NEUROSCIENCE
RESEARCH ARTICLE
C. Vriend et al. / Neuroscience 386 (2018) 295–308

# Global and Subnetwork Changes of the Structural Connectome in *de novo* Parkinson's Disease

**Chris Vriend,[a,b]* Odile A. van den Heuvel,[a,b] Henk W. Berendse,[c] Ysbrand D. van der Werf[b] and Linda Douw[b,d]**

[a] *Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Psychiatry, Amsterdam Neuroscience, De Boelelaan 1117, Amsterdam, Netherlands*

[b] *Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Anatomy & Neurosciences, Amsterdam Neuroscience, De Boelelaan 1117, Amsterdam, Netherlands*

[c] *Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Neurology, Amsterdam Neuroscience, De Boelelaan 1117, Amsterdam, Netherlands*

[d] *Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, MA, USA*

**Abstract—Parkinson's disease (PD) is a neurodegenerative disorder characterized by widespread neuropathological involvement of cortical and subcortical brain areas, which may therefore affect the structural brain network or 'connectome'. Using diffusion tensor imaging (DTI) and graph analysis we studied the structural connectome of medication-naïve PD patients. DTI was acquired in 23 early-stage PD patients and 38 age, sex and education matched healthy controls. We studied global, subnetwork and local network topology using the Brainnetome atlas. At the subnetwork level we focused on the default-mode, frontoparietal, sensorimotor and attention networks. Graph measures included global efficiency, clustering coefficient and betweenness centrality. PD patients showed lower global efficiency and global clustering coefficient compared with healthy controls. This was also evident in all four subnetworks. These findings were largely replicated with the automated anatomical labeling (AAL) atlas and robust across a large range of thresholds. These results suggest that the wiring of the structural brain network of early-stage medication-naïve PD patients is altered relative to healthy controls in such a way that it allows for less integration (global efficiency) and segregation (clustering coefficient) of information processing.**


**Key words: Parkinson's disease, graph theory, structural connectome.**

## INTRODUCTION

In Parkinson's disease (PD), neurodegeneration not only affects dopaminergic projections from the substantia nigra, but also impacts the integrity of white matter fiber bundles (Weingarten et al., 2015). Diffusion tensor imaging (DTI) is currently the method of choice to study white matter integrity *in vivo*. The majority of previous DTI studies in PD have focused on specific tracts or regions of interests (Weingarten et al., 2015). To fully understand the complexity of the pathophysiology of brain disorders, however, whole-brain network architecture should be investigated (Sporns, 2012). Graph analyses allow us to represent the brain as a 'connectome' (Sporns et al., 2005), consisting of nodes (brain areas) and edges (connections). Subsequently, the properties of this network can be further understood using neurobiologically meaningful graph indices (Sporns et al., 2005), such as for example global efficiency and clustering coefficient. Global efficiency provides a measure for how easily information is transmitted through the network, while clustering coefficient measures the tendency of neighboring nodes to cluster together (Bullmore and Sporns, 2009). See 'experimental procedures' for more details. Previous studies that investigated structural brain networks cross-sectionally between PD patients and healthy controls have reported conflicting results with regard to whole-brain clustering coefficient and global efficiency (Kamagata et al., 2018; Li et al., 2017; Nigro et al., 2016; Tinaz et al., 2017; Wen et al., 2017). More research has been performed into the *functional* connectome. At the whole-brain level the results of functional MRI (fMRI) and magnetoencephalography (MEG) studies have also reported mixed results with some reporting lower global efficiency and clustering coefficient in PD patients compared with healthy controls (Olde Dubbelink et al., 2014; Sang et al., 2015; Skidmore et al., 2011), while others found no differences (Baggio et al., 2015; Luo et al., 2015; Tinaz et al., 2017).

*Correspondence to: C. Vriend, Amsterdam UMC, Vrije Universiteit Amsterdam, Department of Anatomy and Neuroscience, p/a sec. ANW O|2, PO Box 7007, 1007MB BT Amsterdam, Netherlands. Fax: +31-20-4448054.
E-mail address: c.vriend@vumc.nl (C. Vriend).

https://doi.org/10.1016/j.neuroscience.2018.06.050
0306-4522/

The abovementioned studies focused almost exclusively on whole-brain (global) parameters or regional graph indices. The brain consists, however, of multiple large-scale distributed subnetworks that encompass (functionally) connected brain areas during both rest and the execution of tasks (Park and Friston, 2013). Functional connectivity studies in PD have shown disruption of various subnetworks, including the default-mode network (DMN), fronto-parietal network (FPN), and attention networks (AN), and dysfunction of these subnetworks correlated with cognitive impairments (Baggio et al., 2015;Chen et al., 2015; Putcha et al., 2016; Trujillo et al., 2015). Moreover the strength of the connectivity between subnetworks, for example the DMN and FPN, is associated with cognitive performance (Baggio et al., 2015; Douw et al., 2016). The integrity of subnetworks is dependent on the white matter tracts that connect the different areas of the brain (Goni et al., 2014; Hermundstad et al., 2013; Honey et al., 2009). In the present study, we not only focused on global and local measures, but also – for the first time – investigated graph indices of structural connectivity at the subnetwork level. Mapping of each of those levels is necessary to get a full understanding of the human connectome (Sporns, 2011) and the connectomic alterations that occur due to PD pathology. Studying the structural connectome at the subnetwork level also allows for investigation of the topology of groups of brain areas that are known to be linked structurally and functionally and associated with specific cognitive and other behavioral functions (Menon, 2011; Crossley et al., 2013; Jacobs et al., 2018; Reineberg et al., 2015; van den Heuvel et al., 2009). We specifically focused on the DMN, FPN, AN and – given the predominance of motor symptoms in PD – the sensorimotor network (SMN). All PD patients were naïve for dopamine replacement therapy. We used two separate atlases, the brainnetome (BNA) and automated anatomical labeling (AAL) atlas, to define the nodes. Probabilistic tractography was used to define the strength of the edges between these nodes. Based on previous studies, we hypothesized that medication-naïve PD patients would exhibit lower global and subnetwork efficiency, especially in the DMN and FPN, compared with healthy controls. We additionally expected lower clustering coefficient at the global and subnetwork level.

## EXPERIMENTAL PROCEDURES

### Subjects and measurements

PD patients were recruited by physicians of the outpatient clinic for movement disorders of the VU University medical center (Amsterdam, The Netherlands) and other regional hospitals in the context of a larger study on PD (Gerrits et al., 2015; Vriend et al., 2015). Patients were naïve for dopamine replacement therapy and recently diagnosed (on average 10 weeks prior to the study) by a movement disorder specialist according to the UK Parkinson's disease Brain bank criteria for idiopathic PD (Daniel and Lees, 1993). We used the Unified Parkinson's Disease Rating Scale motor section (UPDRS-III) (Fahn et al., 1987) and Hoehn and Yahr stage (Hoehn and Yahr, 1967) to assess disease severity and disease stage, respectively. Diagnosis was confirmed after on average three years in 17 out of 23 PD patients during a follow-up study (Trujillo et al., 2015). Exclusion criteria were current use of centrally active drugs, all current or previous severe traumatic head injuries and neurological (other than PD) or psychiatric disorders, including substance use disorders. According to the Mini-Mental State Examination (MMSE), none of the participants showed signs of severe cognitive impairments (all MMSE-scores > 24). Healthy controls were recruited through advertisements. Exclusion criteria for healthy controls were (a history of) severe traumatic head injury or other neurological or psychiatric disorders, including alcohol or drug dependence and current use of centrally active drugs. The Dutch adult reading test (Schmand et al., 1991) was administered to provide a measure of pre-morbid intelligence. Participants additionally performed a computerized version of the tower of London task (ToL). Details of this task are provided elsewhere (Trujillo et al., 2015). Briefly, participants saw two configurations of three colored beads on three vertical posts; a start configuration and a target configuration. Participants were instructed to count the minimal number of steps that were required to go from the start to the target configuration, bearing in mind the following rules: one bead can be moved at a time and a bead can only be moved when there is no other bead on top of it. The number of required minimal steps ranged from one to five (i.e. five difficulty levels). Participants responded by pressing the appropriate key on the keyboard. The task consisted of 100 trials and lasted between 20 and 25 min. Accuracy and reaction times were recorded per difficulty level. We used the mean accuracy and over all five difficulty levels as outcome measure (Kaller et al., 2016). The 15-min delayed recall of the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) was administered as a measure for memory performance. The delayed recall score on the RAVLT was adjusted for sex, age and/or educational level, and transformed to *t*-scores, using the Dutch norms by (Schmand et al., 2012). All methods were performed according to the declaration of Helsinki, including obtaining written informed consent from all participants. The study was approved by the medical ethics committee of VU University medical center.

### Image acquisition

MRI was performed on a Signa HDxT 3 T MRI scanner (General Electric, Milwaukee, U.S.). The scanner was equipped with an eight-channel head coil with foam pads to immobilize the head and reduce motion artifacts. Diffusion weighted echo-planar imaging was collected in 30 diffusion weighted ($b$ = 1000 s/mm$^2$) and five non-diffusion weighted ($b$ = 0 s/mm$^2$) volumes with 49–51 contiguous axial slices, 2 × 2 × 2.4 mm$^3$ voxels, TR = 14,000 ms and TE = 85 ms. Structural images were acquired using a 3D sagittal $T_1$-weighted sequence (TI = 450 ms, TE = 3 ms, voxel size 1 × 0.9 77 × 0.977 mm, 172 slices) for co-registration and parcellation.