	sc
Lateral occipital (19)	-42, -80, -6	5.33	sc	sc	42, -84, 8	5.45	sc	sc
V5 complex (19/37)	-44, -78, -2	5.55	sc	sc	50, -70, -6	5.31	sc	sc
Posterior IPS (19)	-18, -86, 44	4.42	sc	sc	26, -74, 30	4.35	255	0.000
Superior parietal (7)	-22, -46, 48	3.88	117	0.037	30, -52, 56	4.39	290	0.000
	-20, -64, 62	3.46	38	0.675[a]				
Reversed wide flow versus stationary control [RW > SW]								
Foveal V1 (17)	-8, -98, 8	5.61	5554	0.000	10, -98, 4	6.25	sc	sc
Dorsal V2	-24,-104, 10	6.13	sc	sc	22, -98, 10	5.60	sc	sc
V5 (19/37)	-46, -78, 2	5.31	sc	sc	50, -74, 2	4.73	sc	sc
Forward wide flow versus reversed wide flow [FW > RW]								
Ventral V5 (19/37)	-40, -74, -6	4.05	247	0.006	44, -70, -6	3.79	58	0.536[a]
Lateral occipital (19)					44, -80, 6	3.43	sc	sc[a]
Ventral occipito-temporal (37)					40, -56,-14	3.94	3.96	0.000
Fusiform gyrus (20)					46, -48,-16	4.18	sc	sc

Coordinates refer to the voxels of maximum activation within clusters of significant activation ($p < 0.05$, whole brain corrected at cluster-level), extent in voxel number and corrected *p*-values are additionally listed. Exceptions are the clusters marked with 'a' that reached significance at cluster-level ($p < 0.05$), but did reach significance after correction for the entire brain volume. Initial voxel-height threshold was $p < 0.001$, with extent threshold k = 8 voxels. Positive x, y, z coordinates (in millimetres; mm) indicate locations respectively right, anterior and superior to the middle of the anterior commissure. BA = Brodmann's area; ext. = extent; IPS = intraparietal sulcus; sc = same cluster, local maximum of activation is more than eight mm apart from the adjoining focus in this cluster.

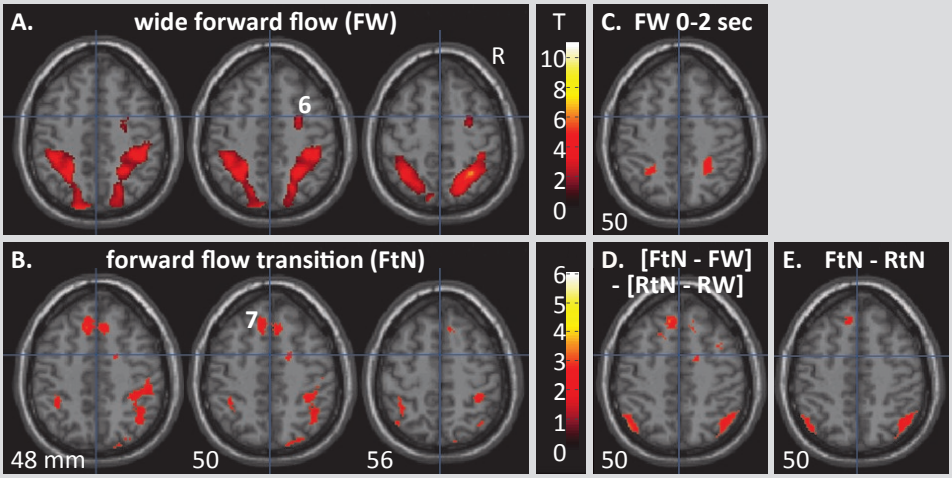
(Figure 3). The coordinates of these clusters are specified in Table 1. When RW was contrasted to SW (condition 2 > 7), no significant activations were seen in the parietal cortex (Figure 3B and Table 1). The finding that parietal activation appeared to occur specifically in FW was confirmed by the direct contrast of FW to RW (condition 1 > 2),

although the circumscript activations in the right superior parietal cortex (x 22, y -58, z 60) and right inferior parietal cortex (x 34, y -34, z 52) remained below formal statistical significance ($p < 0.001$, voxel-level, uncorrected). Significant increases of activation related to FW, when compared to RW, were particularly seen at the ventral parts of V5, bilaterally, and the right fusiform gyrus ($p < 0.05$, volume-corrected) (Figure 3 and Table 1). The preceding visual and parietal cortex activations mainly concerned replications of previously described findings. In the next part of the results section, the condition related effects in motor associated regions are treated, and activations related to the shift from wide to narrow forward flow are presented. These findings concern the primary scope of this study. Since we had a specific hypothesis that predicted increased activation in the dorsal premotor area during FW, possible effects in this region were also assessed at relaxed threshold. At $p < 0.05$ (voxel-level, uncorrected), increased activation was seen at the junction of the lateral aspect of the right superior frontal gyrus and the precentral gyrus, functionally classified as part of the dorsal premotor area, Brodmann's area (BA) 6 (x 28, y -6, z 52) (Figure 4A). No medial frontal activations were seen at this relaxed threshold, while a pattern of distinct parietal activations was seen along the (medial) wall of the intraparietal sulcus, bilaterally (Figure 4A). The ten subjects who rated the perceived illusion of forward self-motion in FW experienced this illusion with scores that ranged between 3 and 9 (scale 0-10). Pearson's correlation between the strength of illusion and the effect in the dorsal premotor area was 0.31 ($p = 0.38$, two-tailed).

Transition from forward wide to narrow flow

The pattern of significant cerebral activations related to the transition from the wide to the narrow field of forward optic flow (FtN), when compared to SW (condition 3 > 7), included the ventral part of V5 and lateral occipital cortex. The FW related activations in foveal V1 and the parietal cortex were no longer seen (Table 2). At a relaxed threshold of $p < 0.05$ (voxel level, uncorrected), activation was seen in the dorsal medial prefrontal cortex with focus of maximum in the left hemisphere (x -8, y 26, z 48) (Figure 4B). At this relaxed threshold, dorsal premotor area had disappeared, which was also the case for the well delineated superior parietal pattern. Increased activation of V1 was not seen either. Medial prefrontal activation was hypothesised to occur in response to reduced stimulation of circuitry providing external support for locomotion. It would thus reflect an increased demand on circuitry implicated in organising the internal generation of motor actions. Next to the comparison of FtN with SW, we contrasted FtN to FW (condition 3 > 1) which provided further support for medial prefrontal activation during the interruption of perceived forward self-motion (Table 2). This contrast also revealed a bilateral signal

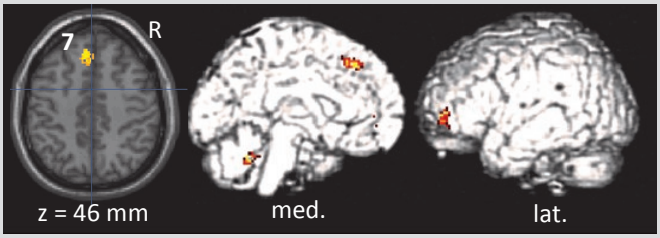
Figure 4 | Responses in visuomotor circuitry by interrupting optic flow



Increases in activation related to wide-field forward flow (FW, duration ranging from six to twelve seconds) (A) and the transition to the narrow field of forward flow (FtN) (B), each compared to stationary control, particularly illustrating the activations in the dorsal premotor cortex (6) and medial prefrontal cortex (7). Absence of medial prefrontal activation in the initial two seconds frame of FW following stationary control (C) and its presence after contrasting [FtN-FW] to [RtN-RW] (D) as well as FtN-RtN (E) provided arguments against confounding effects (see text) and supported the specificity of the relation between this medial prefrontal activation and FtN, mimicking the natural circumstance of naturally interrupting FW by approaching a narrow corridor. Threshold for statistical significance was $p < 0.05$ (voxel-level uncorrected; extent k = 20). Small volume correction for the right dorsal premotor activation (sphere; radius 10 mm) resulted in a cluster-level corrected *p*-value of 0.275 (condition A), while for the medial prefrontal activation such *p*-value was 0.264 (B). For the contrasts D and E, performed to exclude confounds that might alternatively explain the medial prefrontal activation, corrected *p*-values were 0.220 and 0.345, respectively. Other conventions are similar to the description of figure 3. Coordinates of FtN related activations are reported in Table 2.

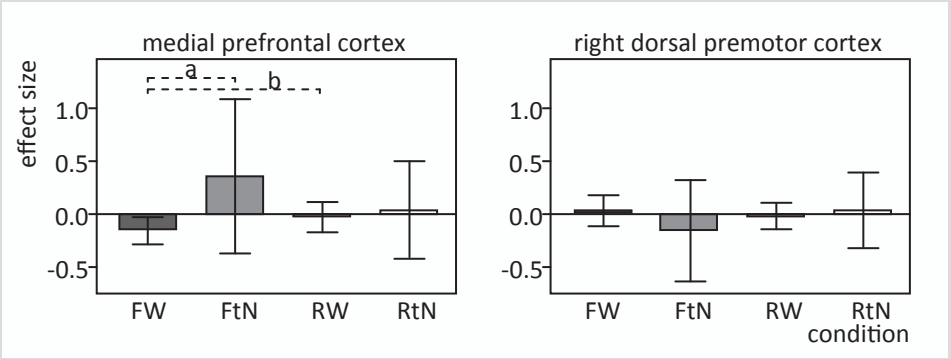
increase in the temporal horn of the lateral ventricles, reaching statistical significance on the left side, which might possibly be related to a venous drainage effect following FW. Alternatively, we considered head motion due to postural adjustment at FtN as a possible cause for artificial signal increases. However, movement parameters that were assessed at single-subject level did not provide support for such explanation. Conjunction analysis of this comparison and the comparison of RW with FW (RW versus FW, inclusive masked by

Figure 5 | Medial prefrontal activation



Increased activation in the medial prefrontal cortex (7) that resulted from conjunction analysis of the comparison FtN > FW and the comparison FtN > FW and the comparison of RW > FW (with inclusive masking) ($p < 0.001$, voxel-level uncorrected; extent k = 20). The single focus of overlapping activations in the medial prefrontal cortex illustrates its selectivity. Other conventions are as in Figure 3. Next to the transversal section, medial and lateral views of a standard left hemisphere volume are depicted. Coordinates are reported in Table 2.

Figure 6 | Relative condition effects in medial prefrontal and dorsal premotor cortex



Relative differences across the conditions forward wide flow (FW), transition from forward wide to forward narrow flow (FtN), reversed wide flow (RW) and transition from reversed wide to reversed narrow flow (FtN) are plotted for the clusters in the medial prefrontal cortex (maximum x -8, y 26, z 48) and right dorsal premotor cortex (maximum; x 28, y -6, z 52). Regions of interest were defined by the demarcation of these clusters at $p < 0.05$; extent threshold 20 (see Figure 4). The effect size for each subject in these clusters was the mean voxel value in each of the two clusters. It represents a percentage of the overall error term and is corrected to a mean of 0. The statistical significance of effect differences was assessed with ANOVA (medial prefrontal cortex $p = 0.021$; dorsal premotor cortex $p = 0.303$). Given the specific prediction of these differences, one-tailed p-values are presented for post-hoc tests. As to correct for multiple comparisons, threshold for statistical significance for the post-hoc tests was set at $p < 0.0125$. a; $p = 0.001$, b; $p = 0.168$.

Table 2 | Cerebral activations related to the interruption of wide forward flow

Brain region (BA)	Left				Right			
	x, y, z	Z	Ext.	p_{corr}	x, y, z	Z	Ext.	p_{corr}
Transition forward wide to narrow flow versus stationary control [FtN > SW]								
Ventral V5 (19/37)	-46, -78,-10	4.08	138	0.005	46, -70, -8	3.69	315	0.000
Lateral occipital (19)					46, -86, -8	5.74	sc	sc
Putative V2 (18)	-32, -96, -6	3.83	66	0.226[a]	32,-100, -4	3.73	sc	sc
Transition forward flow versus forward wide flow [FtN > FW]								
Ventricle (temporal horn)	-22, -50, 10	4.74	163	0.038				
Lateral occipital (19)					44, -90,-10	4.66	80	0.312[a]
Med. prefrontal (18)	-8, 34, 46	3.38	13	0,994[b]				
Conjuction [reversed wide > forward wide flow] + [transition forward > forward wide flow]								
Inf. prefrontal (11)	-26, 50, 4	4.61	344	1.000[b]				
Med. prefrontal (18)	-6, 34, 46	3.88	684	0.962[a]	12, 30, 44	3.33	sc	sc[a]

Coordinates refer to the voxels of maximum activation within clusters of significant activation ($p < 0.05$, whole brain corrected at cluster-level), extent in voxel number and corrected p-values are additionally listed. Exceptions are the clusters indicated with 'a' and 'b', indicating respectively $p < 0.05$ (cluster-level, uncorrected) and non-significant at cluster level. All clusters are generated with voxel height threshold $p < 0.001$; extent threshold k = 8 voxels. Positive x, y, z coordinates (in millimetres) indicate locations respectively right, anterior and superior to the middle of the anterior commissure. BA = Brodmann's area; ext. = extent; inf. = inferior; med. = medial; sc = same cluster, local maximum of activation is more than eight millimetres apart from the adjoining focus in this cluster.

FtN versus FW) raised statistical significance of specifically the medial prefrontal activation (Figure 5 and Table 2). This cluster on the medial aspect of the superior frontal gyrus spread between 18 and 38 millimetres anterior to vertical traversing the anterior commissure (VCA), which implies that it included the rostral segment of the pre-supplementary motor area (BA 6) and the prefrontal cortex adjacent to it (BA 8, 9) (Picard and Strick 1996). The relative effects across conditions FW, FtN, RW, and RtN were plotted for the clusters in the right dorsal premotor and medial prefrontal cortex (Figure 6). The conjunction analysis of FtN versus FW and RW versus FW provided an argument against the possible confound that the medial prefrontal activation might be due to a difference in

stimulus field width between FtN and FW. Other possible confounds intrinsically linked to the transition from wide to narrow visual flow fields might concern (1) the presence of less stimulus adaptation, contrast- and signal-to-noise ratio's in FtN compared to FW and (2) a nonspecific attention effect associated with the stimulus change. Activation of the medial prefrontal cortex, however, was not explained by these alternative suggestions because it remained present by contrasting both [FtN-FW] to [RtN-RW] (Figure 4D) and FtN to RtN (Figure 4E), while it was not seen in the initial two seconds frame of the FW condition following static control (Figure 4C).

DISCUSSION

The present study was designed to test the hypothesis that visual stimulation by wide-field forward flow (FW) facilitates activation of cerebral circuitry implicated in externally driven motor control, while the transition to a narrow flow field (FtN) interrupts such facilitation and induces a shift to neuronal circuitry known to support internally driven motor control. Right parietal-premotor activations evoked by FW provided logical arguments for a potential functional interface between visuospatial motion processing and spatial motor preparation (Wise et al., 1997). The common medial prefrontal activation related to FtN and reversed wide-field flow (RW) is consistent with this concept and may thus imply that the loss of external support from FW was complemented by an increased demand on circuitry implicated in the internal generation of motor action (Rushworth 2008; Brass and Haggard 2008). Although the present results do not ultimately proof the hypothesised manipulation of motor circuitry, the obtained data provide a clear starting point for future studies to explore this issue.

Wide-field forward optic flow (FW)

The applied visual motion conditions were contrasted to a control condition in which a fixed image was displayed. As expected, robust increase of activation in the visual motion area V5 (Watson et al., 1993) occurred in all motion conditions. The present paradigm was not primarily designed to discriminate between optic flow and simpler visual motion stimuli such as incoherent motion or parallel translation. On the other hand, the activations in the ventral segment of V5, the right fusiform gyrus, and the dorsal parieto-occipito junction that were particularly seen in FW and not (or less) in the other motion conditions underscored a distinct relation between these regions and the illusion of forward motion in depth, indeed mimicking the visual feedback arising from natural (forward) locomotion. The specific contributions of ventral V5 and the adjacent fusiform gyrus to processing optic flow is consistent with previous studies that have addressed there

presentation of expanding optic flow, as compared to either incoherent motion (de Jong et al., 1994) or parallel translation (Morrone et al., 2000). The increase of activations in such early visual processing areas during FW, particularly in comparison with RW, has been proposed to reflect the biological significance of forward motion in depth (Wunderlich et al., 2002). The fact that the flow patterns in FW and RW had a similar level of motion coherence indicates that the enhanced activations evoked by FW, compared to RW are indeed not explained by only processing three-dimensional structure from motion (Braddick et al., 2000; Kourtzi et al., 2008).

Along the posterior segments of the intraparietal sulcus, including the precuneus of the superior parietal lobe, significant activation was evoked by FW (expanding optic flow) and not by RW (contracting flow). This difference is consistent with previous studies that showed stronger responses to expanding flow stimuli at this location compared to the responses evoked by incoherent motion (de Jong et al., 1994), parallel translation (Konen and Kastner 2008), and contracting optic flow (Ptito et al., 2001), respectively. We speculate that this stronger parietal activation in FW is related to a higher biological significance of forward, compared to backward, locomotion in human. Moreover, the additional anterodorsal parietal activation for which Ptito et al. (2001) described right-sided dominance coincided with the dorsal extension of intraparietal sulcus activation related to FW in our study. The pattern of activations comprised dorsal and ventral visual processing streams (Goodale and Milner 1992), which points at circuitry optimally equipped for the integration of visuomotor coordinate transformations and environmental feature identification, as naturally occurs in guiding forward locomotion (Aguirre and D'Esposito 1999; Andersen et al., 1997; de Jong et al., 2001; de Jong et al., 1994; Epstein 2008; Snyder et al., 1997; Wolbers et al., 2008).

Although the FW related activation in the right dorsal premotor area did not reach statistical significance after correction for effects in the entire brain volume, the uncorrected result was inferred to reflect a physiological response and not statistical noise. We have three arguments to support this conclusion; (1) the effect was seen in a distinct predefined location; (2) no other frontal activations were seen in the assessed planes, which supported specificity of the dorsal premotor response; and (3) the right hemisphere location of the dorsal premotor area activation logically corresponded with the dominance of the right parietal activation during FW, thus reflecting the expected parietal-premotor coherence (Wise et al., 1997; de Jong et al., 1999).

Spatial processing in the dorsal premotor area concerns both perceptual and motor functions enabling adequate motor preparation (Beudel et al., 2009; Bremmer et al., 2001; Johnson et al., 1996; Pesaran et al., 2006; Shen and Alexander 1997). In a recent fMRI study on virtual forward locomotion, the applied visual stimulus design included the incidental (distant) appearance of geometric objects within the expanding flow of dots (Wolbers et al., 2008). Object locations in preceding stationary trials served as a memorised reference enabling subjects to indicate distinct locations in the dynamic trials. Activation profiles in the precuneus and dorsal premotor area provided arguments for Wolbers and coworkers to propose that the brain uses optic flow for locomotion, in such a way that the precuneus is particularly implicated in successive constructions of updated visuospatial representations while the dorsal premotor area plays a key role in the context-dependent planning of motor actions. Their specific findings provide strong support for our concept that the parietal and right dorsal premotor activations evoked by FW in the present study indeed point at a distinct neuronal pathway along which visual stimuli may modulate the cerebral organisation of motor actions implicated in gait.

We acknowledge that, in our study, the observed effect in the right dorsal premotor area was not robust. To evoke stronger responses in visuospatial and associated motor regions, further enlargement of the visual flow field might be considered to achieve a stronger visual resemblance of real self-motion. It is interesting to notice, in this respect, that visual area V6, which has direct connections with the dorsal premotor area in macaque (Shipp et al., 1998), has only recently been defined as a distinct visual area in human by using extremely wide-field stimulus presentation (Pitzalis et al., 2006), while involvement of this cortical region in visuomotor functions has previously been a reason to label it the ‘human V6 complex’ (de Jong et al., 2001). This effect of visual field width further supports the idea that manipulating the illusion of forward self-motion by distinct changes in radial optic flow is a promising way to study visual modulation of gait control and the underlying functional architecture in the brain.

Aside from visual stimuli, the real perception of self-motion is also derived from other sensory signals such as vestibular, auditory, and tactile information (Britten 2008). Kleinschmidt et al. (2002) obtained fMRI data on this complex issue by using a rotating windmill pattern that did not change but induced either illusory self-motion (circular vection) or the perception a rotating pattern. The illusion of circular vection, compared to perceived object rotation, was related with increased activation in only the cerebellar nodulus together with general visual and vestibular cortex decreases, which was consistent

with vestibular-visual interactions naturally implicated in real self-motion. Unchanged activation levels in both a visual V5 satellite and at the medial parieto-occipital junction were suggested to reflect the ability to maintain a continuous reconstruction of self-motion. This was further motivated by the transient activation increases in the latter during perceptual switches between self-motion and objection motion. These findings may fit our data assuming that the parieto-occipital junction and ventral V5 represent important nodes in an extended visual motion network that efficiently interacts with multiple sensory modalities as well as with (pre)motor regions, which makes it optimally equipped to support locomotion in dynamic circumstances.

Medial prefrontal activation and loss of external motor support

The parietal and dorsal premotor activations in our study disappeared during the transition from wide to narrow forward flow (condition FtN) as well in RW (radially contracting flow). In RW, the centre of maximum within the cluster of V5 activation was dorsal to that in both FW and FtN. In the preceding paragraphs, we argued that activation of the particular ventral V5 segment in FW, which occurred together with occipital-parietal activations, supported that the FW evoked illusion mimicked the most natural condition of perceived forward self-motion. Persistence of this ventral V5 activation in FtN might thus be related to the fact that subjects still perceived a sense of forward self-motion during narrow forward flow, although less strong than in the wide-field flow condition. The lasting activation of ventral V5 might imply that feature assessment of the virtually approaching dot flow continued with similar intensity, while processing of spatial characteristics and possible visuomotor consequences degraded (de Jong et al., 1994; Tootell et al., 2003; Wolbers et al., 2008).

Complementary to the disappearance of the parietal and right dorsal premotor activations, an increase of dorsal medial prefrontal activation was seen during FtN and RW. Although this medial prefrontal effect was not strong, it was significantly larger in FtN compared to preceding FW. This effect was consistent with our hypothesis of activated circuitry implicated in internally driven motor control, induced by the loss of external support from optic flow. The involvement of particularly this medial prefrontal activation was further motivated by its selective presence in the subsequent conjunction analysis of FtN and RW, both compared to FW (inclusive masking). As this conjunction included wide as well as narrow fields of view, the medial prefrontal effect was not due to change in width of the visual field. The balance in visual field width was a major reason to include RW in the study, while a reduced biological significance of RW compared to FW (Wunderlich et al., 2002)

was considered to imply that locomotion with a contracting visual flow field relies stronger on internally driven motor control. The lateral to medial cortical shift in the present study is consistent with the change from parietal to pre-supplementary motor area activation that has recently been described to occur during the intermittent occlusion of feedback in visuomotor control of the upper limb (Ogawa et al., 2006).

Before we further elaborate our conceptual view on the medial prefrontal activation, some remarks need to be made with regard to possible confounds that might alternatively explain this activation. As argued in the preceding paragraph, a difference in width between stimulus fields, which was an intrinsic element of the design, did not account for medial prefrontal activation in FtN. This is also supported by the fact that this activation remained present after contrasting [FtN-FW] to [RtN-RW] as well as by comparing FtN to RtN. The latter additionally provided arguments against nonspecific medial prefrontal involvement caused by (1) the difference in stimulus duration between FtN and FW or (2) a general effect of shifting between stimulus patterns. Indeed, such shift may induce a change in attention, although easily maintained fixation to the central marker did not indicate an imbalance between conditions in this respect. The medial prefrontal activation thus appeared particularly related to FtN, the condition that mimicked the natural circumstance of approaching a narrow corridor. To which extent a shift between connections to putative motor circuitries might be equivalent to a shift in 'motor attention' (Rushworth et al., 2003) remains speculation.

With regard to different motor circuitries, early observations have discriminated selective contributions of the lateral dorsal premotor area and medial supplementary motor area to respectively externally and internally driven movements (Godschalk et al., 1985; Halsband et al., 1993; Mushiake et al., 1991; Passingham 1993). This general concept has been adapted and refined since. The ordering of specialised regions within the medial prefrontal cortex specified a gradual transformation from intention into action (Rushworth 2008; Brass and Haggard 2008). In this, the anterior cingulate cortex plays a role in dealing with stimulus conflicts when they do not unequivocally code for a specific action (Beudel and de Jong 2009; Botvinick et al., 2004), while the pre-supplementary motor area contributes to the final action selection by inhibition and facilitation of the most appropriate motor repertoires in circumstances of conflicting environmental information (Lau et al., 2006). Moreover, the pre-supplementary motor area plays a dominant role in the initiation of movements in the absence of external cues (Lau et al., 2004). The medial prefrontal cortex anterior to the pre-supplementary motor area seems particularly implicated in motor

selection by inhibition of potentially competing motor acts irrespective of environmental circumstances (Brass and Haggard 2007; de Jong and Paans 2007), which is consistent with its proposed role in self-referential mental activity (Gusnard et al., 2001). These previous studies thus support our conclusion that activation of the medial prefrontal cortex in the present study, which partly included the pre-supplementary motor area, may reflect an interface between visual processing and circuitry facilitating the internal generation of locomotion when external visual support is interrupted.

In Parkinson's disease, deficit in self-initiated movements has been related to underactivation of the supplementary motor area (Jahanshahi et al., 1995). Deprived input from the basal ganglia and thalamus to the medial prefrontal cortex, but also to the lateral premotor cortex, has been shown to cause reduced cortical activity in resting state (DeLong and Wichmann 2007; Eidelberg et al., 1994), although structural deficit of the medial prefrontal cortex has also been reported (MacDonald and Halliday 2002). One of the effects of reduced basal ganglia-thalamic input to the lateral premotor cortex is the enhanced influence of external stimuli mediated by the parietal cortex (Praamstra and Plat 2001; Samuel et al., 1997). This implies that external triggers are difficult to suppress and may result in distracted motor action, while the interruption of supporting stimuli may block ongoing movement patterns. The shift from parietal-dorsal premotor activations to medial prefrontal activation that we found in healthy subjects during the transition from wide to narrow forward optic flow may thus help to explain why in Parkinson's disease, a condition with insufficient medial prefrontal cortex function, the internal generation of motor action fails in the circumstance of interrupted external support from wide-field optic flow. This may indeed result in freezing of gait (Hallett 2008). Although entrance of a narrow corridor may still evoke a visual flow containing, e.g., characteristics of the corridor's walls, such features remain longer represented in the central parts of the visual field, without an equable shift to the peripheral field. As a consequence, coherence of the visual flow pattern is interrupted in such a way that the sensation of spatial depth is reduced.

In the present experiment, we made use of a visual stimulus paradigm without motor actions. We acknowledge that the activation of cortical regions known to contribute to movement preparation does not prove covert motor involvement in the present task. Our explanation that a change in sensory stimulation modulates activity in motor circuitry, with a shift in dominance from the representation of externally to internally driven motor actions has therefore a tentative character indeed. On the other hand, motor related

cortical circuitry has been demonstrated to maintain a level of intrinsic activation in resting state without a specific motor task. With covariance analysis of fMRI data in resting state, Xiong et al. (1999) demonstrated that spontaneous activations in the motor cortex were related with a distribution of activations in other regions that constituted a functionally interconnected motor network. Such ongoing intrinsic activity in a distinct brain system, without specific task performance, may even be a general rule of cerebral functioning (Raichle and Gusnard 2005). Raichle and Gusnard (2005) suggested that this ongoing activity provides a condition allowing new sensory information to efficiently modulate the operations of such a functional system. In this respect, visual stimuli might modulate operations of the motor system, aimed to facilitate distinct goal-directed motor preparation, without the necessity of an overt motor response. Future studies, however, need to test the behavioural effects of optic flow modulation on gait control, particularly in patients with Parkinson's disease. In this respect, the experimental paradigm applied in the present study seems to be a promising tool for behavioural and fMRI studies in Parkinson patients.

CONCLUSIONS

The visual presentation of radially expanding optic flow, which evoked the illusion of forward self-motion, activated a putative functional interface with motor related circuitry distributed over posterior regions of the superior parietal cortex and right dorsal premotor area. Interruption of such wide-field flow mimicked the loss of external support for locomotion, which may subsequently challenge the medial prefrontal cortex to facilitate internally generated motor action. These results suggest that the cerebral organisation underlying visuomotor transformations in locomotion resembles circuitry involved in goal-directed movement of the upper limb.

CHAPTER 5

Narrowing wide-field flow affects treadmill gait in left-sided Parkinson's disease

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ABSTRACT

Radially expanding optic flow is a visual consequence of forward locomotion and provides walking support. When presented on a display, it evokes the illusion of forward self-motion. As movements in patients with Parkinson's disease are more vulnerable to external stimuli, we aimed to study the effect of optic flow manipulation on gait progression in these patients. Narrowing wide-field flow was expected to induce slowing of gait in Parkinson patients. Since the right hemisphere is particularly implicated in visuomotor transformations, we additionally explored right hemisphere involvement. Fifteen Parkinson patients (eight right, seven left dominant symptoms) and ten healthy controls viewed optic flow projected on a wide screen while walking on a treadmill, set at subject-tuned constant walking speed. Slowing of gait thus resulted in backward displacement, quantified by centre of mass calculation. Right hemisphere function was examined with the WAIS-III block design. Backward displacement due to narrowing wide-field flow was seen in particularly left dominant Parkinson patients. This visually induced slowing of gait correlated with right hemisphere dysfunction revealed by reduced block design performance in the entire Parkinson group. Gait obstruction by narrowing optic flow in left-sided Parkinson patients indicated enhanced interference of gait by external stimuli, likely mediated by particularly the right hemisphere. Narrowing wide-field flow reduced external support, mimicking circumstances that may provoke freezing at the entrance of a narrow corridor. We discuss possible effects of disturbed lateral and medial premotor function in Parkinson's disease that might explain a dysbalance between external cues and internal drives in gait control.

INTRODUCTION

The strong impact of sensory stimuli on gait in Parkinson's disease (PD) indicates functional changes in both cortical circuitry and the basal ganglia (Braak et al., 2004; Suteerawattananon et al., 2004). Such enhanced influence of external stimuli, either supporting or obstructing movement, has been proposed to result from a disturbed balance between external and internal information streams funnelled through lateral and medial premotor cortices, respectively (Brass and Haggard 2008; Hallett 2008; Lau et al., 2004; Picard and Strick 2001; Praamstra and Plat 2001; Rushworth 2008). Medial premotor areas are particularly connected with the basal ganglia (Alexander et al., 1986; Middleton and Strick 2000) and indeed functionally affected in Parkinson's disease (Dirnberger et al., 2005; Jahanshahi et al., 1995; van Eimeren et al., 2009). This is reflected in freezing of gait (Hallett 2008), which implies that the loss of external support of optic flow cannot be replaced by an internal movement drive at e.g. approaching a narrow corridor seen ahead (Giladi et al., 1992; Giladi et al., 2001a; Okuma 2006).

Optic flow, the visual flow pattern elicited during forward locomotion, supports gait in healthy subjects (Warren et al., 2001) and Parkinson patients (Azulay et al., 1999; Schubert et al., 2005). We recently found with functional magnetic resonance imaging (fMRI) that when visually presented wide-field optic flow (inducing the illusion of forward self-motion) transited into a narrow flow field, a shift from lateral to medial premotor cortices occurred in healthy subjects (van der Hoorn et al., 2010a). Now, we aimed to behaviourally test this visuospatial effect of optic flow manipulations in a walking paradigm *without* actual forward displacement, assessing both Parkinson patients and healthy controls. Subjects walked on a treadmill while watching a screen with wide-field 'forward' optic flow that repeatedly narrowed, representing the virtual entrance to a narrow space. We expected a stronger negative effect of this visual transition on gait progression in Parkinson patients than in healthy subjects. Moreover, as right hemisphere dominance has been implicated in proprioceptive support of normal gait (de Jong et al., 2002), and impaired sensorimotor transformation has been associated with right hemisphere dysfunction in Parkinson's disease (de Jong et al., 1999; Bartels et al., 2006), we hypothesised stronger gait interruption in Parkinson patients with left-sided symptom dominance. We therefore also looked for a correlation between such gait interruption and possible right hemisphere dysfunction in Parkinson patients.

METHODS

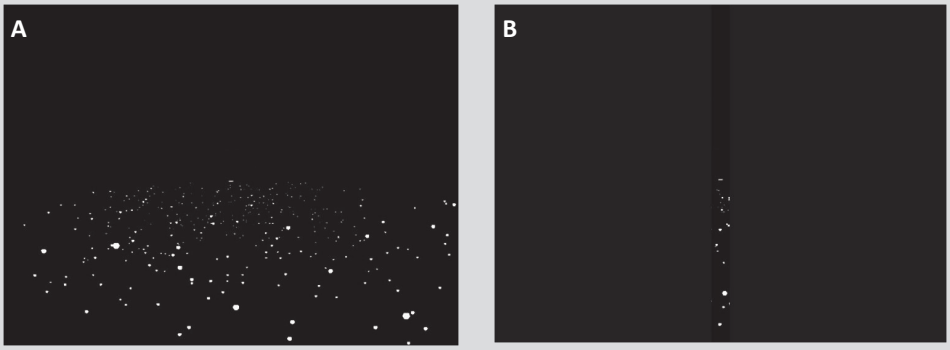
Subjects

Fifteen patients with Parkinson's disease, eight with right-sided symptom dominance (PDR) and seven with left-sided symptom dominance (PDL), as well as ten healthy controls (HC) successfully participated in this study. Two of initially seventeen tested Parkinson patients (one left and one right dominant patient) were unable to walk unassisted on the treadmill and therefore excluded. To obtain optimal insight in a relation with impairments due to Parkinson's disease, patients were tested after twelve-hour medication withdrawal, except for two patients that were tested end-off-dose. Mild to moderate Parkinson patients (without freezing of gait) were selected by a score of 1 up to 3 on the modified Hoehn and Yahr scale (Goetz et al., 2004). The unified Parkinson's disease rating scale (UPDRS) (Fahn and Elton 1987) was conducted immediately prior to the experiment. The dominant side of Parkinson symptoms was derived from the clinical file. Side of onset corresponded with the consistently reported asymmetry, which was confirmed by the right and left item scores of the UPDRS III. In general, scores for the lower and upper UPDRS parts were similarly asymmetric as the total score. Only two right and two left dominant Parkinson patients scored equal for right and left lower part items, while one left dominant patient scored equal on the upper part. Treating clinicians reported the patients as non-depressed. Depression scores were not further obtained. All subjects were non-demented indicated by mini mental state examination (MMSE) (Folstein et al., 1975) and right-handed according to the Edinburgh handedness inventory (Oldfield 1971). None of the participants had interfering neurological, ophthalmologic or lower extremity disorders, except Parkinson's disease in de corresponding group. Education level was classified with a Dutch education scale ranging from 1 (elementary school unfinished) to 7 (university degree) (Verhage 1964). The experiment was approved by the local medical ethical committee. All subjects gave written informed consent.

Task design

Participants walked on a treadmill set at subject-tuned comfortable walking speed after they had familiarised with it first. They wore a safety harness attached to the ceiling with a rope. The externally driven treadmill speed remained constant during the 20 minutes experiment of each subject. Subjects watched stimuli projected on a screen placed about 130 centimetre in front of them (beamer resolution 900 x 600 pixels, Casio XJ-450, Japan). The screen was 171 by 128 centimetre, comprising 65° by 52° of the visual field. Experimental conditions were presented in a pseudo-randomised order using "Presentation" program (Neurobehavioral Systems: Albany, CA, USA).

Figure 1 | Display of the stimulus presentation



A wide-field of dots is shown on the left (A) and a narrow field on the right (B). In the optic flow condition, enlarging dots moved from the centre to the periphery in the lower visual field. In experimental condition 1 (FW-to-FtN), the wide optic flow field (A) transformed to a narrow flow field (B) due to dark grey surfaces that expanded in 1.8 seconds from the horizon in both up and downward direction. In control condition 2 (FW-to-SW), optic flow (A) abruptly stopped moving. In control condition 3 (SW-to-SFn), a stationary wide-field image of dots (A) transformed to a stationary narrow field (B), similar to the transition in the dynamic condition 1.

In all three conditions, white dots on a black background covered the lower half of the monitor screen, with a mean density of approximately 340 dots. For gaze fixation, a short horizontal line was placed at the middle of the virtual horizon. Dots were presented either in stationary or dynamic mode. In the latter, stimuli were composed of 25 frames per second. In two seconds, dots moved radially from the centre of the virtual horizon with increasing speed into the lower part of the screen, while they enlarged proportionally. This dynamic display of 'wide forward flow' generated the illusion of forward self-motion. Mean speed of each dot was derived from a horizontal dot movement with a speed of 7˚ in the first second and 19˚ in the last second, reaching a maximum of 75˚ per second just before leaving the screen.

Wide forward flow (FW) was followed by a gradual transition to a narrow forward flow field (FtN) in experimental condition 1 (FW-to-FtN), which provided the natural illusion of moving into the changing environment. This transition was established by dark grey surfaces that expanded from the horizon in both upward and downward directions in 1.8 seconds. The subsequent vertical narrow flow field centrally subtended 6.6 percent of the screen (5.8°) during 4 seconds (Figure 1). Onset of the transition varied in time to prevent

stimulus anticipation. As a consequence, forward wide flow lasted 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 seconds. Condition 2 (FW-to-SW) served as one of two control conditions. Wide forward flow (FW) stopped, leaving a stationary wide-field (SW) for four seconds. This abrupt stop of optic flow similarly varied between five and fourteen seconds. Condition 3 (SW-to-StN) consisted of a stationary wide-field (SFw) followed by the transition to a stationary narrow field (StN), resulting in a vertical narrow stationary field. Time intervals and surfaces were similar to condition 1. Conditions 2 and 3 thus controlled for non-specific effects of interrupted wide-field flow and visual field narrowing, respectively.

The three conditions were presented in two runs of three blocks each. A block contained ten repetitions of one condition, 'FW-to-FtN', 'FW-to-SW' or 'SW-to-StN'. A block of each condition was shown once in run one and once in run two, resulting in a total of twenty repetitions for each condition. The order of the blocks within run one and two was randomised separately for all subjects, but balanced between all subjects.

Treadmill characteristics

Data recordings were performed using an instrumented treadmill (Enraf-Nonius type Entred, Rotterdam, NL) (Verkerke et al., 2005). Vertical ground reaction forces were measured with four transducers at each corner below the walking surface. The distribution of forces enabled calculation of the centre of pressure. This parameter was subsequently used for computing the centre of mass with low-pass filtering (Caron et al., 1997; Hof 2005; Lafond et al., 2004) based upon inverted pendulum model of human balance (Günter et al., 2011). Although calculating the centre of mass from the centre of pressure has been challenged in quiet standing with lower limb excursions (Günter et al., 2011; Pinter et al., 2008), it remains sufficiently precise for the condition of walking (Hof et al., 2010). The centre of mass indicated the position on the treadmill. As treadmill speed remained constant during the experiment, slowing of gait resulted in backward displacement on the treadmill. Data were recorded with a 16-bits A/D card at 200 hertz under control of a LabVIEW program (National instruments: Austin, TX, USA), which also provided synchronisation between stimulus conditions and data acquisition.

Assessment with the WAIS-III Block design

The block design subtest of the Wechsler adult intelligence scale III (WAIS-III) (Wechsler 2005), representing visuomotor transformation, was applied as general indicator of right hemisphere function. Scores were obtained in the standard manner with the exception that subjects were not restricted by time limits. For attributing the raw test scores,

however, the standard time limits were used as cut-off. Rough scores were converted to the scaled scores which provided the percentile values relative to the norm tables for corresponding age. From these percentiles a commutation to T-values was made.

As lower movement speed in Parkinson patients might be a confounding factor in the block design test, general 'block handling speed' was assessed, twice before and twice after performing the block design test. To that end, a series of four blocks was turned around as quickly as possible, in such a way that the side facing the table was turned upwards. The four blocks were subsequently arranged in a square without considering a specific pattern.

Data analysis

Statistical tests were conducted with SPSS (SPSS Inc: Chicago, IL, USA). Differences in general subject characteristics between left-sided symptom dominant Parkinson patients, right-sided symptom dominant Parkinson patients and healthy controls were tested with a one-way ANOVA. In case data were not normally distributed, the Kruskal-Wallis test was applied. Differences between Parkinson patients and healthy controls, or variables only concerning the left- and right-sided dominant Parkinson groups were tested with an independent sample t-test, or Mann-Witney U test if not normally distributed. A threshold was set at two-tailed $p < 0.05$.

Recorded treadmill data were processed by a custom Matlab program (MathWorks: Natick, MA, USA). Stimulus evoked backward displacement on the treadmill, providing an index for slowing of gait, was calculated for each condition from the mean positions in the 1.8 seconds time frame of transition and the 1.8 seconds before the onset of transition. Similar time frames around the abrupt visual change were compared in condition 2 (FW-to-SW). Statistical significance of the displacement compared to value zero was tested by a one-sample t-test (two-tailed $p < 0.05$). In order to test specificity of the effect of 'narrowing-optic flow' on backward displacement, differences between conditions were assessed with a factorial repeated-measures ANOVA. A separate ANOVA was performed for the Parkinson and healthy control group. Contrasts were made comparing 'FW-to-FtN' with the two control conditions. Given our hypothesis that 'FW-to-FtN' would induce larger backward displacement than control conditions, one-tailed *p*-values are presented when describing these contrasts. The Parkinson group was further explored with a separate ANOVA for the left and right dominant Parkinson patients to screen for a general effect of right hemisphere dysfunction on backward displacement. As left and right dominant Parkinson patients appeared to be different indeed, statistical analysis for group

differences was done between the left-sided dominant Parkinson patients, right-sided dominant Parkinson patients and healthy control group using a one way ANOVA. Post-hoc tests were performed using Bonferroni correction (two-tailed $p < 0.05$).

For both the Parkinson and healthy control group, a Pearson correlation was made between backward displacement in 'FW-to-FtN' and the T-value of the block design test. One-tailed *p*-values are presented as we specifically expected a stronger visual effect in more severely impaired right hemisphere function. As gait might be argued to represent mainly lower limb dysfunction, patients were arranged according predominantly affected upper or lower limb by calculating the differences between the means of corresponding items. Correlations of this upper-lower UPDRS ratio as well as total UPDRS score with the backward displacement were assessed using two-tailed *p*-values.

RESULTS

Subject characteristics

General subject characteristics described in Table 1 include physical and cognitive parameters, Pakinson features, treadmill velocity, block handling speed and block design T-value. All parameters were statistically tested for differences between Parkinson patients and healthy controls, and between Parkinson patients with left-sided symptom dominance, Parkinson patients with right-sided symptom dominance and healthy controls. Only the block handling test showed such difference; the total Parkinson group was significantly slower than healthy controls ($p = 0.012$, $r = 0.49$). The seemingly higher treadmill velocity in Parkinson patients with right-sided symptom dominance (without statistical significance) was mainly due to one outlier with a treadmill walking velocity of 1.22 m/s, which was high above velocity of the other subjects, both patients and healthy controls. Total UPDRS scores in the two Parkinson groups were not significantly different either (t-test, $p = 0.30$, $\beta_{observed} = 0.27$).

Stimulus-provoked backward displacement

Transition from the wide to narrow optic flow field in condition 1 (FW-to-FtN) resulted in a significant backward displacement (indicating slowed gait) compared to zero (no displacement), both in the healthy ($t(9) = 2.857$, $p = 0.019$, $r = 0.69$) and in the Parkinson group ($t(14) = 2.686$, $p = 0.018$, $r = 0.58$). For the subgroup of only left dominant patients, backward displacement was significant too ($t(6) = 3.871$, $p = 0.008$, $r = 0.85$), which was not the case for the right dominant Parkinson group ($t(7) = 0.453$, $p = 0.664$, $r = 0.17$) (Figure 2). In the equivalent transitions of two control conditions, no significant displacement

Table 1 | Subject characteristics

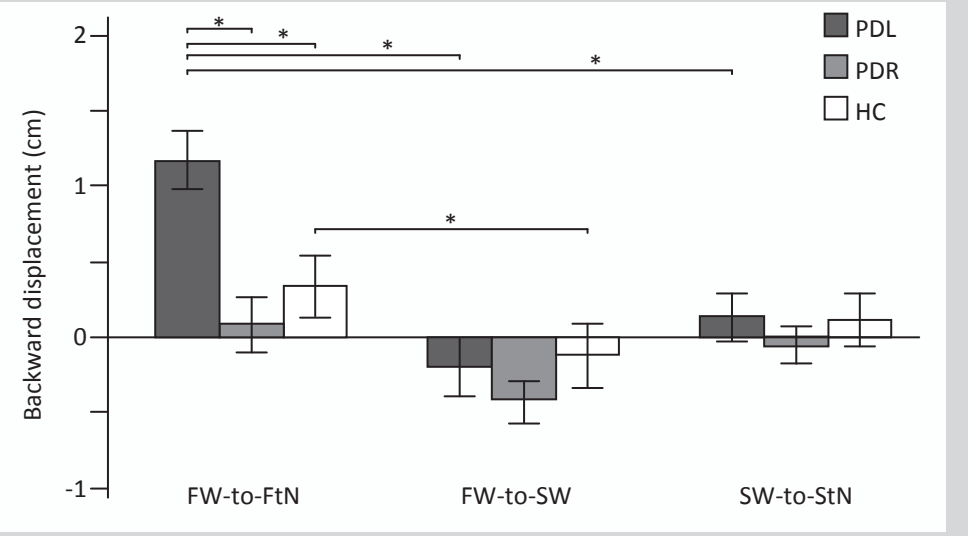
	PD			HC
	PD total	PDL	PDR	
Number (Males/ Females)	15 (8/ 7)	7 (4/ 3)	8 (4 /4)	10 (4/ 6)
Age (yr)	64.9 (7.7)	65.7 (6.7)	64.3 (8.8)	66.3 (7.8)
Weight (kg)	79.5 (15.1)	82.6 (10.5)	76.8 (18.6)	77.1 (8.7)
Height (m)	1.73 (0.08)	1.74 (0.06)	1.71 (0.10)	1.72 (0.08)
Leg length (m)	0.89 (0.05)	0.91 (0.04)	0.88 (0.06)	0.90 (0.04)
MMSE	26.8 (1.6)	26.9 (1.6)	26.8 (1.7)	27.7 (0.9)
Education level	5.0 (0.76)	5.0 (5.8)	5.0 (0.93)	5.2 (0.63)
PD duration (yr)	7.9 (3.4)	8.0 (4.0)	7.8 (2.9)	na
L-dopa equivalent dose (mg)	696 (238)	759 (157)	643 (292)	na
Modified Hoehn & Yahr	2.3 (0.5)	2.3 (0.6)	2.3 (0.4)	na
UPDRS III	24.3 (7.6)	26.6 (6.2)	22.4 (8.5)	na
UPDRS III Right items	8.3 (3.9)	5.7 (2.1)	10.6 (3.7)	na
UPDRS III Left items	8.4 (5.1)	11.9 (3.4)	5.4 (4.3)	na
Treadmill velocity (m/s)	0.56 (0.24)	0.47 (0.15)	0.64 (0.28)	0.53 (0.18)
Block handling time (s)	5.5 (1.5)	5.5 (1.1)	5.6 (1.9)	4.2 (0.9)
WAIS block design T-value	44.3 (7.5)	40.8 (5.8)	47.3 (7.8)	46.8 (6.9)

Mean values of subject characteristics (standard deviation). Education scale ranged from 1-7 (see text methods). PD = Parkinson's disease; PDL = PD with left-sided symptom dominance; PDR = PD with right-sided symptom dominance; HC = healthy controls; MMSE = mini mental state examination; L-dopa = Levodopa; UPDRS = unified Parkinson's disease rating scale; WAIS = Wechsler adult intelligence scale; na = not applicable; yr = years; kg = kilogram; m = metre; mg = milligram; s = seconds.

occurred in these groups (Figure 2). No habituation was observed within conditions, neither for healthy controls nor for the two Parkinson groups.

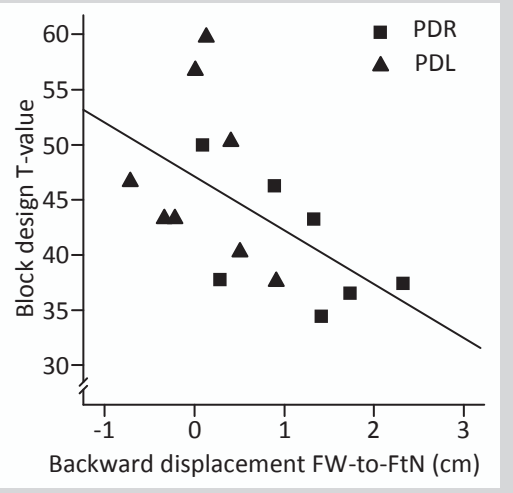
Significant differences in backward displacement were present between the left-sided symptom dominant Parkinson patients, right-sided symptom dominant Parkinson patients and healthy control groups in narrowing wide-field flow (FW-to-FtN), ($F(2,22) = 7.534$, $p = 0.003$). Left dominant patients showed significantly more backward displacement compared to right dominant patients ($p = 0.004$, $r = 0.63$) and controls ($p = 0.020$, $r = 0.56$) respectively, while no difference was found between right dominant patients and healthy

Figure 2 | Effect of narrowing forward optic flow on treadmill position



Mean backward displacement on the treadmill (with standard error) is expressed by positive values (in cm), comparing the mean position in the 1.8 seconds frame after and 1.8 seconds before transition onset in the visual display (* $p < 0.05$). Abbreviations: PDL = Parkinson's disease with left-sided symptom dominance; PDR = PD with right-sided symptom dominance; HC = Healthy controls; FW-to-FtN = transition from forward wide flow-field to forward narrow flow; FW-to-SW = forward wide flow to stationary wide-field; SW-to-Stn = stationary wide-field to stationary narrow field; cm = centimetre.

Figure 3 | Correlation between block design test and gait obstruction



Right-hemisphere involvement in backward displacement of Parkinson patients during treadmill gait is expressed by the correlation between the block design test and the effect of the transition from a wide to narrow forward optic flow field (FW-to-FtN). ■ = data point PDL; ▲ = data point PDR. The thick line shows the overall regression, R^2 = 0.305. cm = centimetre. Other abbreviations see Figure 2.

controls (p = 1.000, r = 0.27). No group differences were seen in the two control conditions 'FW-to-SW' (F(2,22) = 0.658, p = 0.528) and 'SW-to-StN' (F(2,22) = 0.401, p = 0.674).

Condition-specific effects on backward displacement

Specificity of the effect of narrowing the optic flow field on gait velocity was assessed by comparing conditions. Backward displacement due to visual transition in each of the three conditions was significantly different for the total Parkinson group (F(2,28) = 8.116, p = 0.002). 'FW-to-FtN' in Parkinson patients significantly differed from both control conditions 'FW-to-SW' (F(1,14) = 21.495, p < 0.001, r = 0.78) and 'SW-to-StN' (F(1,14) = 5.124, p = 0.020, r = 0.52). Backward displacement in Parkinson patients was thus specifically related to narrowing wide-field flow. Although a significant difference between conditions was also found in controls (F(2,18) = 4.642, p = 0.024), healthy controls' backward displacement in 'FW-to-FtN' was only significant against the control condition 'FW-to-SW' (F(1,9) = 9.805, p = 0.006, r = 0.70) (Figure 2) and not against 'SW-to-StN' (F(1,9) = 2.441, p = 0.076, r = 0.46). The latter might be a reason to be reluctant about the specificity of the narrowing flow effect in healthy controls.

In left dominant Parkinson patients, a significant difference in backward displacement was found between the three conditions (F(2,12) = 9.447, p = 0.003). 'FW-to-FtN' differed from each of the two control conditions, i.e. 'FW-to-SW' (F(1,6) = 33.743, p = 0.001, r = 0.92) and 'SW-to-StN' (F(1,6) = 7.223, p = 0.018, r = 0.74), respectively (Figure 2). No such difference between conditions was found within the right dominant Parkinson group (F(2,14) = 1.741, p = 0.211).

Correlation between tasks

Backward displacement in 'FW-to-FtN' significantly correlated with performance on the block design test in all Parkinson patients (age-corrected scores; p = 0.016, r = -0.552) (Figure 3). A lower score on the block design test was related with a larger backward displacement in narrowing wide-field optic flow. This correlation was not present within healthy controls (p = 0.145, r = 0.374). Moreover, it was not the result of a non-specific (patient) confound aside from right-hemisphere impairment because this correlation remained unaffected after correction for education level, block handling speed, total UPDRS scores and MMSE score in the Parkinson group (p = 0.013, r = -0.667). Such corrections neither changed the absent correlation in controls (p = 0.061, r = 0.640). Correlating backward displacement in narrowing wide forward flow and the block design test for only the left or right dominant patients reached no statistical significance, (p =

0.082, r = -0.548) and (p = 0.290, r = -0.232) respectively. Neither total UPDRS score nor the upper and lower UPDRS ratio correlated with displacement in Parkinson patients, (p = 0.975, r = 0.009 and p = 0.129, r = 0.410, respectively). Disease severity therefore did not explain backward displacement.

DISCUSSION

Our results demonstrated that the visual stimulus transition of narrowing a wide 'forward' optic flow field, mimicking the perception of approaching a narrow corridor, evoked clear gait obstruction in Parkinson patients, while only a small (less specific) effect was seen in healthy controls. This was inferred from the recorded backward displacement on the treadmill, which was particularly the case in Parkinson patients with left-sided symptom dominance. The latter pointed at a relation with impaired right hemisphere function, which was further supported by the correlation between gait obstruction and scores on the WAIS block design test (Ben-Yishay et al., 1971; Wilde et al., 2000) in Parkinson patients. Although this correlation was most strongly seen in Parkinson patients with left-sided symptom dominance, it only reached statistical significance in the entire Parkinson group, possibly due to small numbers in the subgroups. Reaching significance for the entire Parkinson group indicates that the negative effect of narrowing the optic flow field in Parkinson's disease indeed concerned the entire Parkinson group. These results are consistent with our a priori hypothesis and the previously described right hemisphere dominance concerning visuomotor transformations (de Jong et al., 1999; Woolley et al., 2010), also in gait (Bartels et al., 2006) and optic flow derived visuospatial perception in Parkinson's disease (Davidsdottir et al., 2008).

External stimulation by 'forward' optic flow has previously been shown to support gait in both healthy controls and Parkinson patients (Schubert et al., 2005; Azulay et al., 1999). Backward displacement might therefore also be expected when this flow pattern abruptly ends by the change into a static display of dots (control condition 'FW-to-SW'). This was, however, not the case. There are two aspects of the task that might be considered in this respect. Compared to free walking, treadmill gait requires more effort, associated with increased attention to proprioceptive feedback from the lower limbs. The basic feeling of such increased attention can e.g. be experienced when walking with eyes closed. The influence of visual cues, relative to that of proprioceptive information, may therefore be smaller in treadmill gait than during free walking based on a more automatic movement pattern. Secondly, abrupt ending of visual motion may induce a subtle motion after-effect (Anstis et al., 1998), also described as the waterfall illusion (Anstis et al., 1998). The gradual

transition from a wide to a narrow flow field may avoid this effect, while it summates the inhibiting effects of (1) losing wide-flow support and (2) the perceived approach of a virtual narrow corridor. The other control condition with a stationary wide dot field did not evoke the illusion of spatial depth. As expected, narrowing this display did not have an effect on gait.

The visual effect on gait was larger in Parkinson patients than in healthy controls, particularly in Parkinson patients with left-sided symptom dominance. This is consistent with previous studies that have shown external interference by visual stimuli on specifically Parkinson gait (Azulay et al., 1999; Davidsdottir et al., 2008). A lateralised effect of increased visual dependence associated with left-sided Parkinson symptoms has previously been shown (Davidsdottir et al., 2008), supporting that motor interference by external stimuli may be particularly mediated in the right hemisphere. Right hemisphere dominance for proprioceptive processing implicated in multilimb movements (de Jong et al., 2002) further supports its role as a logical interface for interaction between perceptual modalities and motor control. Slowed gait due to interference with the visual effect of passing a doorway in Parkinson patients has been demonstrated before (Almeida and Lebold 2010; Cowie et al., 2010). Novelty of the present design was that the stimulus pattern did not mimic all natural characteristics in virtual reality but that it focused on circumscript visual motion features (optic flow) intrinsically associated with locomotion. In this respect, gait effects by optic flow manipulations highlight the cerebral representation of elementary spatial characteristics as an important organisational principle in visuomotor control, also in gait.

Circuitry processing visuospatial information for motor control is particularly distributed over postero-superior parietal areas and the dorsolateral premotor cortex (Wise et al., 1997). If enhanced interference of movement by perceptual stimuli in Parkinson's disease is regarded as a result of striatum dysfunction, reduced output from basal ganglia-thalamic circuitry to the lateral premotor cortex may play a crucial role in the underlying pathophysiology. This model gains support from the recent findings of Young et al. (2010) who demonstrated that asymmetrically changing the speed of optic flow during walking in virtual reality caused veering away from the faster moving wall in healthy controls, while Parkinson patients responded by veering away from the symptom dominant side, i.e. towards the most affected side of the brain. As the output of basal ganglia-thalamic circuitry to medial frontal regions (i.e. supplementary motor area (SMA) and pre-SMA) may be even more affected (Jenkins et al., 1992), interference of gait by external stimuli is

complemented by a failure to keep this movement pattern going by internal drives (Brass and Haggard 2008; Lau et al., 2004; Rushworth 2008). Our recent fMRI study in healthy subjects demonstrated this dissociation in lateral and medial motor regions by differential effects of changing optic flow (van der Hoorn et al., 2010a). This may suggest that in Parkinson patients (1) the right premotor cortex is stronger activated by wide-field optic flow and (2) pre-SMA activation fails at the transition from a wide to narrow optic flow field. A study with fMRI in Parkinson patients might answer these questions, and may also provide further insight in possible compensatory mechanisms implicated in cerebral motor control in Parkinson's disease.

To conclude, right hemisphere dysfunction appeared to be involved in the interference effect of narrowing wide-field optic flow on treadmill gait in Parkinson's disease. This was inferred from the strong effect in Parkinson patients with left-sided symptom dominance and the correlation between visually evoked backward displacement and block design results in all Parkinson patients. Dissociation of medial and lateral premotor functions may provide a model to explain this visually evoked slowing of gait in Parkinson's disease.

CHAPTER 6

Parkinson changes of activation in visuomotor brain regions during perceived forward self-motion

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ABSTRACT

Radial expanding optic flow is a visual consequence of forward locomotion. Presented on screen, it generates illusionary forward self-motion, pointing at a close vision-gait interrelation. As Parkinson gait is more vulnerable to external stimuli and patients rely more on optic flow, we used functional magnetic resonance imaging to explore effects of this stimulus on motor related cerebral circuitry in healthy controls and patients with Parkinson's disease. Narrowing wide-field flow mimics approaching a narrow corridor, known to induce freezing of gait in Parkinson patients. This condition was hypothesised to activate medial premotor areas in controls stronger than in patients.

Fifteen healthy controls and 22 Parkinson patients, of which seven experienced freezing of gait, watched wide-field flow, interruptions by narrowing or deceleration and equivalent control conditions with static dots. Statistical parametric mapping revealed that wide-field flow interruption evoked activation of the (pre-)supplementary motor area in controls, which was decreased in Parkinson patients, most pronounced in patient with freezing. During wide-field flow, dorsal occipito-parietal activations were reduced in patients relative to controls, with stronger functional connectivity between right visual motion area V5, pre-supplementary motor area and cerebellum (in patients without freezing). Non-specific 'changes' in stimulus patterns activated dorsolateral fronto-parietal regions and the fusiform gyrus. This attention associated network was stronger activated in controls than in Parkinson patients.

Parkinson patients thus appeared compromised in recruiting medial frontal regions facilitating internally generated virtual locomotion when visual motion support falls away. Reduced dorsal visual and parietal activations during wide-field optic flow in Parkinson's disease were explained by impaired feedforward visual and visuomotor processing within a magnocellular (visual motion) functional chain. Compensation of impaired feedforward processing by distant fronto-cerebellar circuitry in Parkinson's disease is consistent with motor responses to visual motion stimuli being either too strong or too weak. Although attention was not an experimental condition, the 'change' related activations pointed at covert (stimulus driven) attention. Reduction of the latter might imply that visual stimuli themselves are inappropriate for inducing motor responses, while cognitive activities may easily interfere with walking. We thus discerned cerebral networks associated with processing either specific visual motion stimuli or more general covert attention, of which impairment plays a role in freezing of gait in Parkinson's disease.

INTRODUCTION

Goal-directed movement implies sensorimotor transformations that enable effective interactions with surrounding space and objects placed in it (Culham and Valyear, 2006; de Jong et al., 2001; Jeannerod et al., 1995; Wise et al., 1997). Walking is a specific motor action characterised by multilimb movements organised to achieve fluent locomotion, which heavily relies on visual representations of near and distant spatial environment. Aside from putative targets and obstacles that may guide motor control, forward locomotion itself generates a characteristic streaming motion of environmental features through the visual field. This 'optic flow' implies a radial expansion from the central point on the horizon ahead, provided that the observer does not fixate a specific object (Warren et al., 2001). Optic flow is not only a visual consequence of locomotion, it also supports gait (Warren et al., 2001) and generates the illusion of forward self-motion when presented on a static display (Duffy, 1998). This visual motion stimulus thus appears to be intimately connected with the cerebral organisation underlying locomotion. Support for the latter might be inferred from the involvement of premotor activations in recent functional magnetic resonance imaging (fMRI) studies (Azulay et al., 1999; de Melo Roiz et al., 2011; Suteerawattananon et al., 2004). In the present study, we used fMRI to explore responses of visuomotor circuitry evoked by visual motion stimuli in elder healthy subjects and patients suffering from Parkinson's disease.

In Parkinson's disease, the effect of external stimuli on movements, either in a supporting or obstructing fashion, appears to be even stronger than in healthy subjects (de Jong et al., 1999; Freeman et al., 1993; Praamstra et al., 1998; Praamstra and Plat, 2001). This also holds for walking (Morris et al., 1996; Schubert et al., 2005). In this respect, the effect of optic flow is underscored by the observation that improvement of gait by presentation of parallel traverse lines on the walking surface (Azulay et al., 1999; de Melo Roiz et al., 2011; Suteerawattananon et al., 2004) is dependent on the perceived motion flow of stripes due to walking itself (Azulay et al., 1999). This was assessed using stroboscopic light indicating that responsiveness of involved visuomotor circuitry favours dynamic more than static environmental features. The latter is consistent with the supporting effects of optic flow presented on screen during treadmill gait in Parkinson patients (Davidsdottir et al., 2008; Griffin et al., 2011; Schubert et al., 2005) and visual motion manipulation during ground walking (Davidsdottir et al., 2008; Griffin et al., 2011; Schubert et al., 2005).

The inability to maintain the cyclic pattern of walking is reflected in freezing of gait, which is a most disabling symptom that frequently occurs in Parkinson patients (Giladi et al.,

2001b). A provocative environmental factor is for instance the transition to narrow spaces like a corridor or doorway (Cowie et al., 2010; Giladi et al., 1992; Okuma, 2006). On the other hand, visual stimuli may also provide support to overcome freezing of gait (Griffin et al., 2011; Nieuwboer, 2008; Schubert et al., 2005; Snijders et al., 2010; Suteerawattananon et al., 2004). Given the indications that optic flow provides a basic cue for gait support, we recently employed a treadmill paradigm with presentation of a wide-field radial flow pattern that gradually narrowed, mimicking the illusion of entering a narrow corridor (van der Hoorn et al., 2012a). During the transition to a narrow flow field, backward displacement due to slowing of gait was seen in Parkinson patients particularly with left-sided symptom dominance.

In attempts to explain the failure to maintain performing a visuomotor action in circumstances of incongruence between visual stimuli and intended movement, disequilibrium between medial and lateral premotor functions should be considered. Visual information contributing to motor control is particularly processed along a dorsal (occipito-parietal) pathway involving lateral premotor regions, while internally driven action is particularly funnelled via the (pre-)supplementary motor area (SMA), located on the medial hemisphere surface (Brass and Haggard, 2008; Hallett, 2008; Lau et al., 2004; Picard and Strick, 2001; Praamstra and Plat, 2001; Rushworth, 2008). These medial premotor areas are dominant output targets from basal ganglia-thalamic circuitry (Alexander et al., 1986; Middleton and Strick, 2000) and indeed functionally affected in Parkinson's disease (Dirnberger et al., 2005; Jahanshahi et al., 1995; van Eimeren et al., 2009). As a consequence, adverse external stimuli or loss of supporting stimuli cannot be met by internally driven action initiation mediated by SMA activity. In Parkinson's disease, reduction of optic flow stimuli at approaching a narrow doorway may thus result in freezing of gait because a compensatory motor drive cannot be recruited due to impaired SMA function. In young healthy subjects, we indeed gained support for this concept by demonstrating that the transition from a wide to narrow optic flow field evokes (pre-)SMA activation (van der Hoorn et al., 2010a).

In line with these arguments, we aimed to test the hypothesis that observing the transition from a wide to narrow optic flow field also recruits medial frontal (pre-)SMA activation in elderly healthy subjects while it is reduced in Parkinson patients. Moreover, we wanted to assess whether wide-field optic flow might evoke a stronger effect on the dorsal premotor cortex in Parkinson patients compared to healthy control subjects. As optic flow represents a basic visual motion stimulus, intrinsically linked to locomotion, manipulation of this

specific stimulus pattern was considered to provide a tool to explore Parkinson's disease related changes in the dorsal visuomotor pathway.

METHODS

Subject inclusion

Initially, 24 Parkinson patients were tested, of which seven suffered from freezing of gait (PD_FOG). For these seven freezing patients (mean age 62.1 years, SD ± 9.5; three males), freezing was documented by the Dutch freezing of gait questionnaire (Giladi et al., 2000). Two Parkinson patients without freezing of gait (PD_nFOG) were excluded from further analysis because they exhibited too many movements during scanning, thus resulting in the final inclusion of fifteen Parkinson patients without freezing of gait (60.9 years ± 12.1; nine males). In addition, fifteen age-matched elderly healthy controls (HC) (60.5 years ± 6.2; nine males) were included (Table 1). The conclusions we finally dray in this study are based on the dataset of these two balanced groups of fifteen subjects each, which was optimally constituted for rigorous image statistical analysis. None of the subjects had neurological, ophthalmologic or lower extremity disorders, other than Parkinson's disease in de patient group. Patients were tested after twelve-hour medication withdrawal to obtain optimal insight in Parkinson associated dysfunction. The study was approved by the medical ethics committee of the university medical centre Groningen. All subjects gave written informed consent according to the declaration of Helsinki. Procedures and task instructions were explained at least one week before scanning as well as immediately before the experiment.

Behavioural assessments

Mini mental state examination (MMSE) (Folstein et al., 1975) and the Edinburgh handedness inventory (Oldfield, 1971) were conducted to underscore that participating subjects were non-demented and right-handed. Education level was classified with a Dutch education scale, ranging from 1 (uncompleted elementary school) to 7 (university degree) (Verhage, 1964). In patients, the motor part of the unified Parkinson's disease rating scale (UPDRS) (Fahn and Elton, 1987) was conducted immediately prior to the experiment. Furthermore, data concerning the modified Hoehn and Yahr scale (Goetz et al., 2004), levodopa-equivalent dose, disease duration and dominant side of Parkinson symptoms were collected. Disease duration and dominant side of Parkinson symptoms were derived from the clinical file. The side of symptom dominance, which was consistent with the UPDRS asymmetry, was similar to the side of symptom onset.

Table 1 | Subject characteristics

	PD			HC
	PD total	PD_nFOG	PD_FOG	
Number (Males/ Females)	22 (12/ 10)	15 (9/ 6)	7 (3 /4)	15 (9/ 6)
Age (yr)	61.3 (11.2)	60.9 (12.1)	62.1 (9.5)	60.5 (6.2)
MMSE (0-29)	27 (26-28)	27 (26-28)	27 (27-29)	27 (26-28)
Education level (1-7)	6 (5-6)	5 (5-6)	6 (5-6)	5 (5-6)
PD duration (yr)	7.1 (4.2)	6.1 (3.8)	9.4 (4.2)	na
L-dopa equivalent dose (mg)	690 (367)	609 (276)	871 (490)	na
Modified Hoehn & Yahr (1-5)	2.5 (2.0-2.5)	2.5 (2.0-2.5)	2.5 (2.0-2.5)	na
UPDRS III (0-56)	25.1 (8.3)	21.6 (4.9)	32.7 (9.3)	na
FOG questionnaire (0-24)	4.1 (4.8)	1.2 (1.3)	10.1 (3.7)	na
Block handling time (s)	4.8 (2.1)	5.2 (2.3)	4.1 (1.7)	3.8 (1.1)
WAIS block design T-value	47.4 (12.4)	44.6 (12.0)	53.4 (12.0)	50.2 (8.0)

Subject characteristics quantified by mean value (standard deviation) or by median (interquartile range) for non-Gaussian data. Possible range of variable are displayed behind the variable names. Range of the Education scale is explained in the methods. Abbreviations: FOG = Freezing of gait; HC = healthy controls; L-dopa = Levodopa; MMSE = mini mental state examination; PD = Parkinson's disease; PD_FOG = PD patients with FOG; PD_nFOG = PD patients without FOG; UPDRS = unified Parkinson's disease rating scale; WAIS = Wechsler adult intelligence scale; na = not applicable; mg = milligram; s = seconds; yr = years.

The block design subtest of the Wechsler adult intelligence scale (WAIS) III (Wechsler, 2005), representing visuomotor transformation, was applied as general indicator of right hemisphere function. Scores were obtained in the standard manner with the exception that subjects were not restricted by time limits, although the standard time limits were used as cut-off for the raw test scores. Rough scores were converted to scaled scores that provided the percentile values using norm tables for the subject's corresponding age. From these percentiles a commutation to T-values was made. As reduced movement speed in Parkinson patients might be a confounding factor in the block design test, general 'block handling speed' was assessed, twice before and twice after performing the block design test. To that end, a series of four blocks was turned around as quickly as possible, in such a way that the side facing the table was turned upwards. The four blocks were subsequently arranged in a square without considering a specific pattern.

Wide-field visual presentation of a radially expanding flow of dots (optic flow) generates the illusion of forward self-motion (Duffy, 1998). Immediately following the fMRI scanning protocol that included the presentation of visual motion conditions, subjects were asked to rate this illusion for the conditions wide-field flow (FW), narrow-field flow (FN), wide-field static dots (SW) and narrow-field static dots (SN) on a scale from zero to maximal (0-10).

Statistical analyses of subject characteristics and performance

Statistical tests of group characteristics, Parkinson parameters and behavioural assessment of the WAIS block design test were conducted with SPSS 19 (SPSS Inc: Chicago, IL, USA). Normality of data was tested with the Shapiro-Wilk test. Differences between groups for normal distributed data were tested with an independent t-test or one-way ANOVA for respectively two or more groups. If equal variance was violated according to Levene's test for equality of variances, we used the adjusted values of the t-test. Non-Gaussian data were tested with a Mann-Withney-U test or Kruskall Wallis for respectively two or more groups. For the latter, follow-up pairwise comparisons were conducted using a Wilcoxon test and correcting across these comparisons using the least significant difference procedure.

With regard to the ratings of illusionary perceived forward self-motion, differences between healthy controls, Parkinson patient without freezing and Parkinson patients with freezing were tested with the Kruskal-Wallis test for non-Gaussian data ($p < 0.05$, two-tailed). Within group differences were tested with the Friedman test for non-Gaussian data ($p < 0.05$, two-tailed). Follow-up pairwise comparisons were conducted using a Wilcoxon test and correcting across these comparisons using the least significant difference procedure.

Task design fMRI

During scanning, subjects watched stimulus patterns on a screen via a mirror placed approximately 11 centimetres from the face, with a mirror-screen distance of 64 centimetres. The screen dimensions were 44 by 34 centimetres, comprising 25.5° by 32.7° of the visual field. A projector with a monitor refresh rate of 30 hertz and a resolution of 1024 x 768 pixels (Barco, Belgium) projected the computer-generated stimuli on the screen. The experimental conditions were presented using the "Presentation" program (Neurobehavioral Systems, Inc. Albany, CA, USA).

All conditions consisted of white dots on a black background in the lower half of the screen, with a mean density of approximately 340 dots. A small horizontal line was used for gaze fixation and placed at the middle of the virtual horizon in all conditions. Dot patterns were presented either in static or in dynamic mode. In the latter, stimuli consisted of 25 frames per second. Each dot radially moved with increasing speed from the centre towards the bottom edge of the screen in two seconds. The mean speeds of a dot was 4.9° in the first second and 7.9° in the last second, reaching a maximum of 26° per second at disappearance from the screen. Dots proportionally enlarged along their trajectory. This dynamic stimulus pattern of wide-field flow (FW) generated the illusionary perception of forward self-motion.

Ordered in two conditions, FW was interrupted either by narrowing the flow field or by deceleration of dot movement. The gradual transition to a narrow flow field (FtN) was established by dark gray surfaces that expanded from the horizon in both upward and downward direction in 1.8 seconds, leaving a midline vertical narrow flow field (FN) of 1.3°, 4 percent. This transition evoked the natural illusion of entering a narrow corridor like a doorway. Stopping wide-field flow (FtS) was achieved by a linear reduction of dot velocity within 1.8 seconds, leaving a stationary wide-field. In order to assess specificity of interrupting particularly wide-field flow, transition (StN) from a stationary wide-field (SW) to a stationary narrow field (SN) with equal surfaces as in FtN served as control. After each of the transitions, the stimulus pattern lasted for 2.2 seconds. Until onset of the next stimulus condition, a rest condition with the central fixation line on an empty black background was shown, supporting continuous gaze fixation.

Stimuli were presented in a block design with six blocks ordered in two runs. In between the runs, a T1 anatomical scan was made. A block was constituted by six repetitions of each of the three stimulus trials [FW-FtN-FN], [FW-FtS-SW] and [SW-StN-SN], respectively. Trials were randomised for each block. In order to avoid stimulus anticipation, the duration of a stimulus pattern before transition varied between five and ten seconds (in whole numbers). The intervening rest condition with only the central fixation bar lasted 2-10 seconds. This design resulted in 36 repeats for each condition, except for FW with twice as much repeats.

MRI DATA ACQUISITION

Data acquisition was performed using a 3 Tesla Philips MR system (Philips medical systems, Best, the Netherlands) with a standard 8-channel head coil. A 3D T1-weighted anatomical

scan was acquired with repetition time 9 ms, echo time 3.6 ms, flip angle 8°, field of view 232 x 256 x 170 mm, 170 slices without slice gap, voxelsize 0.9 x 1 x 1 mm. Functional images were acquired with a gradient-echo T2* blood oxygen level dependent (BOLD) contrast technique using with a repetition time 2000 ms, echo time 28 ms, flip angle 70°, field of view 224 x 224 x 137 mm, 39 slices without slice gap, voxelsize 3.5 x 3.6 x 3.5 mm. Two runs of 485 volumes each were obtained. MRI data acquisition took about 40 minutes.

Data analysis fMRI

Preprocessing and statistical analyses of images were conducted with statistical parametric mapping (SPM) (Friston et al., 1995) version 8 (2008, wellcome department of cognitive neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). All obtained volumes were used for data analysis. Preprocessing with SPM included realignment, coregistration and spatial normalisation (template of Montreal neurological institute, MNI). Thereafter, an isotropic eight millimetres full-with at half-maximum Gaussian filter was applied to smooth the data spatially.

All conditions were modelled in a block design for the statistical analyses of regional difference in cerebral activations. Conditions were implicitly contrasted at subject level against the rest conditions with a short central horizontal line. Regressors describing head motion linear, quadratic and derivative for the three linear and three rotational movement parameters were included.

Conditions were analysed at group level by a three-way ANOVA for repeated measurements in which group, subject and condition were modelled. Group consisted of three levels; healthy controls, Parkinson patient without freezing and Parkinson patients with freezing. Condition consisted of five levels, FW, FtN, FtS, SW and StN. Subjects and groups were assumed to be independent, equal variant with regard to subject and unequal variant with regard to group. Conditions were assumed to be dependent and unequal variant due to different stimulus durations. As side of symptom onset has been suggested to influence the effect of optic flow in Parkinson patients (van der Hoorn et al., 2012a), this was included as covariate. Within and between groups comparisons were made. We compared wide-field flow (FW) with a static dot field (SW). The effects of interrupting wide-field flow (FtN and FtS) were both compared with narrowing a static dot field (StN). For FtN, this resulted in a well-balanced control condition. Although FtS and StN were not balanced for the dimensions of the visual field, StN controlled for effects due to change in the presented stimulus pattern. We additionally explored activation increases related to

the three conditions characterised by a changing stimulus pattern (FtN, FtS and StN) when contrasted to the stable patterns (FW and SW). In this way, we aimed to gain insight in functional circuitry implicated in visual attention that might be relevant for understanding differences in visuomotor transformations between healthy controls and Parkinson patients.

The contrasts listed above were used for both within and between group comparisons. Thresholds for within group comparisons were initially set at $p < 0.001$ (voxel-level uncorrected) and extent threshold (k) of eight voxels. Comparing condition related activations between groups was performed by explicit masking at $p = 0.05$ with a subsequent threshold $p < 0.001$ (uncorrected, extent threshold eight voxels). For each contrast, clusters corrected for whole brain volume at $p < 0.05$ (FWE) were considered statistically significant. Cerebral activations were rendered on either T1 brain slices or on the surface of a standard MNI brain in SPM. Brain regions were identified by checking the coordinates onto the automated anatomical labelling template in MRIcron (Rorden et al., 2007).

To explore differences between Parkinson patients with either right of left dominant symptoms (PDR; PDL), we designed a second three-way ANOVA for repeated measurements in which again group, subject and condition were modelled. In this model, group consisted of the three levels; healthy controls, Parkinson patients with right-sided symptom dominance and Parkinson patients with left-sided symptom dominance. The presence or absence of freezing of gait was included as covariate. Other settings equalled our first model. Within group comparisons and between groups comparisons were set at the same thresholds.

Functional connectivity of right V5

As the motion sensitive area V5 had the expected critical role in the current study (de Jong et al., 1994; Morrone et al., 2000), and the right hemisphere has been described to play a dominant role in both normal visuomotor function (Halligan et al., 2003; Rossetti et al., 2003) and affected gait in Parkinson's disease (Davidsdottir et al., 2008; Schubert et al., 2005), we employed a functional connectivity analysis of right V5. Functional connectivity was assessed by using the psychophysiological interaction (PPI) method (Friston et al., 1997), which expresses the influence of neural activity of one over other cerebral regions. A nine millimetre sphere was selected around right V5 (x 48, y -70, z 0).

An individual PPI analysis was performed for each subject. PPI was computed as the cross-product of the extracted eigenvariate time series of right V5 and the convolved 'psychological' task effect (FW compared to SW). This PPI was entered as regressor in the first level PPI analysis along with two other regressors. The original eigenvariate of right V5 was included next to the convolved psychological variable, which results in a PPI analysis excluding the main effect of task but looks at the synchrony of neural activity between right V5 and other cerebral regions depending on the psychological variable (FW versus SW).

Brain regions with a positive regression slope with right V5 dependent upon the 'psychological' variable were indentified for each subject. These contrasts were entered in a second-level ANOVA with three groups (healthy controls, Parkinson patients without freezing of gait and Parkinson patients with freezing of gait), which were assumed to be independent but unequal variant. The functional connectivity of right V5 depending on the wide-field flow versus the stationary wide-field within a group were tested at $p < 0.05$ voxel level corrected for whole brain volume (FWE). Between group differences were shown by exclusive masking using an initial threshold of $p < 0.05$ (uncorrected) with a subsequent conservative threshold of $p < 0.05$ voxel level corrected for whole brain volume (FWE). A cluster extend threshold of eight voxels was used for within and between group analysis.

Correlation between medial premotor activation and WAIS block design test

The behaviourally assessed WAIS block design task for visuomotor abilities was expected to correlate with the ability to activate medial premotor areas during narrowing specifically the optic flow field (FtN > StN). To that end, we used the human motor area template (Mayka et al., 2006) to create an independent region of interest constituted by the supplementary motor area (SMA) and pre-SMA, bilaterally. Extracting mean betas for this region was done using the MarsBar toolbox in SPM (http://marsbar.sourceforege.net). Mean beta's during StN were subtracted from those obtained in FtN.

As we specifically expected that poorer visuomotor abilities measured by the WAIS block-design task resulted in reduced medial premotor activation, correlations with one sided *p*-values were used. A Pearson's correlation was used for an uncontrolled correlation of the WAIS block design T-values (age corrected) with the medial premotor activations, while a partial correlation was used for calculating the correlation further controlled for block handling speed, MMSE, education level, UPDRS and Parkinson's disease onset side.

RESULTS

Group characteristics

Basic characteristics of healthy controls, Parkinson patients without freezing of gait and Parkinson patients with freezing of gait did not significantly differ with regard to age ($F(2,36) = 0.073$, $p = 0.930$), education level ($H(2) = 1.670$, $p = 0.434$) and MMSE ($H(2) = 2.828$, $p = 0.367$ (Table 1). Neither were such differences found for block handling speed ($F(2,36) = 2.492$, $p = 0.098$) or performance on the WAIS block design task ($F(2,36) = 1.954$, $p = 0.098$). Significant differences were not seen either when the group of healthy controls was compared with a single composite group op all Parkinson patients.

Compared to patients without freezing, patients with freezing had higher scores on the motor part of the UPDRS ($t(20) = -3.696$, $p = 0.001$) and rated higher on the freezing of gait scale ($t(20) = -6.202$, $p = 0.001$). The latter included two questions concerning the impact of deteriorated gait, unrelated to the presence of possible freezing of gait. No significant differences were seen between the two Parkinson group for the modified Hoehn and Yahr stage ($U = 41.00$, $p = 0.367$), Parkinson's disease duration ($t(20) = -1.864$, $p = 0.77$) and levodopa equivalent dose ($t(20) = -1.619$, $p = 0.121$) (Table 1).

Perceived illusion of forward self-motion

Wide-field flow evoked a clear perception of forward self-motion in all three groups. This was underscored by the significant within group differences for the wide- and narrow-field presentations in flow and static mode (FW, FN, SW and SN; $p < 0.001$). In FW, this illusion was stronger than in SW and SN for all groups. When compared to FN, the illusion in FW was rated significantly stronger ($p < 0.05$) by controls and patients without freezing, while patients with freezing did not perceive significant differences in forward self-motion between FW and FN. Comparing ratings between groups showed that the perception of forward self-motion during FW was equally strong for all groups; healthy controls median 3 (interquartile range 1-7), Parkinson patients without freezing 4.5 (0-7), Parkinson patients with freezing 5.5 (2-8); $H(2) = 0.675$, $p = 0.713$. In FN, this sensation was virtually absent for all groups: healthy controls 0 (0-1.5), Parkinson patients without freezing 0 (0-0), Parkinson patients with freezing 0 (0-5); $H(2) = 2.263$, $p = 0.270$. It was fully absent in SW and SN for all three groups (each 0; 0-0).

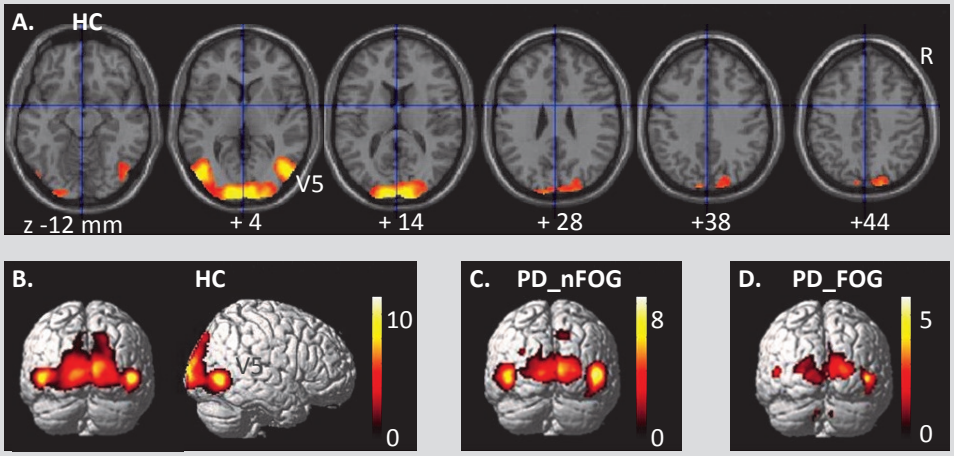
... indicate locations respectively right, anterior and superior to the middle of the anterior commissure. Abbreviations: post. = posterior; sc = same cluster; sup. = superior.

Table 2 | Cerebral activation in wide-field flow contrasted to a wide stationary field

Brain region	Left			Right		
	x, y, z	T-value	Ext.	x, y, z	T-value	Ext.
HC						
Cuneus V1/V2	-8, -100, 12	9.33	2200	0, -100, 0	10.05	sc
				24, -96, 2	6.61	sc
V5 visual complex	-48, -76, 0	9.49	545	52, -72, -2	5.74	sc
	-42, -90, 0	5.00	sc			
Post. sup. parietal cortex				18, -86, 46	5.55	sc
PD_nFOG						
Cuneus V1/ V2	-10, -96, 4	46.53	768	8, -100, 10	7.62	sc
				22, -92, 8	5.79	sc
V5 visual complex	-48, -78, 2	8.18	405	50, -72, 2	8.39	616
PD_FOG						
Dorsal occipital cortex				14, -102, 14	5.75	65
V5 visual complex				46, -72, 0	5.31	24
HC excl PD_nFOG						
Dorsal occipital cortex	-12, -92, 18	6.60	10			
	-20, -98, -6	5.64	22			
HC excl PD_FOG						
Cuneus V1/V2	-12, -92, 4	7.51	171	2, -90, 6	5.87	sc
Dorsal occipital cortex	-4, -94, 22	6.34	sc			
V5 visual complex	-48, -68, -2	7.41	176	50, -62, -2	6.62	46
Post. sup. parietal cortex				18, -86, 44	5.53	12
PD_nFOG excl PD_FOG						
Cuneus V1/V2	-10, -92, 4	5.48	10			
V5 visual complex	-48, -80, -4	8.07	105	54, -76, 8	6.73	49

Regional activations related to wide-field flow (FW) contrasted to a wide stationary field (SW). Initial threshold was $p < 0.001$ (uncorrected, extent threshold k = 8 voxels). The resulting single occipito-parietal cluster was constituted by distinct confluent regional activations. The latter were separated by thresholding at voxel level $p < 0.05$, FWE-corrected. As none of the initially identified local maxima disappeared, the segregated clusters ($p < 0.05$ cluster-level corrected for whole brain) are reported here. The reported coordinates represent maxima that are located more than twelve millimetre apart from the adjoining focus in each cluster. Positive x, y, z coordinates (in millimetre) ... ←

Figure 1 | Cerebral activations evoked by wide-field optic flow



Cerebral activations related to wide-field radial optic flow (FW) contrasted to a wide stationary dot field (SW) in healthy controls (HC) are projected on transversal sections (A) and rendered onto brain surfaces (B). Activations in Parkinson patients without freezing of gait (PD_nFOG) and with freezing of gait (PD_FOG) are displayed in C and D, respectively. Thresholds are set at p = 0.001 voxel-level uncorrected with an extended voxel threshold of eight voxels. T-values are displayed in the colour bars. R = right side of the brain, V5 = visual motion complex V5.

6

Cerebral activations related to wide-field flow

Cerebral activations related to FW (contrasted to SW), which evoked the illusionary perception of forward self-motion, were bilaterally distributed over striate and extrastriate visual cortical regions, including the putative visual motion area V5 (Figure 1, Table 2). Particularly in controls, this pattern of activation extended dorsally into the posterior superior parietal cortex, with a significant cluster in the right hemisphere (Table 2). Left-sided V1/V2 activation was significantly increased in controls relative to Parkinson patients without freezing, as revealed by exclusive masking of the controls pattern by the patients without freezing activations (p < 0.05, cluster-level corrected for brain volume; Table 2). Relative to freezers, activations in controls was increased in V1/V2 and V5, bilaterally, and in the right posterior parietal cortex. These activation differences (particularly in V5) similarly emerged from the pattern of activation increases in patients without freezing when exclusively masked by the patients with freezing pattern. The FW related right posterior parietal activation in controls, which was not seen in the two patient groups, was indeed significantly increased relative to only patients with freezing of gait (exclusive masking; p < 0.05 cluster-level corrected). Relative to non-freezers, such increase in

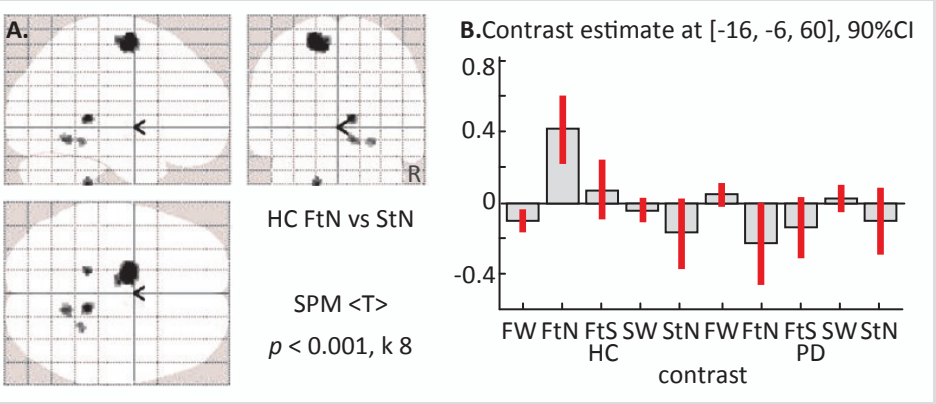
Table 3 | Cerebral activation in changing versus stable visual stimulus patterns

Brain region	Left			Right		
(BA)	x, y, z	T-value	Ext.	x, y, z	T-value	Ext.
HC						
Fusiform gyrus	-28, -66, -10	12.67	22809	30, -52, -16	11.21	sc
				24, -70, -10	10.33	sc
V5 visual complex	-46, -78, -10	9.08	sc	48, -62, -12	8.85	sc
Lingual gyrus (V1/V2)				6, -74, -2	9.64	sc
Middle temporal gyrus				34, -32, 2	5.21	sc
				48, -32, 8	6.43	sc
Dorsolat. occipital cortex	-32, -86, 16	11.35	sc	28, -82, 20	11.50	sc
Post. sup. parietal cortex	-24, -78, 40	6.44	sc	26, -62, 60	7.41	sc
	-26, -52, 52	8.60	sc			
Ant. int. parietal cortex	-34, -46, 46	4.90	sc			
Dorsolat. prefrontal	-38, 4, 28	4.30	333	48, 4, 28	5.89	1097
cortex	-50, -2, 42	3.52	sc	56, 18, 18	4.33	sc
Dorsal premotor cortex				24, 2, 50	4.21	238
				44, -2, 54	3.55	sc
PD_nFOG						
Fusiform gyrus	-22, -74, -10	6.57	14135	28, -62, -10	8.05	sc
V5 visual complex	-48, -78, -10	6.75	sc	44, -72, -12	7.26	sc
Lingual gyrus (V1/V2)	-4, -76, 2	6.97	sc			
Dorsolat. occipital cortex	-50, -80, 18	5.81	sc	40, -84, 10	7.95	sc
	-28, -88, 18	7.53	sc	26, -80, 28	7.48	sc
	-28, -74, 28	4.85	sc			
Post. sup. parietal cortex	-18, -74, 46	5.99	sc	24, -68, 34	6.67	sc
	-36, -54, 48	5.49	sc	30, -54, 50	5.73	sc
PD_FOG						
Lateral fusiform gyrus	-44, -64, -16	3.54	884	40, -80, -14	4.48	1410
				44, -68, -14	5.09	sc
V5 visual complex	-48, -80, -10	4.36	sc			
Lingual gyrus (V1/V2)				6, -76, -2	4.70	253
Dorsolat. occipital cortex	-24, -84, 14	5.34	sc	36, -88, 8	5.12	sc

See next page for legend →

Regional activations related to change [FtN, FtS, StN] contrasted to stable [FW, SW], initial voxel-height threshold $p < 0.001$ (uncorrected, extent threshold k = 8 voxels). Coordinates refer to the voxels of maximum activation within clusters of significant activation ($p < 0.05$, FWE whole brain cluster-level corrected). The presented local maxima are located more than twelve millimetre apart from the adjoining focus in a cluster. Positive x, y, z coordinates (in millimetre) indicate locations respectively right, anterior and superior to the middle of the anterior commissure. Abbreviations: ant. = anterior; dorsolat. = dorsolateral; inf. = inferior. Other abbreviations as in table 2.

Figure 2 | Narrowing wide-field optic flow



Cerebral activation related to the transition from wide to narrow optic flow (FtN) contrasted to narrowing of a stationary dot field (StN) in healthy controls (HC) is displayed in a glass brain view (A). Responses of the single significant cluster (max x -16, y -6, z 60) are shown for HC and the entire Parkinson's disease (PD) group (B). Threshold is set at $p = 0.001$ uncorrected with an extended voxel threshold (k) of eight voxels. CI = confidence interval; FW = wide optic flow; FtS = stopping of wide optic flow; SW = wide stationary field. R = right side of the brain.

controls only reached a subthreshold level of $p < 0.001$ (voxel-level uncorrected).

Cerebral activations related to wide-field flow interruption

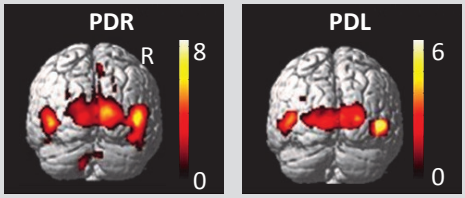
The crucial condition of gradually narrowing the wide-field flow (FtN) was expected to evoke stronger medial frontal activation in healthy controls than in Parkinson patients. Contrasting FtN to StN indeed resulted in a single cluster of significant activation in the SMA of controls, which extended in the pre-SMA (max. x -16, y -6, z 60; T-value = 4.95, $p < 0.05$, cluster-level corrected) (Figure 2). Such activation did not occur in either

Parkinson group. Exclusive masking of activation in controls by subtreshold results of patients without freezing further demonstrated this increased (pre-)SMA activation in controls (p < 0.05, cluster-corrected), which was similarly seen by exclusive masking of controls with freezers. Applying such masking, no significant activation differences were seen between patients with and without freezing of gait in FtN contrasted to StN. A trend of more (pre-)SMA impairment in freezers than in non-freezers might be suggested by the lower contrast estimate for patients with freezing (-0.37) than for patients without freezing (-0.10) during FtN, while during StN these values were -0.12 and -0.09, respectively.

The second condition of interrupting FW, i.e. by gradual deceleration of the radial dot flow (FtS), yielded a similar mediofrontal effect as FtN. Contrasting FtS to StN showed a cluster of increased activation (exclusive masking) in the (pre-)SMA of controls (max. x -2, y -2, z 66; T = 5.23), relative to patients with as well as without freezing of gait (each p < 0.05, cluster corrected). Similarly, exclusive masking revealed increased (pre-)SMA activation in patients without relative to with freezing of gait (p < 0.05, cluster corrected). For the assessment of FtS, the same control condition StN was used as in the comparison with FtN. Although FtS and StN were not balanced for the spatial dimensions of the visual field, a control condition for non-specific change in the visual field appeared to be important (see results related to changing visual patterns). In addition to the FtS related medial frontal activation, contrasting FtS to StN also resulted in bilateral activation in V1/V2 (only significant for the left hemisphere at p < 0.05 whole-brain cluster corrected; max x 14, y -102, z 2), without significant differences between groups.

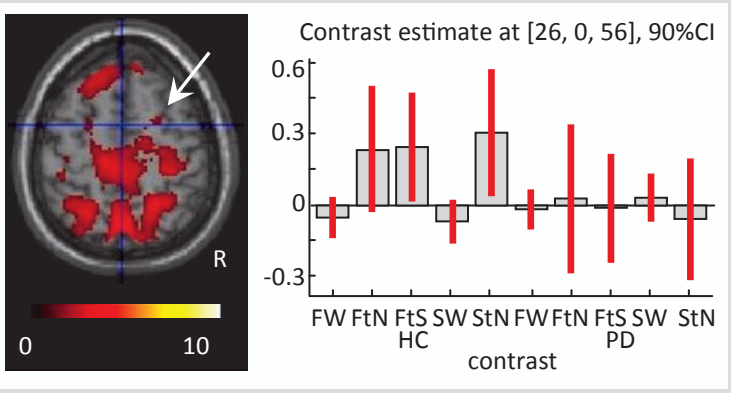
The reduced (pre-)SMA activation in Parkinson patients at interrupting FW was hypothesised to mimic the impaired ability to internally recruit motor circuitry when external support falls away. We therefore assessed whether the magnitude of mediofrontal activation would be associated with a behavioural parameter concerning visuomotor control in Parkinson's disease. To that end, a bilateral SMA and pre-SMA template was applied to demarcate a volume of interest. Increased activation in this volume correlated with higher (age-corrected) scores on the WAIS block-design task in Parkinson patients without freezing (r = 0.54, p = 0.010). Although a similar trend was seen for patients with freezing of gait as well as healthy controls, correlations did not reach statistical significance (freezers r = 0.29, p = 0.264; controls r = 0.36, p = 0.094). The correlation in non-freezers became even stronger when further controlled for block handling speed, MMSE, education level, UPDRS and onset side (r = 0.80, p = 0.003).

Figure 3 | Wide-field optic flow and lateralisation of symptoms



Cerebral activations related to wide-field flow (FW) contrasted to a wide stationary field (SW) are rendered onto a brain surface (posterior view) for thirteen right symptom dominant Parkinson patients (PDR) and nine left symptom dominant Parkinson patients (PDL). Thresholds are set at p = 0.001 uncorrected with an extended voxel threshold of eight voxels. T-values are displayed in the colour bars. R = right side of the brain.

Figure 4 | Right dorsal premotor responses in wide-field optic flow



Contrasting wide-field optic flow (FW) to a wide stationary field (SW) revealed a hardly detectable FW related effect in the right dorsal premotor cortex of healthy controls (HC) by a threshold of p = 0.5 (extended voxel threshold eight voxels). However, the response pattern at this location (max. x 26, y 0, z 56) was particularly characterised by increased activation related to the 'change' conditions in HC, compared to the stable conditions FW and SW. Moreover, these increases were not seen in the Parkinson patients (PD). Abbreviations are as in figure 2.

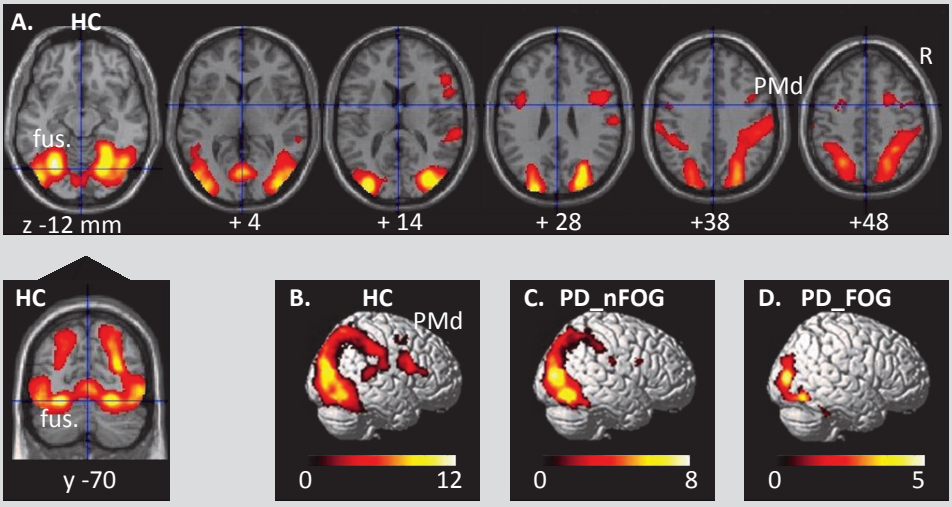
As the involvement of a 'mesencephalic locomotor region' has recently been described to be either hyperactive (Snijders et al., 2011) or impaired in freezing of gait (Shine et al., 2013), we looked for subthreshold effects at the described location (p < 0.05, voxel-level uncorrected). FtN contrasted to StN showed a small cluster (nine voxels) in controls (x 6, y 28, z -20; T-value = 2.07), which was not seen in either Parkinson patients with or without freezing of gait. As we do not regard this observation as a significant result of our study, it will not be further elaborated in the discussion of the paper.

Effect of side of Parkinson symptoms on wide-field flow activation

Given a general dominance of the right hemisphere in visuospatial processing, we explored possible differences between hemispheres related to the side of symptom dominance in Parkinson patients. To that end, Parkinson patients with right and left dominant symptoms (respectively *N* = 13 of which 5 freezers and *N* = 9 of which 2 freezers) were compared with a separate ANOVA controlling for freezing of gait binary. The only difference in brain activation was seen in FW contrasted to SW (Figure 3, see further). No significant differences were seen between patients with right- and left-sided symptom dominance during the interruption of FW, neither in FtN nor in FtS. At subthreshold level ($p < 0.05$, cluster-level, uncorrected) activation differences were not seen either.

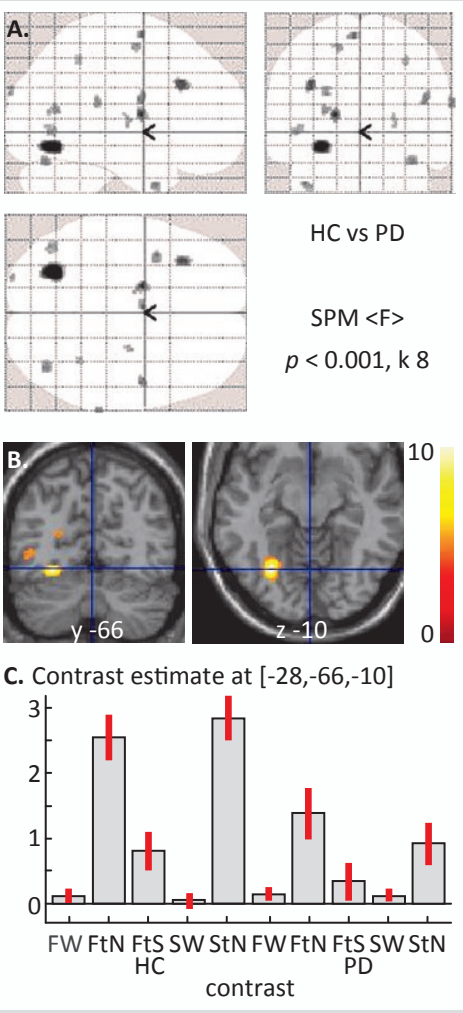
Relative to Parkinson patients with right-sided symptom dominance, the left-sided dominant Parkinson patients showed decreased activation during FW contrasted to SW

Figure 5 | Non-specific 'change' in the stimulus pattern



Cerebral activations related to the conditions with non-specific 'change' in the presented visual stimuli (FtN, FtS, StN) contrasted to the stable stimulus patterns (FW, SW) in healthy subjects (HC) are projected on transversal sections and a coronal one (A) and rendered onto brain surfaces (right lateral view; B). Activations in Parkinson patients without freezing of gait (PD_nFOG) and with freezing of gait (PD_FOG) are displayed in C and D, respectively. Thresholds are set at $p = 0.001$ uncorrected with an extended voxel threshold of eight voxels. T-values are displayed in the colour bars. Fus. = fusiform gyrus, PMd = dorsal premotor cortex. Other abbreviations are as in figure 2.

Figure 6 | Main difference between HC and Parkinson patients



The F contrast of the differences between healthy controls (HC) and the entire Parkinson group (PD) highlights the left fusiform gyrus, shown in a glass brain view (A) and by sections in both transversal and coronal sections (B). Responses of the left fusiform gyrus in the experimental conditions are shown for HC and PD patients (C). Red bars show 90% confidence interval. Other conventions and abbreviations are as in figure 2.

(p < 0.05, cluster corrected; right symptom dominant patients' increases exclusively masked by left symptom dominant patients) in the dorsal extension of right V5 (x 40, y -66, z 8) and a right lateral occipital area at a more ventral location (x 46, y -70, z -16) (Figure 3). A right posterior parietal activation decrease (x 8, y -78, z 54; T-value = 3.96) remained at subthreshold significance level, which was similarly the case for left V5 activation. No activation decreases were seen in right-sided relative to left-sided symptom dominant Parkinson patients (using exclusive masking). Right symptom dominant patients showed a similar distribution of activations as healthy controls, while left symptom dominant patients showed similar changes relative to healthy controls as to right symptom dominant patients.

Cerebral activation related to changing stable visual patterns

Two observations from the preceding results were a reason for additional analysis. First, in contrast to our expectation (van der Hoorn et al., 2010a), we did not find (right) dorsal premotor activation related to FW. Second, V5 activation was not restricted to FW, but appeared to be strong in both FtN and StN as well. As V5 activation was similarly strong in

these two conditions, the specificity of particularly interrupting FW by FtN was adequately balanced by the introduction of StN, controlling for V5 activation due to the apparent motion effect of gradually narrowing the dot field. It did, however, point at a hidden variable. Plotting the effect size at the dorsal premotor site of hardly detectable change in FW contrasted to SW (x 26, y 0, z 56) revealed a characteristic increase of activations related to exclusively FtN, FtS and StN in healthy controls only (Figure 4). As this profile of responses distinguished the conditions with change in the visual stimulus pattern, we subsequently contrasted these three conditions of change to the stable patterns FW and SW. This resulted in a robust pattern of significant activation increases in controls comprising fusiform gyri, putative V5, the anterior portion of the inferior wall of the calcarine sulcus (peripheral field representation of V1), dorsolateral extrastriate visual cortex, medio-posterior (superior) and antero-lateral (inferior) parietal cortex, bilaterally, right dorsal premotor cortex and the dorsolateral prefrontal cortex of both hemispheres (Table 3, Figure 5A-B).

In Parkinson patients without freezing, these activations related to visual change were less robust, while dorsal premotor activation was absent (Table 3, Figure 5C). Patients with freezing showed even less activation, without medial fusiform and parietal activations (Table 3). The importance of left fusiform function in our paradigm was further underscored by the fact that this focus of activation (x -28, y -66, z -10) was the main denominator that discriminated the healthy control group and Parkinson groups (F-test healthy controls contrasted to Parkinson patients; F = 10.02, p = 0.002, FWE-corrected at voxel level) (Figure 6). We did not find a correlation of this fusiform gyrus activation with either UPDRS or Hoehn and Yahr scores in the Parkinson patients. Neither was a correlation seen with the WAIS block design task or illusion of FW related forward self-motion in either healthy controls or the Parkinson groups.

Distant effects of right V5

As FW contrasted to SW revealed a general reduction of visual cortex activation in Parkinson's disease and no associated premotor activation, we tested whether particularly the right visual motion area V5 (x 48, y -70, z 0) might nevertheless have a stronger influence on premotor regions in Parkinson's disease than in controls. Functional connectivity using PPI revealed significant effects in V1/V2 of controls (Figure 7) while in Parkinson patient without freezing of gait additional effects were particularly seen in the medial prefrontal cortex, pre-SMA (x -4, y 26, z 50, dorsally extending onto plane z 58), and the anterior lobes of the cerebellum (p < 0.05, FWE cluster corrected) (Figure 7). No

significant distant effects were seen from right V5 in patients without freezing of gait. Exclusive masking of the effects in Parkinson patients with freezing by the effects in controls showed that the V5 effects on the medial prefrontal cortex (left dominant) and right cerebellum were stronger in this patient group than in healthy controls (Figure 7).

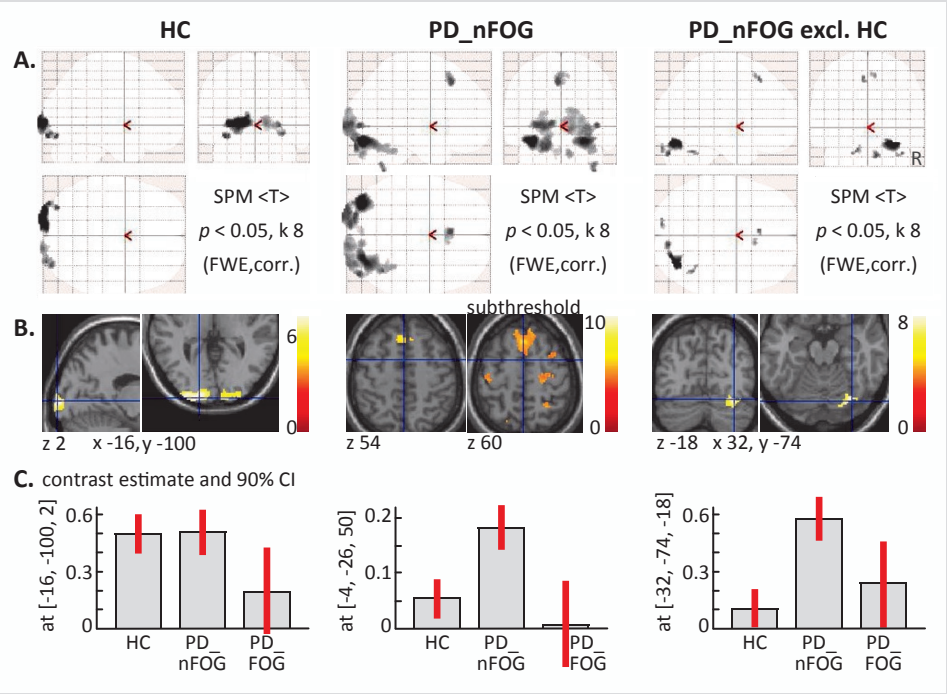
DISCUSSION

Our results demonstrated that wide-field radial optic flow, which generated the illusionary perception of forward self-motion in both healthy controls and Parkinson patients, was related with reduced visual cortex activation in Parkinson patients. On the other hand, functional connectivity of right visual motion area V5 with medial prefrontal cortex (pre-SMA) and cerebellum was stronger in Parkinson patients without freezing of gait than in healthy controls. The latter might point at functional circuitry implicated in enhanced stimulus effects on movement (including locomotion) known to occur in Parkinson's disease. The conditions with gradual transition from wide-field flow to either narrow flow or a wide static field, which was considered to mimic a circumstance requiring a stronger internal effort to maintain (virtual) locomotion when visual support falls away, evoked (pre-)SMA activation only in controls and not in the two Parkinson patient groups. The number of included patients in the patients with freezing group (N = 7) was small, which is a reason to refrain from drawing firm conclusions concerning this Parkinson subgroup. Keeping this restriction in mind, the obtained patterns of activation generally suggest that Parkinson patients with freezing represented advanced Parkinson's disease relative to patients without freezing (N = 15), a finding that also emerged from the differences between UPDRS scores. Finally, we identified a distribution of activations related to non-specific 'change' in the presented patterns of stimuli. In controls, these activations included the dorsal occipital-parietal cortex lateral to the regions of wide flow induced activation, together with fusiform gyrus and right premotor regions. These activations were less robust in Parkinson patients. Although the experiment was not primarily designed to test these effects, the obtained results pointed at Parkinson related changes in visuospatial attention.

Reduced visual cortex activation and enhanced distant interactions in Parkinson's disease

The stimulus pattern of wide-field optic flow generated the illusionary perception of forward self-motion in all three groups. In healthy controls, the flow related distribution of activations comprised the visual motion area V5, ventrally extending in particularly the right hemisphere, posterior V1/V2 and dorsal extrastriate visual cortex extending more

Figure 7 | Functional connectivity of right V5



Cerebral regions that were identified by their functional connectivity with the right visual motion area V5 (using psychophysiological interaction, PPI) during wide-field radial optic flow (FW) contrasted to a wide stationary field (SW). These regions are displayed in glass brains (A) and and projected on sections (B) for healthy controls (HC), Parkinson patients without freezing of gait (PD_nFOG) and for the latter when exclusively masked with HC at p = 0.05. Thresholds are set at p = 0.05 FWE corrected for whole brain volume with an extended voxel threshold of eight voxels. In addition, subthreshold effects in a transversal section at z = 60 are shown for PD_nFOG, threshold T = 4.5 (extended cluster threshold of eight voxels). T-values are displayed in the colour bars. The corresponding graphs (C) show the contrast estimates and 90 percent confidence intervals (CI) for the maxima in the left fusiform gyrus, the pre-SMA and right cerebellum respectively.

strongly in the right parietal cortex. This dorsal pathway activation, which is consistent with circuitry implicated in dynamic visuospatial processing (Andersen et al., 1997; Goodale and Westwood, 2004), was less robust in Parkinson's disease. Given the observations that external stimuli have a larger impact on motor control in Parkinson patients than in healthy controls, the observed reduction of visual cortex activation and the absence of dorsal premotor involvement in FW (contrasted to SW) in Parkinson might, at first sight, suggest

the opposite effect, i.e. a reduced information flow onto motor related circuitry. On the other hand, reduced visual activation may reflect a less elaborate level of information processing within the visual cortex. Such visual information is processed in a highly segregated fashion, with parvo (colour) and magnocellular (motion) streams that can already be distinguished at the retinal level and remain to a certain extent separated in the primary visual cortex V1 (van Essen et al., 1992). In Parkinson's disease, these basic visual processing streams may be affected independently (Silva et al., 2005). Integration in the visual cortex complements such segregation (Sincich and Horton, 2005). Feedback processing is one of the manifestations of such integration, which is reflected e.g. in the variance whether visual motion input in V1 precedes or follows input in V5 (ffytche et al., 1995; Lamme and Roelfsema, 2000; Laycock et al., 2007). Reduced visual activations and enhanced functional connectivity of right V5 with medial frontal-cerebellar circuitry in Parkinson's disease might thus reflect an impaired level of integration in visual cortical areas, with the consequence of dominating distant interactions along the segregated processing stream of visual motion funnelled through V5.

Enhanced functional connectivity between early visual processing sites and distant action related regions, with a reduced contribution of intermediate occipito-parietal regions, might functionally result in less fine-tuned responses to visual stimuli, i.e. inducing responses that are either too strong or too weak. Such unbalanced responses due to 'by-passing' optimal parietal processing in sensorimotor planning would be consistent with the role of the parietal cortex providing 'sensory' information for feedforward processing implicated in motor planning (Desmurget et al., 1999; Desmurget and Grafton, 2000; Imamizu and Kawato, 2008; Wolpert et al., 1995). This means that in normal conditions, the predicted sensory consequences of planned movements are used to optimise preparation of such movements. Such parietal feedforward function is supported by interactions with the cerebellum (Blakemore et al., 1998; Blakemore and Sirigu, 2003; O'Reilly et al., 2008; Shadmehr and Krakauer, 2008; Sultan et al., 2012). In this respect, the association of medial prefrontal (pre-SMA) and cerebellar functions suggested from the increased functional connectivity of right V5 might point at an alternative, compensatory strategy for impaired sensation-based feedforward processing in Parkinson's disease. Considering such (pre-)SMA contribution to compensation, its involvement in error detection and serial ordering (Mushiake et al., 1991; Nakajima et al., 2009; Rushworth et al., 2004) is an argument to propose that this compensation is based on a mechanism of error correction facilitated by a wider reference frame for assessing predictions. Wider referencing would imply that sensory predictions are not restricted to immediate

movement fragments but are made in the context of a larger time scale with movement patterns constituting series of events (Bengtsson et al., 2009; Beudel et al., 2009; Schubotz, 2007; Stadler et al., 2011).

With regard to the perceptual domain, an association between impaired visual processing and enhanced effects in Parkinson visual perception has been demonstrated to play a role in the generation of visual hallucinations in this disease (Boecker et al., 2007; Meppelink et al., 2009; Ramírez-Ruiz et al., 2007). This suggest a similar mechanism of dysfunction in dorsal and ventral visual processing streams, characterised by a reduced level of integration in visual cortex processing leading to excessive distant effects. While over-responding based on impaired prediction of the sensory consequences of motor actions may occur along the dorsal visual processing stream, impairment of fine-tuned prediction based on fragmented features in new perceived scenes leads to enhanced 'filling in' with hallucinatory perceptions evoked along a ventral pathway (Burke, 2002; Santhouse et al., 2000). Such equivalence is consistent with the observation of Davidsdottir et al. (2005) that freezing was the only motor symptom in Parkinson patients that was associated with visual hallucinations and impaired contrast sensitivity at lower spatial frequencies.

Interrupting wide optic flow

Narrowing the wide flow field evoked a single significant cluster of (pre-)SMA activation in healthy controls which was absent in the two Parkinson groups (FtN contrasted to StN). This confirmed the main hypothesis of our study. A lower contrast estimate in freezers than in non-freezers might hint at more (pre-)SMA impairment in Parkinson patients with freezing of gait. Interrupting wide-field flow by gradual deceleration (FtS contrasted to StN) did also reveal medial frontal activation comprising SMA and pre-SMA in healthy controls, while at this focus of maximum activation, a strong reduction was seen in patients with relative to patients without freezing of gait. It should be recognised that the activation increase resulting from FtN contrasted to StN was most specifically associated with the interruption of perceived forward self-motion because possible effects of e.g. attention to change, due to narrowing itself, was balanced by narrowing a static dot field (StN). The other condition of interruption (deceleration, FtS) was controlled for non-specific change by similarly using StN, although FtS and StN were not optimally balanced for visual field dimensions. In both FtN and FtS, recruitment of the (pre-)SMA is considered to reflect its contribution to an internal drive to continue virtual locomotion when external support from visual flow falls away. This is consistent with the crucial involvement of the SMA and pre-SMA in the internal generation of movements, relative to externally driven action

(Deiber et al., 1999; Lau et al., 2004). The fact that our Parkinson patients were compromised in such SMA recruitment fits the previously described functional impairment of this important outflow target of the basal ganglia (Alexander et al., 1986; Haslinger et al., 2001; Jahanshahi et al., 1995; Jenkins et al., 1992; Schell and Strick, 1984).

As phrased before, the small number of patients with freezing of gait does not allow final conclusions concerning circuitry specifically impaired in relation with this symptom. In general, however, the patterns of activation obtained in the tested conditions suggest that in Parkinson patients with freezing of gait, underlying disease is in a more advanced stage. While patients with freezing of gait patients rated significantly higher on the freezing of gait scale, this was also the case for the motor part of the UPDRS. Reduced (pre-)SMA activation at the loss of (virtual) gait-support thus appears to be a more general than a specific indicator related to freezing of gait, pointing at an important role in visuospatial coordination which fails at specific epochs of changing visual motion in Parkinson's disease. Previous fMRI activation studies addressing freezing of gait in Parkinson's disease made use of visuomotor tasks that included either imagery walking in virtual reality (Snijders et al., 2011a) or actual bipedal movements providing visual feedback by virtual progression in a displayed corridor (Shine et al., 2013a). Snijders and co-workers found hyperactivity in the 'mesencephalic motor region' during gait imagery in patients with freezing of gait (relative to patients without freezing of gait), while reduced activations were seen in medial frontal regions. In the study of Shine and co-workers, reduction of bipedal movements (virtual freezing of gait) was induced by visual instructions that inflicted an increased cognitive load in Parkinson patients. These changes resulted in lateral fronto-parietal activation increases and decreased activation of the sensorimotor cortex and caudate nucleus. Controlled for the visually presented cognitive load, region of interest analysis showed reduced activation in the 'mesencephalic motor region', which correlated with the freezing of gait severity.

Foci of reduced medial frontal activations associated with Parkinson's disease in general as well as patients with freezing was a common finding in our study and that of Snijders and co-workers, including the variance in the condition specific foci of maximum activation within SMA, pre-SMA and cingulate motor cortex. With regard to effects specifically associated with freezing of gait, e.g. on the 'mesencephalic motor region', final conclusions cannot be drawn from our study due to the low number of Parkinson patients with freezing of gait. Moreover, one may assume that in the Snijders study, compared to a strict visual stimulus paradigm, motor imagery did recruit more extended motor related circuitry,

indeed enabling identification of such freezing related change in mesencephalic activation which we did not. In this respect, these studies are complementary because our study highlighted the Parkinson associated functional changes in medial frontal and visual cortex regions when challenged by a specific visual motion stimulus. In addition, we demonstrated a distribution of activations associated with non-specific 'change' in the presented visual pattern that resembled previously described spatial attention networks (Gitelman et al., 1999; Ptak, 2012; Raichle, 2011). The lateral fronto-parietal regions of activation decrease in our Parkinson patients (relative to controls) were similar to the fronto-parietal activations associated with inhibited bipedal movements due to cognitive load in the Parkinson patients of Shine et al. (2013a). While in their study, an increased cognitive demand was intrinsically associated with both a decrease of bipedal movements and the consequent slowing of virtual progression in the displayed corridor, our analysis enabled a dissociation between global attention to spatial change and the specific effect of interrupting wide-field flow, i.e. interrupting the illusionary perception of forward self-motion.

Attention to spatial change

The absence of right dorsal premotor activation was a reason to explore subthreshold responses in this cortical region, which revealed that responses at this location were specifically evoked by change of the stimulus pattern, i.e. FtN, FtS as well as StN. Moreover these responses were significantly stronger in healthy controls than in Parkinson patients. Contrasting the conditions characterised by 'change' to the 'stable' stimulus patterns FW and SW resulted in a distribution of robust activations bilaterally comprising the fusiform gyrus, dorsolateral visual, parietal and dorsolateral prefrontal cortex, together with right dominant dorsal premotor activation. Particularly the dorsal parietal-dorsal premotor-prefrontal pattern of activations pointed at a functional network implicated in spatial attention processing (Gitelman et al., 1999; Ptak, 2012; Raichle, 2011). Although subjects were not instructed to explicitly detect changes in the presented stimulus patterns, differences between the conditions made it plausible to infer that the ‘change’ related distribution of activations indeed represented a neuronal mechanism of processing covert spatial attention.

While goal-directed attention to distinct features in a visual scene clearly involves processing in a top-down fashion, covert attention points at more prominent bottom-up mechanisms of detecting unpredictable change (Corbetta and Shulman, 2002; Egeth and Yantis, 1997; Heinze et al., 1994; Moore et al., 2003). The fusiform gyrus can be recruited

in both ways. The circumstance of covert attention (to change) in our experiment provides the main argument to assume that its activation is particularly due to bottom-up processing, while fusiform gyrus participation in an otherwise dorsal visual pathway points at a visuospatial function associated with novelty detection or saliency processing (Hahn et al., 2006; Litt et al., 2011). Classically, the fusiform gyrus plays a prominent role in the ventral visual stream concerning e.g. shape and object recognition, which is distinguished from dorsal pathway processing of visuospatial characteristics (Goodale and Milner, 1992; Haxby et al., 1994). On the other hand, early ventral occipito-temporal contributions to spatial processing are particularly revealed in experimental settings with objects placed outside a target point of central fixation (Fischer and Boch, 1985; Fischer et al., 2011; Levy et al., 2001; Moore et al., 2003). Functional coherence of the fusiform gyrus and parietal cortex, as we found in the 'change' conditions of our experiment, may therefore be associated with the assessment of 'objects' (or basic shapes) in a dynamic environment. Such assessment becomes relevant during e.g. locomotion, when unexpected (extra-fovealy projected) obstacles need to be avoided (Riecke et al., 2007; Schindler et al., 2004; Snijders et al., 2010a). Changes in the visual patterns we employed indeed occurred in primarily the peripheral visual field. This held for narrowing the dot field, both in flow and static mode, as well as for deceleration, which implied that the largest change of radial dot speed occurred in the peripheral part of the display. An additional argument that ‘change’ related activations predominantly occurred in the peripheral visual field can be concluded from the anterior calcarine activation, which topologically represents the peripheral field (Horton and Hoyt, 1991; Wandell et al., 2007).

We already discussed the consequences of impaired visual motion processing in Parkinson’s disease in the preceding paragraphs, particularly with regard to reduced feedforward processing in motor preparation. At a more general level, one may propose that impaired novelty detection in a changing visually recorded environment may lead to the consequence that motor adjustments are made too late. This seems consistent with the suggested disruption of (right hemisphere) visual and 'executive attention' networks, which was inferred from reduced resting state functional connectivity in Parkinson patients with freezing of gait (Tessitore et al., 2012). A consequence would be that in visual circumstances requiring stronger internally driven motor control, this may not only fail in Parkinson’s disease due to impaired recruitment of medial prefrontal regions, but that the initial cue for such recruitment may not be strong enough either. It should be kept in mind, in this respect, that the specificity of (pre-)SMA activation that we found in healthy controls at interrupting the illusion of forward self-motion was due to contrasting two

'change' conditions (FtN versus StN), thus pointing at a response strongly associated with higher order network consequences of visual motion processing such as e.g. motor intention. The general 'change' activations included lateral but no medial prefrontal regions, neither in healthy controls nor in Parkinson patients. This underscores the distinction between neuronal circuitries related either to general visual attention or to specific visual motion processing in our paradigm. One might oppose that lateral fronto-parietal activations related to the 'change' conditions may similarly reflect top-down visual processing (Corbetta and Shulman, 2002; Gilbert and Li, 2013). We agree that the latter may play a role too and that in Parkinson's disease, impaired attention may contribute in various ways to dysfunction of motor behaviour, including gait (Lord et al., 2010; Yogev-Seligmann et al., 2008). The fact, however, that our design did not include an explicit attention condition, favours a dominance of bottom-up attention related processing.

Right hemisphere impairment in Parkinson visuomotor control

The absence of a correlation between freezing of gait and the WAIS block design task did not provide support for a relation between freezing of gait and right hemisphere dysfunction in Parkinson's disease, although such correlation has previously been reported (Nantel et al., 2012). The low number of patients in the group with freezing group may have played a role in this negative result. On the other hand, the correlation between (pre-)SMA activation during FtN and the WAIS block design task indicates that impaired right hemisphere function is associated with the reduced ability to recruit an internal drive to maintain virtual locomotion when the perceived forward self-motion is interrupted. This might support the discussed option that impaired bottom-up visual motion processing fails to provide the optimal cues for (pre-)SMA activation. More support for involvement of the right hemisphere came from differences between patients with right- and left-sided symptoms dominance during wide-field optic flow. In this condition, right-sided symptom dominant Parkinson patients (dominated by left hemisphere disease) showed more activation of the dorsal stream (including the right posterior parietal cortex) compared to left-sided symptom dominant patient (dominated by right hemisphere disease). These results point at consistency with previously described right hemisphere dominance concerning visuomotor transformations (de Jong et al., 1999; Woolley et al., 2010), including gait (Bartels et al., 2006) and optic flow derived visuospatial perception in Parkinson's disease (Davidsdottir et al., 2008). Furthermore, they fit well with a previously suggested relation between left symptomatic Parkinson's disease and freezing of gait occurrence (Cohen et al., 2012).

CONCLUSIONS

Our findings indicated that the compromised ability of Parkinson patients to internally generate action for maintaining virtual locomotion when external support of wide-field flow falls away is based on impaired (pre-)SMA activation. Reduced dorsal occipito-parietal activation during wide-field flow in Parkinson's disease was argued to reflect reduced visuospatial integration, with the effect that predicted sensory consequences of movements cannot be optimally implemented in motor preparation. This impaired occipito-parietal function was associated with enhanced functional connectivity of a segregated magnocellular functional stream through right visual motion area V5 with distant medial fronto-cerebellar circuitry. In this way, compensation of impaired early stage feedforward processing is logically based on a shift to more distant fronto-cerebellar feedforward processing. The latter implies, however, that motor responses to visual motion stimuli may be either too strong or too weak in Parkinson's disease. Furthermore, the identified lateral fronto-parietal pattern of activations related to non-specific stimulus change pointed at covert spatial attention involved in e.g. salience detection. Reduction of the latter would imply that visual stimuli themselves might be inappropriate for evoking a motor response. Parkinson dysfunction of covert spatial attention to simple visual stimuli is consistent with previously described enhanced interference effects of cognitive tasks performed while walking, which indeed may lead to freezing of gait. We were thus able to distinguish cerebral networks associated with either processing specific visual motion stimuli or sustaining more general covert attention implicated in virtual locomotion and its dysfunction in Parkinson's disease.

CHAPTER 7

Transcallosal connections of the opposite dorsal premotor regions support a lateralised specialisation for action and perception

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Submitted

ABSTRACT

Lateralisation of higher brain functions requires that a dominant hemisphere collects relevant information from both sides. The right dorsal premotor cortex, particularly implicated in visuomotor transformations, was hypothesised to be optimally located to converge visuospatial information from both hemispheres for goal-directed movement. This was assessed by probabilistic tractography and a novel analysis enabling group comparisons of whole-brain connectivity distributions of the left and right dorsal premotor cortex in standard space (16 subjects). The resulting dominance of contralateral dorsal premotor connections was characterised by right dorsal premotor connections with left visual and parietal areas, indeed supporting a dominant role in visuomotor transformations, while the left dorsal premotor cortex showed dominant contralateral connections with the frontal lobe. Ipsilateral right dorsal premotor connections were also stronger with posterior parietal regions, relative to the left dorsal premotor connections, while ipsilateral connections of the left dorsal premotor cortex were stronger with particularly the anterior cingulate, the ventral premotor and anterior parietal cortex. The pattern of dominant right dorsal premotor connections thus points at a specific role in guiding perceptual information into the motor system, while the left dorsal premotor connections are consistent with action dominance based on a lead in motor intention and fine precision skills.

INTRODUCTION

The relation between movements and sensation of a given body-side and functions of the contralateral hemisphere reflects an essential characteristic of cerebral lateralisation. Beyond this symmetrical division, each of the two hemispheres shows specialisation with a lateralised dominance, particularly in the human brain. Where the left hemisphere is generally dominant in manual skill and language, a dominant right hemisphere function concerns the integration of more global spatial sensory information in motor action. Information concerning extrapersonal space is particularly obtained by visual senses, while somatosensory stimuli provide information about personal space (Bottini et al., 2009). Particularly for visuomotor integration right hemisphere dominance has been well described (Callaert et al., 2011; Corballis 2003). Symptoms resulting from lesions of the right hemisphere, particularly when the parietal cortex is involved, indeed include visuospatial disorientation and visuomotor deficit, but also neglect for either contralateral space or the affected body side may occur (Bogen and Gazzangia 1965; Corbetta and Shulman 2011; Franco and Sperry 1977; Halligan et al., 2003; Perenin and Vighetto 1988; Rossetti et al., 2003; Vallar and Perani 1986). In this respect, the intact right hemisphere has been proposed to be more visually 'intelligent' than the left, equivalent to the superior capacities of the left hemisphere in other cognitive domains (Corballis 2003). How such segregated hemisphere specialisations are integrated in whole brain neuronal networks, empowering one's sense of unity in perception and action (Bogen and Gazzangia 1965; Franco and Sperry 1977; Gazzaniga 2005), remains an issue to be solved. In the present study, we are able to demonstrate differences between the left and right dorsal premotor cortex (PMd) regarding their patterns of connections in ipsilateral and contralateral hemispheres. These characteristic distributions represent a possible flow of information from two hemispheres to each of the two dorsal premotor cortices, consistent with the distinction of perceptual dominance of the right and global action dominance of the left hemisphere concerning goal-directed movements.

Dorsal parietal-premotor circuitry plays a specific role in processing spatial aspects of visuomotor transformations (Binkofski et al., 1999; de Jong et al., 1999; Galletti et al., 2001; Johnson et al., 1996; Shipp et al., 1998; Wise et al., 1997). While in humans the right hemisphere is dominant in such transformations, goal-directed actions within extrapersonal space implies perception of, as well as movements made into both visual hemifields. This means that the right hemisphere uses information about the outside world derived from both hemispheres. The right dorsal premotor cortex is thus logically positioned to support visuomotor integration and guide the resulting movement

instructions also to the opposite dorsal premotor cortex (Boussaoud et al., 2005). Similarly, the stronger involvement of the right dorsal premotor cortex in complex bilateral movements, relative to the left dorsal premotor cortex, suggests more efficient access to bilateral hemisphere information (de Jong et al., 2002; Sadato et al., 1997; van den Berg et al., 2010; Wenderoth et al., 2004). We therefore hypothesised that, in addition to ipsilateral parietal input, the right dorsal premotor cortex receives more sensory information from the left hemisphere compared to the contralateral input received by the left dorsal premotor cortex. Although the left dorsal premotor cortex contributes to specific left hemisphere functions, such as language and dexterous skill (Mechelli et al., 2005; Saur et al., 2008), the ventral premotor cortex is more involved in these functions and has stronger connections within the ipsilateral hemisphere (Tomassini et al., 2007).

In order to compare the ipsi- and contralateral hemisphere connections with each of the two dorsal premotor cortices, we employed probabilistic diffusion tensor imaging (DTI) and a novel analysis approach. Where DTI is often used to visualise in vivo white matter connections of the brain based on predefined seed and target regions, in the present study a whole brain connectivity distribution was generated with the dorsal premotor cortex as seed region. Next, normalised whole brain connectivity distributions were implemented in the construction of group maps. The latter were used for voxel based statistical testing of a lateralised dominance of connections with either the right or left dorsal premotor cortex.

METHODS

Subjects

Sixteen healthy right-handed subjects, mean age 26.8 years (SD ± 9.8), 9 females, participated in the study. None of the subjects had neurological or psychiatric disorders. All subjects were right-handed as indicated by the Edinburgh handedness inventory (Oldfield 1971). The experiment was approved by the local medical ethical committee. All subjects gave written informed consent according to the declaration of Helsinki.

Data acquisition

Data acquisition was performed using a 3 Tesla Philips MR system (Philips medical systems, Best, the Netherlands) with a 32-channel head coil. Anatomical images were based on a T1-weighted 3D ultrafast gradient echo sequence with repetition time 9 ms, echo time 3.5 ms, flip angle 8°, field of view 232 x 256 x 170 mm, 170 slices without slice gap and a voxelsize of 0.9 x 1 x 1 mm. DTI images were acquired with a diffusion weighted spin echo sequence. The protocol comprised 60 independent diffusion gradient directions with *b* values of 1000

s/mm^2 followed by a *b*0 image. Further scanning parameters were repetition time 8830 ms, echo time 61 ms, flip angle 90°, field of view 240 x 240 x 138, 55 slices without slice gap and a voxelsize of 2.5 x 2.5 x 2.5 mm. To assess quality of the diffusion data, signal-to-noise ratios (SNR) were calculated by SNR = S/σ where S is the signal in a 2D region of interest of 10 x 10 = 100 voxels with maximal uniform brain signal and σ is the standard deviation of those 100 voxels (Lagana et al., 2010). The same 2D region was used to calculate the SNR for each diffusion direction as SNR might vary among directions (Lagana et al., 2010). The resultant total mean SNR was 7.7 (± 1.3) with 5.1 as minimal value 10.0 as maximal value for one direction.

Image processing

Diffusion images were processed using tools from the FMRIB software library (FSL) version 4.1.9 (www.fmrib.ox.ac.uk/fsl). Diffusion images were realigned to the *b*0-image to compensate for eddy currents (Jenkinson and Smith 2001). The brain images were automatically extracted from the entire head images (Smith 2002) and manually corrected. We calculated probabilistic distributions on multiple fibre directions at each voxel in the diffusion data using a multiple-fibre extraction (Behrens et al., 2003; Behrens et al., 2007). A Bayesian estimation of diffusion parameters obtained using sampling technique (BEDPOST) was conducted (Woolrich et al., 2009) with gradients corrected for slice angulations. For each subject, T1 images were coregistered with diffusion images by a nonlinear transformation preceded by a linear transformation (Jenkinson and Smith 2001). The same procedure was done to co-register T1 images to MNI. Both steps resulted in a transformation matrix, which was used to convert diffusion images to MNI or back through the T1 transformation matrices.

Each subject´s T1-weighted image was automatically segmented (Zhang et al., 2001). Gray and white matter were dilated with 1 x 1 x 1 mm and a threshold was set at 0.2. The overlap between these grey and white matter images was used to create a gray matter/ white matter boundary mask. Standard anatomical MNI space regions of interest of the dorsal premotor cortex were derived from an existing human motor area template (Mayka et al., 2006), which was transformed to T1 anatomical images of each subject using the nonlinear transformation matrix. The T1 dorsal premotor regions were multiplied with the gray matter/white matter boundary mask to select this part within the dorsal premotor region. Thereafter, the gray matter/white matter dorsal premotor regions were nonlinear transformed to diffusion space.

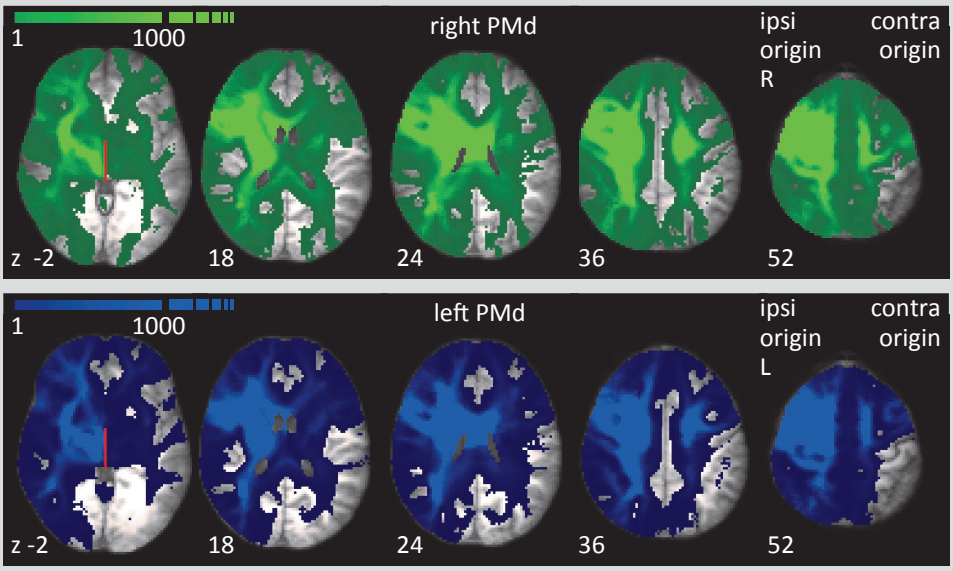
Connections of the right and left dorsal premotor cortex were analysed with probabilistic tractography. We tracked from the grey matter/white matter boundary voxels within our dorsal premotor regions in native diffusion space to generate a connectivity distribution of those regions for each subject. Output generated a connectivity distribution summing the total number of generated tracts for all voxels within the seed region. A single voxel then displays the summed hits for all tracts (i.e. the number of tracts that have passed the voxel). As result, probabilistic tractography is influenced by the size of the seed region next to the number of samples done for each voxel within that seed region. For the latter, we used the default number of 5000 samples. Although the size of the left and right dorsal premotor template in MNI space was equal, transforming it to diffusion space resulted in some differences in size, which might induce a bias towards one side for the seed region size in diffusion space and thereby also for tractography results. The mean size of the right dorsal premotor region in native diffusion space was 580 (± 103) voxels, while for the left it was 560 (± 101) voxels, which was not significantly different when compared with each other ($t(15) = 1.25$, $p_{\text{two-tailed}} = 0.231$). Furthermore, the right dorsal premotor region was larger than the left in eight subjects (67 ± 57 voxels), while the left dorsal premotor region was larger than the right in the other eight subjects (27 ± 23 voxels). This virtually eliminated the possibility of a bias in our diffusion seed region toward one side, thus avoiding a possible confounding bias in the two connectivity distributions. To eliminate the possibility of faulty tracking to the contralateral hemisphere through 'kissing' fibres in the brain stem, we included an exclusion mask in the midsagittal plane from the third ventricle downward through the brain stem between the cerebral peduncles, with a boundary anterior and posterior by the surrounding cerebrospinal fluid. It should be noted that in this way tractography did not reach the contralateral cerebellum, thus excluding its assessment.

Comparison of left and right dorsal premotor connections

To compare the connectivity distribution of the right and left dorsal premotor cortex, we used a novel approach to test hemisphere differences of connections at group level. Maps of DTI data for each hemisphere were superimposed at each other in MNI space and tested for group differences using permutation statistics. To that end, first, the two separate images of the cerebral connectivity distribution for the right and left dorsal premotor cortex were transformed from diffusion to MNI space through T1 by two nonlinear transformations. The original dorsal premotor tracts (transformed in MNI space) were visualised by calculating the median over all subjects for each voxel for both the right and left dorsal premotor cortex (Figure 1). Intrinsically linked to the methods of probabilistic

tractography, these median group images are prone to a distance bias because areas at larger distance from a given seed region are less likely to demonstrate their tracts as nearby areas. In our analysis, however, this issue did not play a role because left-right comparisons were made between tracts that both originated from symmetrically equal right and left dorsal premotor seed regions and passed distant voxels that were positioned in a similar symmetrical way, thus equally far from their seed dorsal premotor region. We therefore only draw conclusions from the images originating from the statistically tested differences between the two dorsal premotor regions. To test for such differences, we flipped the connectivity maps of the left dorsal premotor region. Furthermore, we

Figure 1 | Tractography of the right and left premotor cortex



Median tractography values over all subjects for each voxel are shown for the right (green) and left (blue) dorsal premotor cortex (PMd). The left dorsal premotor connectivity distribution is mirrored to ease comparison of the right and left dorsal premotor region. Results are displayed on a mean T1 MR image of all sixteen subjects transformed into standard MNI space. Positive z coordinates refer to the distance of transversal sections (in millimetres) superior to the plane traversing the anterior and posterior commissures. The colour scale indicates the total number a tract passed a voxel. Values above 1000 are represented by the same colour intensity. The contralateral cerebellum was not reached via the cerebral peduncles due to a midsagittal exclusion mask through the brain stem (red line). ipsi origin = ipsilateral to seed region; contra origin = contralateral to seed region; R = right side of the brain; L = left side of the brain.

separately subtracted for each subject (1) the right from the left mirrored and (2) the left mirrored from the right connectivity maps. This resulted in two connectivity maps for each subject displaying the differences of the right and left mirrored dorsal premotor region, now displayed in MNI space as ipsilateral and contralateral to the seed region. The two resulting connectivity distributions provided the input for the subsequently conducted voxel-based group testing of these connectivity maps by using a one-sample non-parametric permutation test with 5000 permutations for each voxel (Nichols and Holmes 2002). This resulted in an uncorrected *p*-values map of differences displaying which voxels showed more contribution to the right than left dorsal premotor cortex in both the ipsi- and contralateral hemisphere and another uncorrected *p*-value map showing it the other way around, which voxels showed more contribution to the left than right dorsal premotor cortex. For multiple comparison adjustment, we set a threshold of $p < 0.001$. An extended cluster threshold of twenty voxels was used to filter out meaningless small clusters using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Furthermore, a mask was applied to exclude all voxels outside the brain.

RESULTS

Right dorsal premotor connectivity dominance

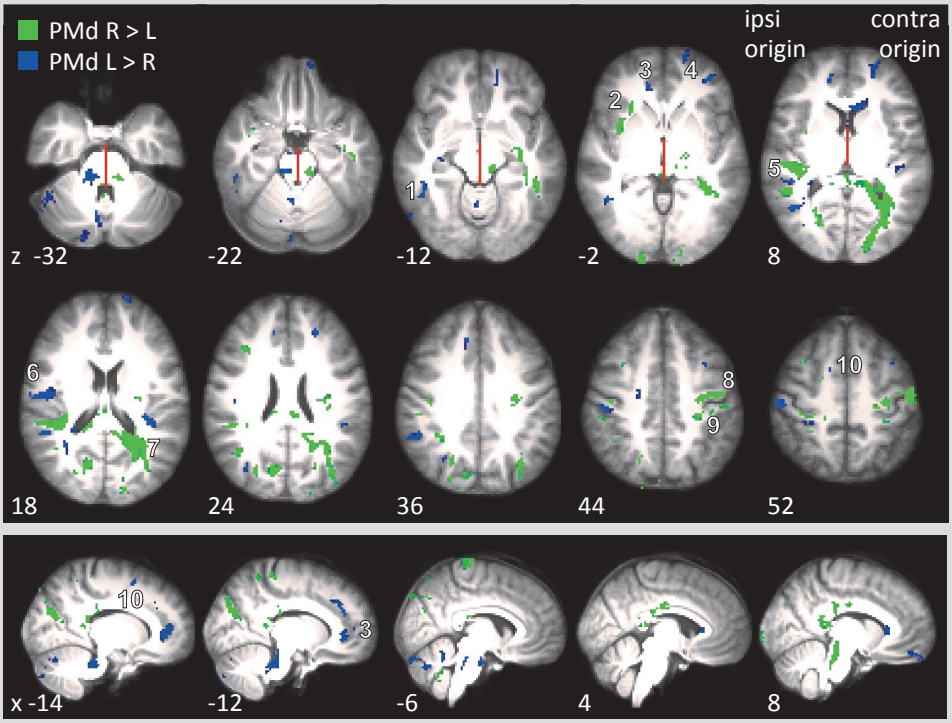
In general, the right dorsal premotor cortex had more connections distributed within the left hemisphere compared to the contralateral hemisphere connections of the left dorsal premotor cortex. These contralateral connections of the right dorsal premotor cortex were particularly made with parietal and occipital cortex regions (Figure 2; green clusters). The largest cluster comprised the posterior part of the fronto-occipital fasciculus ending along the calcarine sulcus, bordering the lingual, fusiform- and middle occipital gyri. This cluster also spread along the posterior segment of the intraparietal sulcus. Another dominant cluster in the contralateral hemisphere was seen around the central sulcus, both in the postcentral gyrus underlying the somatosensory cortex, and in the precentral gyrus including the motor representation of the hand. Within the corpus callosum, the right dorsal premotor connections outnumbered those of the left dorsal premotor cortex in the posterior midbody and splenium. In the ipsilateral hemisphere, a dominance of right dorsal premotor connections with occipito-parietal regions was also found, but this was less pronounced than for the connections with contralateral posterior brain regions (Figure 2).

Left dorsal premotor connectivity dominance

Although the right dorsal premotor cortex was generally dominant with regard to the pattern of contralateral connections, a few contralateral connections of the left dorsal

premotor cortex with rostral parts of the prefrontal cortex were more intense compared to the right dorsal premotor cortex equivalents (Figure 2; blue clusters). Such anterior

Figure 2 | Difference in connectivity distributions of the left and right dorsal premotor cortex



Differences between the left (L) and right (R) dorsal premotor cortex (PMd) are shown on transversal sections of a mean group anatomy (N = 16) in standard MNI space. The z coordinates refer to the distance of transversal sections (in millimetre), either superior (positive) of inferior (negative) to the plane traversing the anterior and posterior commissures. The x coordinates refer to the distance of sagittal sections (in millimetre) to the midsagittal plane, either ipsilateral (negative) or contralateral (positive) to the origin of the dorsal premotor seed region. Thresholds are set at $p < 0.001$ with an extended voxel threshold of twenty voxels. The contralateral cerebellum was not reached via the cerebral peduncles due to a midsagittal exclusion mask through the brain stem (red line). 1 = inferior temporal gyrus; 2 = external capsule; 3 = anterior cingulate gyrus; 4 = superior and middle frontal gyrus; 5 = superior temporal gyrus; 6 = ventral premotor cortex; 7 = fronto-occipito fasciculus; 8 = precentral gyrus; 9 = postcentral gyrus; 10 = pre-supplementary motor area.

dominance was also seen in the corpus callosum with left dorsal premotor connections outnumbering the right dorsal premotor connections in the genu of the corpus callosum. The left dorsal premotor cortex, relative to the right dorsal premotor cortex, showed more ipsilateral connections with medial premotor regions, comprising the anterior cingulate and pre-supplementary motor area (pre-SMA). Such dominance of left ipsilateral dorsal premotor connections was also seen for connections with the ventral premotor and anterior parietal cortex as well as a few temporal cortex regions. In addition, we saw ipsilateral connections in the cerebellum when the left dorsal premotor cortex was defined as seed region. With regard to cerebellar connectivity, it should be kept in mind that its basic pattern of crossed cerebral-cerebellar connections could not be assessed due to the midsaggital mask through brainstem and diencephalon, which was used to exclude faulty dorsal premotor tracking along 'kissing' fibers in the brainstem (Figure 2; red line).

DISCUSSION

The present study demonstrated a hemisphere specific difference between the left and right dorsal premotor cortex regarding the distribution of its connections. The dominance of connections between the right dorsal premotor cortex and particularly contralateral occipito-parietal regions, relative to the contralateral connections of the left dorsal premotor cortex, provided support for the hypothesis that the right dorsal premotor cortex is dominant in the integration of visual information to prepare purposeful movements. Consistent with such dominance of connections with posterior brain regions, these right dorsal premotor connections outnumbered the left dorsal premotor connections in the posterior segments of the corpus callosum. Connections of the left dorsal premotor cortex with the contralateral prefrontal regions were dominant to those of the right dorsal premotor cortex with the prefrontal cortex, while transcallosal connections were stronger represented in the anterior callosal segments. Where previous DTI studies have indentified the location of strong reciprocal connections within the corpus callosum that predominantly run between homologous areas of both hemispheres (Hofer and Frahm 2006; Huang et al., 2005), our study enabled identification of lateralisation differences between transcallosal connections of the right and left dorsal premotor cortex.

Although the visual system already contributes to visuomotor control by maintaining a functional segregation between parvo- (colour) and magnocellular (motion) processing streams, the parietal cortex is further implicated in higher order visuospatial and visuomotor processing along a dorsal visual stream (Goodale and Westwood 2004; Halligan et al., 2003; Rossetti et al., 2003; Shipp et al., 1998). Integration of lateralised visual

characteristics in whole-field visual processing may already take place along highly focused transcallosal connections between the occipital lobes (Clarke and Miklossy 1990; van Essen and Zeki 1978; Watson et al., 1993). A consequence of right hemisphere dominance in human visuomotor integration is a more complex transcallosal innervation to enable efficient access to sensory information from both hemispheres as well as an effective transfer of movement parameters, not only to the adjacent right motor cortex but also to the left (pre)motor cortex. The latter is reflected by the right dorsal premotor connections with the precentral gyrus, of which the posterior surface contains the primary motor cortex, while the premotor cortex spans its anterior and lateral surfaces. The crucial role that we attributed to the right dorsal premotor cortex concerning visuomotor transformations is thus supported by the identified pattern of dominant connections with particularly occipito-parietal regions relative to the left dorsal premotor connections.

Dominance of the contralateral connections with the right dorsal premotor cortex not only concerned vision related tracts. Additional dorsal premotor connections with parietal regions point at involvement of the right dorsal premotor cortex in general sensorimotor processing, including the integration of somatosensory information. Right-sided dominance concerning the latter is consistent with right parietal-premotor circuitry previously described to be involved in the integration of proprioceptive information in motor control (de Jong et al., 2002; Naito et al., 2005), which may be particularly beneficial for coordinating bilateral movement.

While sensorimotor transformations involved in motor preparation are often characterised by bottom-up processing, the same connections may facilitate a reciprocal information flow in a more top-down fashion. In attention, these two directions characterise the distinction between sensory driven and goal-directed attention respectively (Corbetta and Shulman 2002). The dominance of contralateral connections of the right dorsal premotor cortex with particularly posterior parts of the brain, relative to the left dorsal premotor connections, is indeed consistent with functional circuitry implicated in spatial attention (Gitelman et al., 1999; Raichle 2011). In this way, hemisphere specific characteristics of right dorsal premotor connectivity contributes to understanding neuronal mechanisms that underlie a lateralised higher order brain function such as spatial processing in both sensorimotor transformations and attention.

For the left dorsal premotor cortex, connections were stronger with prefrontal regions, relative to the prefrontal connections of the right dorsal premotor cortex. This particularly

concerned ipsilateral connections with cingulate motor areas and the pre-SMA, and contralateral connections with the lateral surface of the anterior prefrontal cortex. Although we did not start with a specific hypothesis concerning connections of the left dorsal premotor cortex, stronger involvement in circuitry comprising these frontal regions fits left hemisphere dominance underlying right-handedness. In this respect, medial premotor regions may contribute to right-hand dominance by accommodating a lead in the internal generation of action (Lau et al., 2004) as well as recruiting overlearned movement sequences (Boecker et al., 1998; Lewis et al., 2004). The dominance of left dorsal premotor connections with the ventral premotor and anterior parietal cortex in the ipsilateral hemisphere, relative to such connections of the right dorsal premotor cortex in the opposite hemisphere, may further support a contribution of specifically the left dorsal premotor cortex to fine precision movements (Binkofski et al., 1999; Dafotakis et al., 2008; Raos et al., 2006; Sakata et al., 1997). A concerted function of the left dorsal premotor cortex and medial premotor areas has also been associated with a left hemisphere function such as speech (Hartwigsen et al., 2013; Vingerhoets et al., 2013). The presence of a dominant left hemisphere tract from the dorsal premotor cortex to the temporal cortex may further support its involvement in 'classical' left hemisphere networks underlying language (Hickok et al., 2011; Knecht et al., 2000).

CONCLUSION

To conclude, the patterns of particularly contralateral hemisphere connections of the right dorsal premotor cortex indicated a lateralised dominance related to visuomotor control. This was based on the stronger connections of the right dorsal premotor cortex with occipito-parietal regions of the opposite hemisphere. Relative to the connections of the right dorsal premotor cortex, left dorsal premotor connections were stronger with prefrontal areas, ipsilateral ventral premotor and the anterior parietal cortex representing action dominance based on a lead in motor intention and fine precision skills. These two patterns of lateralised right and left dorsal premotor connections may thus reflect a hemisphere specific dominance for perception and action, respectively.

CHAPTER 8

General discussion

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In this thesis we focussed on various aspects of lateralisation in Parkinson's disease. This characteristic asymmetry of symptoms is poorly understood. Firstly, we showed that the side of symptoms is related to general cerebral asymmetry indicated by handedness **(chapter 2-3)**. This relation will be further discussed, followed by considerations on handedness and dopamine asymmetry. Lateralisation associated with freezing of gait comprised the second main part of this thesis. Although we were unable to demonstrate a specific relation of freezing of gait with left symptom dominant Parkinson patients in the retrospective analysis of patient data **(chapter 2)**, literature provided support for this relation (see below). We studied visuomotor control as underlying mechanism of freezing of gait by using optic flow manipulations on gait **(chapter 5)**, which showed that enhanced disturbances in Parkinson patients correlated with impaired right hemisphere testing. Cerebral activation studies **(chapter 4 and 6)** provided results indicating involvement of a right lateralised visuomotor network together with an impaired recruitment of medial premotor areas in patients when support for 'virtual' locomotion falls away. Finally, arguments were obtained for a dominant role of the right dorsal premotor cortex to integrate information of both sides of the outside world, i.e. of both hemispheres, to enable performance of a right lateralised visuomotor function in healthy subjects **(chapter 7)**. Results of these studies will be set in a broader perspective with respect to the relation of side of symptom dominance with freezing of gait and cerebral circuitry involved in freezing of gait. In the latter, the main results with specific attention to lateralisation aspects within these circuitries will be discussed.

HANDEDNESS IN RELATION TO PARKINSON SYMPTOM SIDE

We showed that the side of symptom dominance in Parkinson's disease was related to general cerebral asymmetry indicated by handedness (chapter 2-3). By means of a retrospective analysis of the correlation between handedness and dominant symptom side in Parkinson patients we demonstrated that right-handedness was associated with right-sided dominance of Parkinson symptoms (chapter 2). Results appeared to be the other way around for left-handed patients showing more left-sided dominance of Parkinson symptoms. The group of left-handed patients, however, was too small to draw reliable conclusions. A reason for this inconclusiveness may also have been caused by the fact that out of the 1000 patients indentified using the retrospective approach, lack of documentation made that only 30 percent was suitable for analysis. Furthermore, the relation of right-handedness with right-sided dominance of Parkinson symptoms shown in chapter 2 was not definitively convincing as some other studies demonstrated a similar relationship, while others failed to find such relation. On the other hand, no studies

reported an inverse relation, which was the reason to think that lack of power was the main problem why some studies failed to find the hypothesised relation of hand dominance with dominant side of symptoms. To solve both the issue of a small left-handed patient group as well as the inconsistent reported association for right-handed patients, we performed a meta-analysis (chapter 3). This large group of 4405 patients with Parkinson's disease from ten studies unequivocally showed a substantial and statistically significant association between the dominant side of Parkinson symptoms and hand dominance. Right -handed patients showed a significant excess of about 60 percent for right-sided dominance of Parkinson symptoms, while the reverse was true for the left-handed patients with a significant excess of about 60 percent left-sided dominance of Parkinson symptoms (van der Hoorn et al., 2012b). The dominant hemisphere thus appeared to be more prone to Parkinson's disease.

In this way we clearly answered the first question stated in this thesis, showing that the side of symptoms in Parkinson's disease was related to general cerebral asymmetry indicated by handedness. However, answering the question is still far away from explaining it. The origin of the relation or even the origin of lateralisation of Parkinson symptoms is still an enigma (Djaldetti et al., 2006). Our results tempted to speculate about the origin of lateralisation of Parkinson symptoms, even more because asymmetry of symptoms is a core characteristic of Parkinson's disease.

It has been argued often that the onset of symptoms are simply noticed earlier within the dominant hand, as more use implies more attention to the dominant hand (Melamed and Poewe 2012; Uitti et al., 2005). This seems unlikely as the onset side remains the worst affected side during disease progression (Pirker 2003). Furthermore, the most affected side of the brain identified by dopamine-PET relates to the dominant side of symptoms in Parkinson's disease (Pirker 2003), thus excluding attention as a confounding factor.

The relation between handedness and Parkinson onset, inflicted by dopaminergic degeneration, may suggest that handedness is related to dopamine decline within the brain. Considering that hand dominance might imply an increased metabolic demand, possible negative consequences of oxidative stress would then occur in the corresponding (contralateral) hemisphere (Jenner 2003). Enhanced oxidative stress might then contribute to toxicity inflicted by excitatory neurotransmitters as well as dopamine metabolites. A wider extension of functional networks within the dominant hemisphere may lead to enhanced basal ganglia activity in this hemisphere as strongly interconnected cortical fields

have more common striatum projections (Yeterian and Van Hoesen 1978). Corticostriatal projections are excitatory (DeLong and Wichmann 2007; Obeso et al., 2008). As a consequence, the excitatory drive associated with wider corticostriatal projections within the dominant hemisphere could thus lead to excitotoxic effects in the long run. Normal motor lateralisation in association with an increased level of nigrostriatal dopamine turnover in the dominant hemisphere found support by human in vivo fluorodopa PET measurements (de la Fuente-Fernández et al., 2000) and dopamine-2 receptor binding dominance (Larisch et al., 1998; Verstappen et al., 2007).

Further support for lateralisation of striatal dopamine may be inferred from schizophrenia, which has been argued to result from a dopamine overactivity within the striatum (Abi-Dargham et al., 2000; Hietala et al., 1995; Laruelle et al., 1999; Seeman et al., 1975).The latter is consistent with the fact that blocking dopamine receptors is an effective treatment for positive symptoms in schizophrenia (e.g. hallucinations) (Abi-Dargham et al., 2000). Schizophrenia has been reported to occur more frequently in non-right-handed (left- or mixed-handed) people (DeLisi et al., 2002; Dragovic and Hammond 2005; Gur 1977; Sommer et al., 2001). Even in healthy adolescents, schizophrenia-like positive items (e.g. hearing noises and voices that others do not hear) already occurred more frequently in non-right-handed people (van der Hoorn et al., 2010b).

Animal studies provided further inside in a link between handedness and dopamine. Turning preference in rodents showed similarities with handedness in humans providing a model to study human handedness (Filipov et al., 2005; Glick et al., 1982). Rats showed a turning preference toward the hemisphere with lower dopamine levels in the nigrostriatal pathway (Zimmerberg et al., 1974). Parkinson patients showed a same turning preference toward the affected (lesser dopamine containing) basal ganglia, consistent with the observation in unilateral lesioned rats (Bracha et al., 1987). Human right-handers and left-handers showed opposite turning preference, which implies a relation between handedness in humans and dopamine lateralisation (Mohr et al., 2003). Unfortunately, a direct comparison of handedness and dopamine lateralisation has not been conducted in healthy subjects, although a relation has been suspected as early as in 1982 (Glick et al.) when the first dopamine lateralisation in humans was shown. This has later been demonstrated more often although not consistently (de la Fuente-Fernández et al., 2000; Laakso et al., 2000; Larisch et al., 1998).

FREEZING OF GAIT AND THE DOMINANT SIDE OF PARKINSON SYMPTOMS

Although we were unable to show earlier onset of freezing of gait in left symptom dominant Parkinson patients compared to right dominant patients (chapter 2), others did (Giladi et al., 2001a). Given the role of a right lateralised parieto-premotor network in freezing of gait (Azulay et al., 1999; Bartels et al., 2006; Suteerawattananon et al., 2004) and in multilimb cyclic antiphase movements (de Jong et al., 2002), we expected that freezing of gait would be associated with left-sided symptom dominant Parkinson patients reflecting disturbances of this visuomotor network in the more affected right hemisphere. We may not have found this due to the high number of missing data using a retrospective approach. Of the total of almost 1000 patients, we were only able to use 184 patients for this analysis because their files contained no reliable documentation concerning disease duration at the time of first report of freezing of gait. Unlike the constancy of handedness, variation and thus inaccuracy about the reported time of onset of freezing of gait may be caused by follow-up frequency or not attending to the item during a visit. A prospective study of 800 patients of which 57 developed freezing of gait, significantly demonstrated that Parkinson patients with the initial symptoms on the left side developed 1.55 times more likely freezing of gait than Parkinson patients with the initial symptoms on the right side (Giladi et al., 2001a). Furthermore, they clearly showed a relation of freezing of gait with disease duration, progress of the disease, rigidity, bradykinesia and gait. In contrast, tremor as initial symptoms was related to a decreased risk of developing freezing of gait (Giladi et al., 2001a). This thus provides support for the idea that freezing of gait is related to left symptom dominant Parkinson patients. Moreover, the relation of freezing of gait with bradykinesia and rigidity may add to the suspicion that a misbalance of external and internal movement generation including a lack of internal generation of movement contributes to freezing of gait.

The side of symptom dominance was also a parameter assessed in our treadmill and fMRI studies and showed some arguments for a right hemispheric involvement in freezing of gait as well. This will be covered in the next paragraphs.

FREEZING OF GAIT RELATED CEREBRAL CIRCUITRIES

To further understand the mechanisms underlying freezing of gait, particularly with respect to visuomotor transformations, we used a basic visual stimulus intrinsically associated with locomotion instead of a more natural virtual reality scenery. Radially expanding optic flow, the visual pattern elicited during forward locomotion, similarly generates the illusionary perception of forward self-motion when presented on a static screen (Duffy 1998; Gibson

1954; Kovács et al., 2008). This gave us the opportunity to study the effect of optic flow manipulations in stationary subjects while providing them the illusion of forward self-motion. Participating subjects indeed perceived forward self-motion during wide optic flow in our fMRI experiments (chapter 4 and 6). This concerned young and elderly healthy subjects as well as Parkinson patients with and without freezing of gait. With respect to cerebral circuitry in the freezing of gait patient group it should be kept in mind that the group was small (*N* = 7). Although clear conclusions could be drawn for the Parkinson patients without freezing (*N* = 15), conclusions about the freezing of gait Parkinson group should be handled with care. On the other hand, our results indicated that this small group was similar to patients without freezing of gait except that they were more extensively affected.

As expected, narrowing wide-field optic flow, mimicking a narrow passage that may induce freezing of gait, induced a shift from right lateral to medial premotor activations in young healthy subjects, consistent with a transition from externally stimulated to internally driven virtual movements. Although we found activations during wide-field optic flow in elderly healthy subjects (chapter 6), its distribution was less extensively than in the young healthy subjects (chapter 4), a difference which we has not anticipated to find. Particularly the right dorsal premotor cortex was not activated in the elderly control subjects. Furthermore, Parkinson patients showed reduced activation of visual areas during wide optic flow, while functional connectivity pointed at enhanced coupling of the right visual motion area V5 with medial prefrontal-cerebellar feedforward circuitry (chapter 6). Circuitry representing externally driven motor control during wide optic flow and the compensatory feedforward circuitry during wide optic flow will be treated first. Thereafter, optic flow interruptions will be discussed. Consistent with our hypothesis, Parkinson patients lacked the medial premotor activation, representing impairment of internal motor generation when the external support of wide optic flow fell away (chapter 6). The involvement of visuospatial attention and the mesencephalic locomotor region will be discussed last with respect to freezing of gait related cerebral circuitry. The main results of these subjects will be set in the context of the thesis' subject of cerebral lateralisation.

Externally driven motor circuitry in freezing of gait

The fMRI experiment in young healthy subjects showed that wide-field forward optic flow activated the dorsal visual stream comprising the visual and parietal cortex together with the right dorsal premotor cortex (chapter 4). In concordance with our hypothesis these results reflected a pathway for externally triggered motor control. Dorsal activation in

elderly comprised visual and parietal areas as well but not the dorsal premotor cortex (chapter 6). The absent dorsal premotor cortex remains unclear, but it might represent less extensive visuomotor processing confined by consistent parietal processing in normal ageing, while premotor links are more variable. Ambiguity remained as we were unable to compare both young and elderly healthy subjects directly due to different study designs. Furthermore, activation and resting state studies between young and elderly healthy subjects showed indeed differences in the premotor areas (Meier et al., 2012; Wai et al., 2012; Wu et al., 2007a; Wu et al., 2007b), while optic flow has been described to induce similar effects on gait performance in the two (Chou et al., 2009). The explanation of absent right dorsal premotor activation during wide optic flow in elderly healthy subjects thus remains speculative and could as well be due to differences in study design as to reflect cerebral processing differences in normal ageing. On the other hand, we did show a right-sided dominance of the parietal activation in elderly healthy subjects and Parkinson patients corresponding with the right-sided dominance in young healthy subjects (chapter 4 and 6) and previously shown right-sided dominance of optic flow (de Jong et al., 1994; Ptito et al., 2001). The location of right dominant posterior parietal activation is consistent with right-sided damage known to induce visuomotor problems such as spatial hemineglect and optic ataxia (Halligan et al., 2003; Perenin and Vighetto 1988; Rossetti et al., 2003; Vallar and Perani 1986). This also holds for disturbed gait (Huitema et al., 2006). The parietal and right dorsal premotor relation was further underscored by its lateralised connectivity distributions, which reflected its dominant role in visuomotor processing (chapter 7). There is thus support for recruitment of a right lateralised externally driven motor pathway in healthy elderly and Parkinson patients, although less extensively than in the young healthy subjects. Furthermore, visual areas were less activated in Parkinson patients, particularly in patients with freezing of gait (chapter 6). A compensatory feedforward mechanism in patients mediated by the medial prefronto-cerebellar circuitry was demonstrated with connectivity analysis (chapter 6). Compensatory circuitries are important to understand freezing of gait, also as they can provide insight in therapeutic strategies that might train recruitment of these compensatory circuitries. This distant feedforward compensation might induce overshoot of reactions in the dorsal stream as it bypasses early feedforward processing at the level of the parietal areas. This dorsal pathway overshoot might be the compeer of overshoot in the ventral pathway resulting in visual hallucination (Meppelink et al., 2009). Moreover, the immediate link of (early) visual and medial prefrontal cortex might point at a pathway by which simple cues recruit previously internalised motor programmes such as dribbling a football or riding a bicycle (Snijders and Bloem 2010; Snijders et al., 2011b).

Areas mediating internally generated movements in freezing of gait

Narrowing optic flow, mimicking circumstances of a narrow passage, induced interrupted gait on treadmill walking and activated medial premotor areas in young as well as elderly healthy subjects (chapter 4-6). Reducing the external support by gradually stopping wide optic flow, employed in elderly healthy subjects, similarly provoked such medial prefrontal activation (chapter 6). This medial frontal activation, comprising both the supplementary motor area (SMA) and pre-SMA, has been implicated in the preparation of internally driven movement in contrast to the externally driven movement mediated through the lateral premotor cortex (Godschalk et al., 1985; Halsband et al., 1993; Mushiake et al., 1991; Passingham 1993). The absence of this medial premotor activation in Parkinson patients in response to the loss of perceiving virtual forward locomotion, is proposed to reflect the inability of patients to start up an internal self initiated movement when external support of movements drops (Jahanshahi et al., 1995). This lack of medial premotor activation was even more in patients with freezing of gait (chapter 6). In this way, narrowing forward optic flow helps to explain why in Parkinson's disease, a condition with well described impairment of medial prefrontal cortex function (Cunnington et al., 1997; Gerschlager et al., 1999; Jenkins et al., 1992; Yu et al., 2007), the internal generation of motor action fails in the circumstance of interrupted external support from wide-field optic flow. This has indeed been claimed to cause freezing of gait (Hallett 2008).

The visual stimulus transition of narrowing a wide forward optic flow field, mimicking the perception of approaching a narrow corridor, indeed evoked clear gait obstruction in non-freezing Parkinson patients during treadmill walking. Only a small (less specific) effect was seen in elderly healthy subjects (chapter 5), which is similar to the optic flow effects that has been described in young healthy subjects (Chou et al., 2009). The effect of narrowing optic flow on treadmill gait was most pronounced for left-sided symptom dominant Parkinson patients, which pointed towards a relation with impaired right hemisphere function. The correlation between gait obstruction and performance on the block design task in Parkinson patients provided further support for right hemisphere involvement (chapter 5). In the subsequent fMRI experiment (chapter 6), this block design task served as an index for the right hemisphere visuomotor function and correlated with (pre-)SMA activation in Parkinson patients without freezing of gait during optic flow narrowing.

Visuospatial attention circuitry in freezing of gait

Although it was not anticipated in our study, healthy elderly showed a network comprising dorsolateral visual, parietal, prefrontal and right premotor regions that was activated by

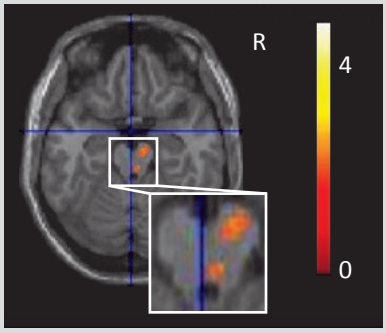
non-specific visual 'changes'. This was reduced in Parkinson patients, which was even more pronounced in Parkinson patient with than without freezing of gait (chapter 6). This network has been implicated in spatial attention processing (Gitelman et al., 1999; Ptak 2012; Raichle 2011) and is consistent with the right-sided dominance described for visuospatial attention (Corbetta et al., 1993). Independent from the dynamic characteristic of optic flow and the visual dependency on it by Parkinson patients, visuospatial attention apparently plays a role as well (Azulay et al., 2006; Morris et al., 2005; Morris et al., 1996). The absence of an explicit attention task in our experiment is an argument for bottom-up (stimulus driven) visual attention, which was thus affected in Parkinson's disease. This may imply that, next to impaired recruitment of medial frontal areas during narrowing optic flow, the cue to recruit these 'attention' areas might not be strong enough either (chapter 6). Bottom-up attention probably played a role in the study of Shine and co-workers as well (2013a). The virtual reality stimulus in their study stopped when they were not able to maintain the coupled antiphase movements of the legs. This association pointed at an increased cognitive load due to incongruent cues. The conjoined stop of the virtual reality progression and antiphase movements was related with increased superior parietal and dorsolateral prefrontal cortex activation. Subjects in the Shine study thus showed increased visuospatial attention processing especially concerning the changing environment, which is to a certain extent similar to our non-specific 'changes'. The impact of increased visuospatial attention in the changed environment was further underscored as the activations could not be attributed the cognitive load of incongruent cues only (Shine et al., 2013a; Shine et al., 2013b). In this light, the correlation with impairments of this network and freezing of gait pointed to affected attention in freezing of gait patients (Shine et al., 2013a). The latter provided additional support for our inference that patients with freezing of gait are essentially more severely affected Parkinson patients.

Mesencephalic locomotor region in freezing of gait

Recently, the role of a mesencephalic locomotor region has been emphasised in freezing of gait. Snijders and co-workers (2011a) found that such mesencephalic locomotor region was more activated in patients with than without freezing of gait during imagination of gait. Contrarily, Shine and colleagues (2013a) showed a decreased activation in the mesencephalic locomotor region during motor blocks in anti-phase movements of the legs while imagining gait. Furthermore, they demonstrated that freezing of gait severity correlated with reduced activation in the mesencephalic locomotor region.

We did not find a significant change of activation in the assumed mesencephalic locomotor region during narrowing optic flow. Aside from the low number of patient with freezing of gait, this might be due to our visual paradigm, which did not include an explicit motor task or imagined gait. Nevertheless, further exploring narrowing of wide forward flow compared to a static narrowing at a reliant threshold (p = 0.05 uncorrected) did reveal a small cluster of mesencephalic activation in the healthy controls thus suggesting a relation with internally generated virtual gait maintenance (Figure 1). This activation of the mesencephalic locomotor region was not found in Parkinson patients neither with nor without freezing of gait. This, although weakly present, hints at reduced mesencephalic locomotor activation in freezing, more than enhanced compensatory mesencephalic locomotor region activation, as described by Shine et al. (2013a) and Snijders et al. (2011a) respectively.

Figure 1 | Subtreshold mesencephalic locomotor region activation of healthy controls in narrowing optic flow



Subtreshold cerebral activation related to the transition from wide to narrow optic flow contrasted to narrowing a stationary dot field in healthy controls is displayed on a section trough the mesencephalic locomotor region (z = -20). Threshold is set at p = 0.05 uncorrected with an extended voxel threshold of eight voxels. The colour bar displays T-values. R = right side of the brain.

CONCLUSIONS

In this thesis, we showed that the dominant hemisphere for handedness is more prone for a dominant disease load in Parkinson's disease. The possible relation between handedness and dopamine lateralisation was discussed but needs to be further explored. We gained support for an association between right hemisphere dysfunction and freezing of gait, but no conclusive evidence for a correlation with left-sided symptom dominance. By optic flow both in wide-field mode and with the transition to a narrow field, the latter mimicking approaching a narrow passage, we demonstrated that virtual freezing of gait is due to an impaired right lateralised visuomotor network along with a decreased ability to substitute externally driven by internally generated motor action in patients. In Parkinson's disease, impaired visual motion processing was found during wide-field optic flow while a stronger functional link existed between the right visual motion area V5 and medial fronto-

cerebellar circuitry. This combination of impaired and enhanced effects provided a model for compensatory feedforward processing in visuomotor control.

FURTHER DIRECTIONS

Despite the well known lateralisation of Parkinson's disease, understanding its cause is still far away. Consequently, this implies a challenge for further research. Some areas for further research in relation to the topic of the current thesis will be described in this section.

Even though we showed a relation between dopamine related lateralisation and handedness, it remains difficult to explain its cause. It should be subject of further research to expand both our basic knowledge of human hand dominance as well as the origin of lateralisation in Parkinson's disease. Both handedness and dopamine lateralisation might depend on a third yet unknown factor that cause both or they might be caused by different factors, which might or might not be related to each other. More likely, handedness and dopamine lateralisation are multifactorial in origin as both have genetic and environment factors (Levy 1976; Schapira and Jenner 2011), of which some might be shared. This includes the possibility that dopamine lateralisation is influenced by oxidative stress inflicted by hand use. Further research should therefore focus on dopamine lateralisation in relation to handedness and to try to find and further test possible explanatory factors for the asymmetrical dopamine degeneration in Parkinson's disease. Oxidative stress should be considered as such a factor. This might include a preferably longitudinal study imaging dopamine activity with PET using ^{18}Fluro-dopa and oxygen consumption with either ^{15}Oxygen-PET or maybe even a quantitative MRI sequence (An et al., 2001).

Left and right symptom dominant Parkinson's disease differ from each other, also with respect to cerebral networks (Riederer and Sian-Hulsmann 2012; Schendan et al., 2009) and visuospatial characteristics (Blonder et al., 1989; Schendan et al., 2009). Research concerning Parkinson's disease would thus benefit from considering the side of Parkinson dominance. At least, this parameter should be taken into account when the focus of research is potentially influenced by cerebral lateralisation (e.g. language in Parkinson's disease). If so, side dominance should be registered along with considering how this confounding factor should be handled. Furthermore, looking explicitly at these lateralisation differences is a fascinating area. A strategy to gain further insight would be to introduce a dual task and test whether gait is more interfered by a right than left hemispheric task. On the other hand, it will be difficult to design tasks for the right and left

hemisphere that are fully balanced for cognitive and visual load, which is required to prevent methodological confounds.

We showed that a basic cue provided by optic flow, was able to recruit a more automatic externally driven motor program. Next to focussing on the network involved in visuomotor cortex, it might be worthwhile to test whether other specific basic cues might similarly be able to recruit automatic motor programs. One might, in this respect, consider rhythmic auditory cues or even emotional cues. Auditory cues are known to support gait and overcome freezing of gait (Nieuwboer 2008; Suteerawattananon et al., 2004), while the impact of emotion is suggested by the typical description that Parkinson patients are able to run away without hesitation when a bystander shouts ´fire fire fire´. With respect to visuomotor control involving visual, parietal and premotor areas of predominantly the right hemisphere, research to further characterise the network involved is worthwhile. In this respect, a fruitful approach might be to test the effect in visuomotor areas during bypassing freezing of gait in both right and left dominant Parkinson patients. For instance, effects of optic flow could be tested by using specific optic flow glasses during optic flow narrowing on treadmill gait and during fMRI for assessing cerebral activation. In this respect, a topic of interest is whether specific cues are beneficial in distinct subtype of freezing of gait. Beside a narrow passage, freezing of gait can be provoked by initiating walking, turning, approaching a destination and dual tasking (Schaafsma et al., 2003). By studying freezing of gait in relation to optic flow interruptions (i.e. narrowing), we focussed on narrow passage induced freezing of gait. Results from our studies cannot be directly translated to other types of freezing of gait, as different mechanisms might play a role as well. It is however, worthwhile to consider how results of our study with an optic flow narrowing might be extrapolated to other freezing of gait subtypes. It should, on the other hand, be emphasised that this speculation is not extensively supported by current research. First, it might be speculated that turning influences the visual input in such way that wide optic flow is interrupted and replaced by translational flow. Translational flow induces less activation than radial optic flow (Konen and Kastner 2008), while in addition we showed that interruption optic flow by a gradual stop showed similar dysfunction of the medial premotor area (chapter 6). For freezing at initiation of gait, it might be speculated that wide optic flow is involved as it absent while standing still, indeed requiring more from the internal movement generation system. To explain freezing of gait evoked by dual tasking has even more speculative character when saying that it relates to internal motor generation, triggering freezing of gait due to medial premotor disturbances due to a reduced attention for action (Rushworth et al., 2003). Next to a basic sensory stimulus such

as optic flow, we demonstrated that attention plays an independent role in modulating the balance between internally and externally driven movement (chapter 6). These speculations do point out that we still need to go further to explain freezing of gait fully, making openings to treatment strategies harder, but they do point at additional questions.

Imaging the brain provides a powerful tool to investigate cerebral function and structure in vivo. We used the technique of both functional magnetic resonance imaging (fMRI) and a novel approach to compare connectivity distribution with probabilistic diffusion tensor imaging (DTI). Both techniques enable visualisation of cerebral lateralisation. Although DTI methods still contain many caveats, the technique is highly valuable as it is the only technique to visualise white matter tracts in living humans. Our novel DTI approach is able to statistically visualise differences in white matter tracts for a similar region in the right and left hemisphere. This approach can be extended to visualise connectivity distribution differences of one region of interest in two groups. Comparing one region in two groups (e.g. healthy and patient) has a high potential addition for research displaying in vivo white matter differences in addition to functional differences investigated with fMRI. This kind of research is thus able to expand our knowledge of the brain in health and diseases, in contrast to diagnostic imaging research concerned with the effect, efficiency and effectiveness of using imaging in individual patient care.

CHAPTER 9

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CHAPTER 10

Summary/ Samenvatting

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SUMMARY

Cerebral functions are lateralised in such a way that one hemisphere is more involved in or better structured to organise a specific function than the other hemisphere. Handedness is an obvious lateralised function of the brain, in which the left hemisphere outperforms the right for the fine-tuning of movements of the contralateral hand in right-handed persons, while it is the other way around for left-handers. As handedness corresponds with general cerebral asymmetry, it may serve as an indicator of general cerebral lateralisation. To perform motor actions into surrounding space, visual information of this environment is integrated with the planning of movements, i.e. visuomotor integration. This is a right dominant function, which involves visual areas, parietal areas and the right dorsal premotor area. Neurodegenerative diseases may also present with a lateralised symptom dominance. Parkinson's disease is such lateralised disorder showing disturbed movements on one side of the body more than the other side, which is still a mysterious but core characteristic of the disease. Furthermore, in Parkinson patients disturbances of right dominant visuomotor function have been reported, which may result in freezing of gait, a severely disabling but poorly understood symptom in Parkinson patients.

In this thesis, we addressed several aspects of lateralisation in Parkinson's disease. We aimed to (1) investigate lateralisation dominance of symptoms in Parkinson patients in relation to general cerebral asymmetry (indicated by handedness) and (2) investigate the mechanism behind freezing of gait in Parkinson patients by manipulating optic flow, mimicking circumstances during freezing of gait due to a narrow passage. In the latter topic, we expected to find an association between such freezing and left-sided Parkinson symptoms as a reflection of right hemisphere dysfunction. Studies concerning the second topic are described in chapters 4-7, while the first topic is treated in chapters 2-3. The studies that we described in these chapters will be summarised in the following paragraphs.

Chapter 2 and 3 addressed the subject of lateralisation of Parkinson symptoms in relation to cerebral asymmetry indicated by hand dominance. In chapter 2, we investigated the correlation between handedness and side of symptom onset in Parkinson patients in a retrospective database of about 1000 patients with Parkinson’s disease. However, only 30 percent of these patients were suitable for analyses as information about hand dominance was frequently missing. In the remaining sample, which was still quite large (N = 287), we demonstrated that right-handedness was associated with right-sided dominance of Parkinson symptoms. The results suggested an effect the other way around for left-handed

patients showing more left-sided dominance of Parkinson symptoms. The group of left-handed patients, however, was too small to draw reliable conclusions. The relation of right-handedness with more right-sided dominance of Parkinson symptoms might, however, still be questioned because in the literature various conclusions have been reported. Some other studies demonstrated a similar relationship, while others failed to do so. On the other hand, as no studies have reported an inverse relation, we thought that lack of power was the main problem why some studies failed to find a relation of hand dominance with the dominant side of symptoms.

To resolve both the issue of the small group of left-handed patients as well as the inconsistent literature concerning an association of right-sided symptom dominance with right-handedness, we performed a meta-analysis (chapter 3). A total of ten studies comprising 4405 patients with Parkinson's disease were included. We were able to demonstrate a substantial and statistically significant association between the dominant side of Parkinson symptoms and hand dominance. Right-handed patients showed a significant excess of about 60 percent for right-sided dominance of Parkinson symptoms, while the reverse was true for the left-handed patients with a significant excess of about 60 percent left-sided dominance of Parkinson symptoms. The dominant hemisphere thus appeared to be more prone to Parkinson's disease. Despite the definitively established relation, the cause of symptom lateralisation remains part of a mystery. We discussed some causal factors underlying the relation between handedness and dopamine asymmetry (chapter 2, 3 and 8). For instance, an asymmetrical increase of metabolic demand associated with handedness might lead to dopamine lateralisation due to negative consequences of oxidative stress in the corresponding dominant hemisphere. This would then lead to an increased vulnerability of the dominant hemisphere in Parkinson's disease, a topic which remains, however, open for further research.

Freezing of gait was hypothesised to be associated with left-sided symptom dominant Parkinson patients. This was based on previously shown right hemisphere involvement in visuomotor control and freezing of gait. We were unable to obtain support for this hypothesis from a retrospective assessment of our patient database (chapter 2). On the other hand, a prospective study by Giladi and others did provide support for it. We further approached this issue by an experimental strategy of testing visuomotor control in freezing of gait in Parkinson patients by manipulating optic flow. By narrowing wide-field flow, the approach of a narrow corridor was mimicked, a circumstance which is known to evoke freezing of gait (Chapter 4-6). By using this basic visual stimulus instead of a realistic virtual

reality, we were able to study specific visual stimuli characteristic for visuomotor related changes involved in freezing of gait including lateralisation differences. Radially expanding optic flow is a pattern of visual motion generated during forward locomotion. When presented to a stationary subject, wide-field optic flow evokes the illusion of forward self-motion. These effects illustrate an intimate relation between particularly this visual stimulus and motor processing underlying gait. Parkinson patients showed enhance responses to visual stimuli, which may either support or obstruct movement. The latter is clearly seen in freezing of gait, which may be provoked by the approach of a narrow passage. On the other hand, visual stimuli like optic flow provide an extra support for gait in Parkinson patients and are helpful to overcome freezing of gait. We hypothesised that narrowing optic flow, mimicking narrow passage induced freezing of gait, reduced the external support and thereby put more load on the internal generation of movement. The latter is particularly mediated through the medial premotor area. Furthermore, we expected that disturbances in premotor activation in Parkinson patients would be most clearly seen in patients with freezing of gait.

To behaviourally test our optic flow paradigm and to establish an effect of narrowing optic flow on gait in Parkinson patients, we conducted a treadmill experiment, which is described in chapter 5. Parkinson patients as well as healthy elderly controls walked on a treadmill while viewing wide optic flow and its manipulations presented on a screen in front of them. We demonstrated that narrowing wide optic flow resulted in gait disturbances in Parkinson patients, which was most pronounced in patients with left-sided dominant symptoms (i.e. most affected in the right hemisphere). We obtained further evidence for a right hemisphere involvement from the observation that poorer visuomotor abilities measured by the block design task, was related with a stronger deterioration of gait in Parkinson patients induced by narrowing wide optic flow.

To gain insight in the neuronal mechanisms by which optic flow influences motor related circuitry, we conducted an fMRI experiment in young healthy subjects while manipulating optic flow (chapter 4). We demonstrated that the dorsal functional visual stream up until the right dorsal premotor cortex was activated by wide-field "forward" optic flow, logically reflecting a pathway for externally triggered motor control. Medial prefrontal activation was shown when the flow field was narrowed, which we explained as internally generated actions when the external support for virtual locomotion falls away. The next experiment with elderly healthy controls showed that the external visuomotor pathway comprised similar visual areas with dorsal extension into the superior posterior areas, also most

pronounced in the right hemisphere. However, the extent of activation did not include the right dorsal premotor area (chapter 6). Similar to healthy young subjects, the elderly subjects showed activation of medial prefrontal areas, comprising the supplementary motor area (SMA) and pre-SMA during narrowing optic flow. This was considered to reflect a challenge for internal motor generation. An additional condition of stopping wide optic flow by deceleration that was employed in the elderly showed similar medial premotor activations. Parkinson patients, both with and without freezing of gait, were unable to recruit the (pre-)SMA, neither during narrowing nor during gradually stopping wide flow. This inability to internally take over movement generation when external support falls away was more pronounced in patients with than without freezing of gait. In the fMRI optic flow study in Parkinson patients and elderly subjects (chapter 6), we unexpectedly found activations pointing at a reduced attention to non-specific visual 'changes' in Parkinson patients again most pronounced in patients with freezing of gait. Finally, we showed that reduced visual motion processing occurred in combination with enhanced functional connectivity of the right motion sensitive area V5 with the distant medial frontal and cerebellar motor regions in Parkinson patients without freezing of gait. This bypassing of close (parietal) feedforward together with enhanced distant medial fronto-cerebellar feedforward processing was concluded to functionally underlie less fine-tuned responses to visual stimuli, i.e. inducing responses that are either too strong or too weak.

In a final experiment, we explored whether the connectivity distribution of the dorsal premotor cortex would provide an indication of a right lateralised visuomotor function. To that end, we employed probabilistic tractography and a novel approach to visualise and perform voxel-based statistics of group connectivity distributions between areas of interest. In healthy subjects, right lateralised visuomotor integration is particularly supported by the right dorsal premotor area. The latter indeed showed a connectivity distribution associated with that function, including visual and parietal areas (chapter 7). For the left dorsal premotor area we demonstrated a connectivity distribution in concordance with dominance for handedness and language, adding to the legitimacy of the right visuomotor results.

In conclusion, the results described in this thesis showed a standing discussion in the lateralisation by unequivocally demonstrating that the dominant hemisphere for handedness is more prone to become the dominant affected hemisphere in Parkinson's disease. The origin of this relation is still a mystery, but the establishment of this earlier frequently discussed correlation provides a strong motivation to formulate explanatory

hypotheses and set-up experiments addressing these hypotheses. Secondly, we showed that manipulation of the visual motion pattern optic flow, mimicking the approach of a narrow passage, induced more pronounced disturbance of gait in Parkinson patients with dominant right hemisphere impairment. We further showed that the enhanced vulnerability for these stimulus circumstances relies on a diminished right lateralised visuomotor network along with a decreased ability to substitute external stimulus driven by internal motor generation in patients. The reduced visual activation by wide-field optic flow in Parkinson patients occurred together with stronger connectivity of right visual motion area V5 with medial fronto-cerebellar circuitry, which pointed at a compensating feedforward mechanism in visuomotor planning. Aside from the visual motion effects, disturbances in the visual attention network pointed at the role of disturbed (covert) attention in freezing of gait in Parkinson patients together with altered feedforward processing.

SAMENVATTING

De Nederlandstalige samenvatting van dit proefschrift, met name bedoeld voor de lezer die niet onderlegd is in de neurowetenschappen, beschrijft in grote lijnen de achtergrond van de uitgevoerde onderzoeken, de verkregen resultaten en de conclusies welke daaruit kunnen worden getrokken.

Bewegingen worden aangestuurd door de grote hersenen. Dat is zo georganiseerd dat bewegingen van de rechter hand worden gecoördineerd door de linker hersenhelft en omgekeerd, die van de linker hand door de rechter hersenhelft. Bij de fijne afstelling van bewegingen worden de grote hersenen ondersteund door andere hersendelen zoals de kleine hersenen en diepe hersenkernen. Bijna alle mensen hebben een betere fijne afstelling van bewegingen van één hand ten opzichte van de andere, oftewel er is sprake van handvoorkeur. Hiermee is handvoorkeur een voorbeeld van een gelateraliseerde functie, wat wil zeggen dat de ene hersenhelft betere aansturing verzorgt of meer betrokken is bij de aansturing dan de andere hersenhelft. Het grootste deel van de mensen (± 90 procent) is rechtshandig wat betekent dat de linker hersenhelft dominant is voor fijne motoriek. In een klein deel van de bevolking (± 10 procent) is de linker hand beter in het uitvoeren van bewegingen dan de rechter hand. Zij hebben een tegenovergestelde lateralisatie van de handfunctie waarbij de rechter hersenhelft dominant is voor fijne motoriek.

Bewegingen dienen een doel en worden uitgevoerd in een omgeving. Stel, een blokje moet vastgepakt worden. Hiervoor is het nodig om te weten waar in de omgeving dat blokje zich bevindt. Door te kijken, kan het blokje gelokaliseerd worden. Ook tijdens het grijpen wordt de beweging afgesteld op dat wat gezien wordt. De hersenen controleren of de positie van de hand overeenkomt met de geplande beweging en zorgen voor een juiste afstelling tussen dat wat gezien wordt (visuele informatie) en de beweging (motore actie). Deze integratie van zien en bewegen wordt visuomotore integratie of controle genoemd. Deze visuomotore controle is een rechts gelateraliseerde functie, oftewel, de rechter hersenhelft speelt hierin een grotere rol dan de linker hersenhelft.

Hoewel reeds lang bekend is dat bepaalde hersenfuncties gelateraliseerd zijn, is hierover nog weinig bekend. Dit geldt zowel voor lateralisatie van functie in gezonde als disfunctie in zieke mensen. De ziekte van Parkinson is hiervan een kenmerkend voorbeeld, waarbij deze veelvoorkomende ziekte een stoornis van bewegen laat zien die aan één kant meer uitgesproken is. De ziekte begint aan één kant en gedurende het ziektebeloop blijft aan

deze kant de meest uitgesproken. De ziekte van Parkinson ontstaat door verlies van cellen in de hersenstam die de stof dopamine produceren, waarbij dit verlies dus ook aan één kant meer uitgesproken is. In dit proefschrift hebben wij een aantal aspecten van lateralisatie bij de ziekte van Parkinson onderzocht. Als eerste wilden wij de mogelijke relatie tussen de lateralisatie van Parkinson klachten en hersenlateralisatie aangegeven door handvoorkeur onderzoeken. Verder wilden wij het mechanisme onderzoeken dat ten grondslag ligt aan loopblokkades in Parkinson patiënten. De gedachte hierbij was dat lopen beïnvloed wordt door visuele prikkels, waarbij de rechter hersenhelft een dominante rol speelt in de wisselwerking tussen deze prikkels en de organisatie van beweging. Dit hebben wij onderzocht in een loopband experiment en met scans van de hersenactiviteit gedurende een taak. Dit zal verderop uitgelegd worden. Hier volgt het eerste deel, de relatie tussen hersenlateralisatie en de meeste aangedane kant bij Parkinson patiënten.

Zoals boven al kort werd opgemerkt, hebben Parkinson patiënten aan één lichaamszijde meer ziekte verschijnselen dan aan de andere zijde. Dit komt overeen met het verlies van dopamine productie door cellen in de diepe kernen in de hersenen. Hoewel deze asymmetrie een karakteristiek kenmerk is van de ziekte van Parkinson (zelfs zo opvallend dat men zich bij symmetrische ziekte extra achter de oren krabt of het wel de ziekte van Parkinson is), wordt nog niet begrepen hoe deze asymmetrie ontstaat. Omdat hand dominantie correspondeert met de algehele lateralisatie van de hersenen is handvoorkeur te gebruiken als algemene maat voor hersenlateralisatie. Door dit vervolgens te relateren aan de meest aangedane hersenhelft bij Parkinson patiënten, was het mogelijk om te kijken of hersenlateralisatie gerelateerd is aan de asymmetrie van de symptomen van de ziekte van Parkinson.

Wij toonden in een eigen patiëntengroep aan dat dit inderdaad het geval was voor rechtshandige patiënten, welke vaker meer Parkinson uitingen aan de rechter lichaamshelft bleken te hebben **(hoofdstuk 2)**. Voor linkshandige patiënten leek dit omgekeerd. De linkshandige groep was echter te klein om een betrouwbare uitspraak te doen. Deze onzekerheid kwam omdat linkshandigheid veel minder voorkomt. Omdat ook de relatie tussen rechtshandigheid en rechtszijdige dominantie van Parkinson symptomen niet overtuigend door alle voorgaande studies gevonden was, voegden we de resultaten van alle bekende studies samen. Dit resulteerde in een grote groep van in totaal 4405 patiënten waarmee definitief werd aangetoond dat rechtshandigen vaker (60 procent) rechtszijdig klachten krijgen, terwijl linkshandigen vaker (60 procent) linkszijdig klachten krijgen. De dominante hersenhelft voor handvoorkeur is dus duidelijk vatbaarder voor het

krijgen van de ziekte van Parkinson **(hoofdstuk 3)**. Hoewel de oorzaak van dit verband nog steeds niet bekend is, toont het bestaan van dit verband meer inzicht waar gezocht kan worden naar de oorzaak van de kenmerkende asymmetrie in de ziekte van Parkinson.

Het tweede deel van het proefschrift betreft onderzoek naar de wisselwerking tussen visuele beelden en doelgerichte bewegingen, waarbij dit onderzoek verder toegespitst is op het fenomeen van visuomotore controle en loopblokkades bij Parkinson patiënten. Tijdens het blokkeren van lopen, 'bevriezen', voelt het alsof de voeten vastgelijmd zijn aan de grond. Dit is een probleem met een grote impact voor patiënten, onder andere ook doordat ze frequenter vallen. Patiënten die de meeste symptomen aan de linker lichaamshelft hebben, hebben een sterker aangedane rechter hersenhelft. Gezien de rol van juist de rechter hersenhelft in visuomotore controle en eerdere aanwijzingen voor disfunctie van de rechter hersenhelft in loopblokkades, verwachtten we dat loopblokkades meer zouden voorkomen in patiënten met linkszijdige symptoom dominantie. Hoewel wij dit bij de retrospectieve studie met dossiergegevens van eigen patiënten niet aantoonden **(hoofdstuk 2)**, werd dit wel in een prospectieve studie door Giladi en collegae gevonden. We hebben de mogelijke relatie tussen visuomotore interacties en loopblokkades in Parkinson patiënten vervolgens onderzocht in een experiment waarbij we gebruik maakten van optische flow. Dit dynamische patroon van visuele waarneming ontstaat tijdens het lopen waarbij objecten die veraf zijn in het centrum van het gezichtsveld worden weergegeven, terwijl objecten wanneer ze dichtbij komen met toenemende snelheid naar de randen van het gezichtveld verplaatsen. Deze optische flow is in abstracte zin nog het beste te vergelijken met filmpjes die het voorbijtrekken van sterren weergeven voor personen die in een ruimtevaartuig recht vooruit kijken. Omgekeerd geldt dat wanneer dit visuele stimulus patroon op een scherm aangeboden wordt aan een stilstaand persoon het de illusie geeft van voorwaartse zelfbeweging. Optische flow ontstaat automatisch tijdens lopen en ondersteunt het lopen voor Parkinson patiënten meer nog dan dit voor gezonde mensen reeds het geval is. Aan de andere kant worden patiënten met de ziekte van Parkinson ook sterker negatief beïnvloed door het zien van omgevingsfactoren. Met andere woorden, visuele informatie kan het lopen blokkeren bij Parkinson patiënten. Dit kan worden uitgelokt door bijvoorbeeld het naderen van een smalle doorgang (zoals een deurpost). Tijdens het naderen van een smalle doorgang wordt de optische flow versmald. Er blijft alleen nog een centraal deel zichtbaar wat door de smalle doorgang heen gezien kan worden. Doordat optische flow versmalt, vermindert ook de externe ondersteuning die brede optische flow heeft op lopen. Dit noodzaakt tot het overstappen op interne generatie van bewegen. In abstracte vorm kunnen deze omstandigheden nagemaakt

worden door het beeld met optische flow te versmallen. Dit hebben we gedaan in een loopband studie en een studie die de hersenactiviteit meet door middel van functionele MRI scans. Wij verwachtten dat het versmallen van optische flow door het verminderen van de externe ondersteuning in gezonden zou resulteren in een verschuiving van aansturing van bewegingen door externe stimulatie naar intern (uit zichzelf) gegenereerde beweging, zichtbaar in de hersengebieden betrokken bij externe en interne generatie van bewegingen. Aangezien interne generatie van bewegen juist een kenmerkende stoornis is in Parkinson patiënten, verwachtten we dat patiënten een verstoring van deze activatie hebben wat dan ook resulteert in een verslechtering van het lopen in patiënten. Gezien dat de rechter hersenhelft meer dan de linker hersenhelft betrokken is bij visuomotore interacties, verwachtten we dit terug te zien in de resultaten van onze onderzoeken.

In de loopband studie zagen we inderdaad, zoals verwacht, dat het versmallen van optische flow het looppatroon verslechterde in patiënten met de ziekte van Parkinson in vergelijking tot gezonde ouderen **(hoofdstuk 5)**. Dit was meer uitgesproken bij Parkinson patiënten met een meer aangedane rechter hersenhelft, passend bij een visuomotore disfunctie van de rechter hersenhelft. Verdere steun voor dit laatste kwam ook doordat een slechtere visuomotore functie, gemeten met een blokpatronen taak, correleerde met een versterkte negatieve invloed van de optische flow versmalling op het lopen in Parkinson patiënten.

Door middel van het maken van een functionele MRI scan, een scan die de hersenactiviteit gedurende een taak laat zien, zagen we inderdaad dat gezonde personen een netwerk voor externe generatie van beweging activeerden gedurende de brede optische flow **(hoofdstuk 4 en 6)**. Dit rechts dominante netwerk bestond uit visuele gebieden inclusief het gebied V5 in de achterste hersenkwab (occipitaal kwab) dat gespecialiseerd is in verwerking van visuele bewegingen. Verder deden gebieden mee in de daarvoor gelegen pariëtale hersenkwab. Voor jonge gezonden was deze activatie meer uitgesproken dan voor gezonde ouderen en was er bij de gezonde jongeren tevens activatie zichtbaar in het rechter dorsale premotore gebied. Samen tonen deze gebieden een netwerk dat betrokken is bij aansturen van bewegingen onder sterke invloed van externe informatie (stimuli). Voor dit laatste gebied (het rechter dorsale premotore gebied) vonden we tevens meer verbindingen met visuele en pariëtale gebieden dan het overeenkomstige linker gebied **(hoofdstuk 7)**. Dit patroon van verbindingen weerspiegelt dat het rechter dorsale premotore gebied informatie uit zowel het linker als het rechter deel van de omgeving verwerkt in respectievelijk de rechter en de linker hersenhelft verzamelt om sensore informatie met

bewegingen te integreren. Dit is in overeenstemming met een rechts gelateraliseerde visuomotore functie. De versmalling van optische flow gaf een verschuiving naar gebieden betrokken bij interne bewegingsgeneratie. Deze gebieden liggen op de middengrens van de voorste hersenkwab, de frontaal kwab, en zijn bekend als de supplementaire motore en pre-supplementaire motore gebieden. Het lukte Parkinson patiënten niet om het wegvallen van de externe ondersteuning op te vangen door activatie van deze gebieden voor interne bewewingsgeneratie **(hoofdstuk 6)**. Dit was het meest uitgesproken in Parkinson patiënten met loopblokkades. Onverwachts vonden we tevens dat 'onbewuste' aandacht voor visuele veranderingen verminderd was in patiënten met de ziekte van Parkinson. Ook dit was het meest uitgesproken in patiënten met loopblokkades. Als laatste toonden we aan dat bij Parkinson patiënten verminderde activatie van visuele gebieden samenging met een verhoogde synchronisatie van de activatie van het rechter visuele bewegingsgebied V5 met het pre-supplementaire motore gebied in de frontaal kwab en de kleine hersenen. De gebieden in de pariëtaal kwab worden daarbij overgeslagen. De pariëtaal kwab is betrokken bij het voorspellen van consequenties van bewegingen. Hoewel het pre-supplementaire motore gebied en het cerebellum hierbij ook betrokken zijn, doen zij voorspellingen en correcties minder precies. Dit kan verklaren dat reacties op visuele stimuli doorschieten in Parkinson patiënten. Met andere woorden, reacties op visuele stimuli zijn te sterk of te zwak.

In dit proefschrift concluderen wij, ten eerste dat de hersenhelft die de dominante hand aanstuurt vatbaarder is voor het ontstaan van de ziekte van Parkinson. Hoewel de oorzaak van deze relatie nog onopgehelderd blijft, zorgt het aantonen van deze relatie voor een aanknopingspunt om verder onderzoek te doen naar deze relatie en de oorzaak van de kenmerkende lateralisatie van de ziekte van Parkinson. Ten tweede zagen we dat het nabootsen van de omstandigheden die loopblokkades kunnen uitlokken leidt tot verslechtering van lopen bij voornamelijk Parkinson patiënten waarbij de rechter hersenhelft het meest aangedaan is. Verder hebben we laten zien dat brede optische flow zorgt voor activatie van een rechts dominant hersennetwerk betrokken bij externe generatie van beweging. Daarentegen gaf vermindering van de externe ondersteuning door optische flow activatie van gebieden betrokken bij interne generatie van beweging in gezonden. Parkinson patiënten lukte het niet om deze overstap te maken naar de gebieden voor interne bewegingsgeneratie op het moment dat de optische flow wegviel. Naast deze visuomotore effecten, speelden verstoringen in 'onbewuste' aandacht voor visuele veranderingen en veranderde predictienetwerken tevens een rol in loopblokkades bij Parkinson patiënten.

List of abbreviations

ANOVA	=	analysis of variance
BA	=	Brodmann's area
BOLD	=	blood oxygen level dependent
CI	=	confidence interval
DTI	=	diffusion tensor imaging
ext	=	extent
fMRI	=	functional magnetic resonance imaging
FN	=	narrow-field flow
FtN	=	transition of wide forward flow to narrow forward flow
FtS	=	transition from wide forward flow to a wide static dot field
FW	=	wide forward flow
FWE	=	family wise error
FOG	=	freezing of gait
HC	=	healthy control
inf	=	inferior
IPS	=	intraparietal sulcus
L-handed	=	left-handed
M-H	=	Mantel-Haenszel
med	=	medial
mm	=	millimetre
MMSE	=	mini mental state examination
MNI	=	Montreal neurological institute
MRI	=	magnetic resonance imaging
ms	=	millisecond
N	=	number
PD	=	Parkinson's disease
PD_FOG	=	PD patients with FOG
PD_nFOG	=	PD patients without FOG
PDL	=	PD with left-sided symptom dominance
PDR	=	PD with right-sided symptom dominance
PET	=	positron emission tomography
PMd	=	dorsal premotor cortex
PPI	=	psychophysiological interaction
OR	=	odds ratio
R-handed	=	right-handed
Rtn	=	transition of wide reversed flow to narrow reversed flow

RW	=	reversed wide flow
ROI	=	region of interest
sc	=	same cluster
SD	=	standard deviation
SE	=	standard error
StN	=	transition of wide stationary field to narrow stationary field
SW	=	wide stationary field
SN	=	narrow stationary field
SMA	=	supplementary motor area
symp	=	symptomatic
TE	=	echo time
TR	=	repetition time
y	=	year(s)
UPDRS	=	unified Parkinson's disease rating scale
WAIS	=	Wechsler adult intelligence scale

Dankwoord

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Ik zou graag de Universiteit Groningen en specifiek de Junior Scientific Masterclass (JSM) Groningen bedanken voor het aanbieden van de vele onderzoeksgerichte cursussen gedurende de gehele duur van de studie geneeskunde. Dit heeft niet alleen mijn interesse voor onderzoek geprikkeld, maar mij tevens voorzien van veel relevante kennis. Zeker niet onbelangrijk, is door hen de mogelijk gecreëerd om een MDPhD traject te doen.

Één van deze cursussen van de JSM heeft tevens geleidt tot de vraag van één van de docenten, Huib Burger, of ik interesse had in een proefproject bij de psychiatrische epidemiologie. Hoewel ik reeds van plan was om later te kijken of ik een proefproject zou kunnen doen bij de neurologie, heb ik dankbaar gebruik gemaakt van het aanbod. Onder leiding van Huib Burger, heb ik zowel mijn interesse en kennis in statistiek verder verstevigd als ook mijn eerste artikel geschreven. Huub, tevens bedankt voor het meedenken bij de meta-analyse.

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gedetailleerde kennis van de anatomie van het brein gezorgd dat deze eigenschappen bij mij versterkt werden.

Prof. dr. Leenders, beste Nico, zonder promotor kan er geen proefschrift komen. Ik ben blij dat jij deze rol op je hebt willen nemen. Daarnaast waardeer ik je kritische blik op de verschillende manuscripten.

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Omdat soms ook gedragmatige data, in mijn geval verkregen door een loopband studie, van belang is om hersenactivaties in een beter perspectief te zetten, heb ik samengewerkt met de afdeling bewegingswetenschappen. Beste prof. dr. At Hof, hartelijk dank voor het meedenken in deze studie en de hulp bij het analyseren in matlab. Wim Kaan, de professionele technische ondersteuning die jij verzorgde was erg goed. Jij hebt gezorgd dat de stimuli die ik aanbood via de laptop correct gekoppeld werden aan de meetgegevens van de loopband.

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Peter, tevens paranimf, wij vormen een goede combinatie. Om mijn dank te uiten, zijn dan ook geen woorden nodig.

Resume/ Curriculum vitae

RESUME

Anouk van der Hoorn was born on 16 November in Zweeloo. She received her secondary education at the dr. Aletta Jacobs college in Hoogezand and graduated in 2005. She started with her medical training the same year at the university of Groningen. Anouk received her medical degree with honour in 2012. Early during her study, in 2006, growing interest in functional MRI resulted in research at the neuroimaging centre in Groningen. A passion was born, which resulted in two other research projects. Many courses of the junior scientific masterclass (JSM) program of the University of Groningen contributed to her growing scientific knowledge. In 2008, she started with her scientific internship at the department of Neurology in Groningen, one again she used functional MRI. This was the start of a fruitful PhD trajectory in which she combined the last years of her medical training with her PhD research. This resulted in this thesis, the lateralisation of Parkinson symptoms and visuomotor control in gait. At present, Anouk receives her training in radiology at the department of radiology in the University Medical Centre Groningen (UMCG).

CURRICULUM VITAE

Anouk van der Hoorn werd geboren op 16 november 1986 te Zweeloo. In 2005 haalde zij haar gymnasium diploma aan het dr. Aletta Jacobs college te Hoogezand. In datzelfde jaar startte zijn met de studie geneeskunde aan de Rijksuniversiteit Groningen. Anouk voltooide haar studie geneeskunde cum laude in 2012. Vroeg tijdens de studie, in 2006, raakt zij geïnteresseerd in functionele MRI en begon met onderzoek op het neuroimaging centrum in Groningen. Dit was het begin van een groeiende interesse in wetenschappelijk onderzoek en werd snel gevolg door een tweetal andere onderzoeksprojecten. De vele cursussen van het junior scientific masterclass (JSM) programma van de rijksuniversiteit Groningen droegen bij in het opbouwen van kennis van wetenschappelijk onderzoek. In 2008 begon ze met haar wetenschappelijk stage onder leiding van dr. De Jong op de neurologie in Groningen, wederom met functionele MRI. Dit was het begin van een MDPhD-traject, wat geresulteerd heeft in dit proefschrift naar de lateralisatie van Parkinson symptomen en loopblokkades bij Parkinson patiënten. Momenteel is Anouk in opleiding tot radioloog bij de afdeling radiologie in het Universitair Medisch Centrum Groningen (UMCG).

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