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2016

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citation for published version (APA)

Javor-Duray, B. N. (2016). *Patterns of neuronal synchrony in parkinsonism: depicting changes in a rat model*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Chapter 5

General discussion

Parkinson's disease (PD) is a chronic neurodegenerative disorder that presents a wide range of motor and non-motor symptoms that have a significant and negative impact on the quality of life of patients. The underlying neuropathology includes the involvement of a group of subcortical nuclei, the basal ganglia. Technical advances over the past decades have provided scientists with the tools to investigate how these deep brain structures function in PD patients. Both invasive recordings from deep brain structures and non-invasive recordings (EEG and MEG) revealed that oscillatory brain activity is altered in PD in close association with motor impairment, cognitive decline, and the effectiveness of therapeutic interventions. However, in human subjects there are severe limitations to exploring the possible origin and mechanisms behind these observations. Animal models offer a range of possibilities to investigate brain activity patterns associated with parkinsonism. They enable us to study the disorder beyond the limitations of human studies: to study parkinsonism without the effects of chronic medication; to explore the function of deep brain structures/basal ganglia (other than the ones used for DBS), also at early stages of the disease; to test the effects of pharmacological agents (not used in existing conventional treatments) and to investigate the neurophysiological correlates of complex movement patterns. Overall, there is now a growing body of literature describing the neurophysiological correlates of parkinsonism in both PD patients and animal models of PD. However, it is as yet not fully understood how the changing patterns in neuronal synchrony evolve over the course of the disease in PD, how these patterns are expressed at the cortico-cortical level, and in what way directional influences between brain regions are affected.

The overall aim of this thesis was to gain a better insight in the changing patterns of neuronal synchrony in response to experimentally induced dopaminergic cell loss in the rat. To this aim, we simultaneously recorded brain activity from the basal ganglia (subthalamic nucleus (STN) and striatum) and the cerebral cortex in the awake, unrestrained behaving hemiparkinsonian rat, following a unilateral 6-hydroxydopamine (6-OHDA) lesion.

Increased synchronization and reorganization of directional influences between cortex and basal ganglia

The results of the experiments in the present thesis describe novel traits of the neurophysiological changes in experimental parkinsonism in the rat using three methodological approaches. First, the analysis of changes in local oscillatory brain activity (relative power) revealed increased resting-state power in the beta frequencies in most brain regions we recorded from (chapters 2, 3 and 4). For convenience, 'beta' indicates 15-40 Hz, an extended definition of beta frequencies to include the most affected frequencies in both rodent models and PD patients [1–6]. As expected, there were clear differences between

hemispheres: in the neurotoxin-lesioned hemisphere, most cortical (primary motor cortex, secondary whisker-related motor area, primary forelimb motor area) and all basal ganglia regions (STN, striatum) presented a peak in the power spectrum around 30 Hz, as described previously for some cortical and basal ganglia sites in this rat model [7–9]. Movement related activity revealed different changes: the increase in beta relative power was restricted to the lesioned hemisphere (chapters 3 and 4), an asymmetry previously described at the level of cortex and basal ganglia [9, 10]. Thus, we confirmed the presence of increased beta power in the hemiparkinsonian rat model and extended these findings to a greater number of cortical areas [3–5, 7, 8, 10–13].

The second approach was to describe the synchronization of brain activity between distributed brain regions during the development (chapter 2) and after the completion of dopaminergic degeneration (chapters 2, 3 and 4). To reduce potentially biasing effects of volume conduction, a phase-based measure of functional connectivity was applied: the Phase Lag Index (PLI; chapters 2, 3 and 4, [14, 15]). The most conspicuous increments in resting-state functional connectivity occurred in the beta band and involved cortico-cortical connectivity within and between hemispheres, and cortico-subcortical connectivity, in line with previous findings in the same animal model [3, 5, 12]. In accordance with previous observations, an increase in beta functional connectivity was also present in the walking condition [5, 12, 13]. However, in comparison to the resting state, this increased connectivity pattern was less widespread and involved fewer area combinations (chapter 3).

The third approach was to assess changes in directional influences between brain regions using Granger causality in response to the dopaminergic cell loss (chapters 2 and 3). We observed increased directional influences between motor cortex and the basal ganglia, which were bidirectional for the STN and the ipsilateral motor cortex (chapter 2). By contrast, the striatum developed into a ‘receiver’ of directional influences from a wide range of cortical areas (mostly from the non-lesioned hemisphere; chapter 3). These results are in accordance with most literature suggesting a cortical drive towards the basal ganglia in the rodent model of PD [16], and also the notion that the cortico-subthalamic relationship might be of a bidirectional nature [12, 17]. In addition, we detected a remarkable increase of Granger causal influences from the non-lesioned towards the lesioned hemisphere after the 6-OHDA lesion that involved even more area combinations during locomotion.

Taken together results, the rat model used in this thesis allowed to expand on findings in previous studies by recording simultaneously and throughout the development of the 6-OHDA lesion from multiple cortical and subcortical regions, and by using unbiased methods to analyse functional (directional) connectivity between brain regions. To begin with, the dynamic evolution of neurophysiological changes over time (chapter 2) showed changes both in relative power and coupling in the beta band, in line with previous studies [4, 5, 12, 18]. In our experiments, interhemispherical synchronization between bilateral

motor cortices emerged prior to the increases in the local oscillatory brain activity (power). This may suggest that the dynamic interactions between (relatively) distant brain areas are more sensitive to the loss of nigrostriatal dopamine than the strength of local oscillatory activity. In chapter 3 we report that the increased beta peak in the power spectrum was restricted to the lesioned hemisphere, whereas the changes in both functional (PLI) and effective (Granger causality) connectivity involved numerous brain regions in both hemispheres. In the walking condition, beta synchronization was not as widespread as in the resting state. By contrast, the increased directional flow from the non-lesioned towards the lesioned hemisphere was more widespread during walking, which might imply that the increased directional influences towards the lesioned hemisphere are part of a compensatory process, that gains importance during locomotion (chapter 3). Moreover, reciprocal directional influences are detected between motor cortex and striatum in intact, behaving rats [19], which seem to be drastically altered after nigrostriatal dopaminergic depletion.

Does the hemiparkinsonian rat model reflect neurophysiological changes observed in Parkinson's disease patients?

The presented results allow us to draw (albeit sometimes limited) comparisons to observations in PD patients. First, the increase in beta power in the 6-OHDA lesioned rat is reminiscent of the increased local oscillatory activity in the beta band recorded from the STN and the motor cortex in PD patients [1, 2, 20, 21]. By contrast, in a longitudinal study MEG recordings have revealed that over the course of the disease (starting from newly diagnosed patients) local power spectra shift towards lower frequencies (<10 Hz) with a relative decrement of higher frequency activity [22–24]. This discrepancy might first of all be explained by differences between species: the frequency bands affected by the parkinsonism may differ between humans and rodents [9, 25]. Perhaps more importantly, the time course of development of the dopaminergic lesion is different: a few weeks in the rodent model compared to decades in patients. Moreover, in humans the underlying neuropathology is more complex, involving systems other than the dopamine system, which further limits the generalizability of the results obtained in the rat model to PD patients. Another potential explanation for the differences in results between studies in rodents and humans may involve the recording method used: in the rats we recorded LFPs from a relatively small population of neurons, whereas MEG signals in humans reflect the activity of larger neuronal populations. This is particularly relevant as power spectral changes are highly variable from one area to another (chapters 3 and 4), an observation supported by electrocorticographical recordings from PD patients [26]. Whereas the data presented in this thesis highlight local changes in neuronal activity, human studies provide a more generalized picture of changes in oscillatory brain activity [22, 27, 28].

The second phenomenon involves the changes in synchronization between distributed brain areas, i.e. functional connectivity. The increase in functional connectivity in the beta band we observed in the dopamine-depleted rat echoes the increased cortico-cortical beta synchronization reported in humans [29, but see 30]. The model data in this thesis suggests that the increased beta synchronization over a wide range of cortical areas may stem from the dopaminergic cell loss in the nigrostriatal system. The finding that this kind of beta coupling is only detectable with chronic disturbance of the dopamine system supports the relevance of our findings to PD patients [4, 5, but see 31]. Increased beta band synchronization was also detected between the basal ganglia and cortex in PD patients, which is in general terms consistent with our findings in the 6-OHDA lesioned rat [2, 32, 33]. In line with our observations in chapter 2, invasive recordings from the basal ganglia revealed increased oscillatory coupling between multiunit/spike activity in the STN and central/motor cortical areas in PD patients [21, 34]. Human studies combining STN and surface measurements revealed that the cortical brain area most coherent with the STN is the motor cortex [21, 35]. The findings in this thesis suggest that this is not the case for activity recorded from the striatum, which was synchronous with activity from functionally diverse cortical areas.

Another approach to study interactions between distant brain areas involves the analysis of directional connectivity. Numerous studies have shown that cortical areas drive the basal ganglia [2, 32, 36, 37] but there are also indications that the interaction between cortex and basal ganglia might be bidirectional [36, 37]. Our findings in the hemiparkinsonian rat model of increased bidirectional causal influences between motor cortex and STN in the lesioned hemisphere are in support of the latter option. Interestingly, the changes in directionality were not restricted to the beta frequencies, but also involved the gamma band. Directionality pattern changes in the gamma band have also been observed in PD patients, but in a behavioural condition quite different from the motor activity (walk) in the present study: patient recordings were performed in a period of temporary abstinence from dopaminergic medication during finger tapping [36]. It is also worth noting that asymmetric directional influences are also present at the level of basal ganglia (STN) in PD patients, in line with our findings showing increased directionality from the non-lesioned towards the lesioned hemisphere [38].

In conclusion, we were able to confirm several neurophysiological features characteristic of PD in the 6-OHDA lesioned rat. However, to reliably compare the findings in the rodent model to observations in PD patients, a number of interspecies and methodological considerations have to be taken into account. Patterns of neuronal synchrony are dynamically changing over the course (often decades) of PD. Increased cortico-cortical coupling is an early-stage phenomenon [23, 24, 30, 39, 40]. During the development of the nigrostriatal dopamine loss in the unilaterally 6-OHDA lesioned rat we

detected significantly increased interhemispheric cortico-cortical synchronization, first at slightly lower frequencies with a peak frequency at ~ 25 Hz that later shifted to ~ 30 Hz when the dopaminergic cell loss was complete. These observations to some extent resemble the observations in PD patients: increased functional connectivity was found in the alpha frequency band in patients soon after the diagnosis of PD, and in the beta frequency band in more advanced stages of the disease [30, 41]. This implies that nigrostriatal dopaminergic degeneration plays an essential role in the dynamic evolution of functional connectivity changes in PD.

Beta activity: friend or foe?

Observations of increased beta activity and excessive synchronization in the beta band in human and experimental parkinsonism have contributed to the concept of ‘anti-kinetic’ beta activity [42]. In healthy individuals, beta activity is reduced before movement onset and ‘pro-kinetic’ gamma activity arises. This pattern is disturbed in PD patients: resting state beta activity is diminished to a lesser extent or later when patients initiate a movement [33, 43–46]. Consistent with this notion, beta activity and synchronization are reduced by dopaminomimetic medication or deep brain stimulation [29, 47, 48]. However, as more evidence accumulates, the exclusive detrimental role of beta activity is questioned. Beta activity seems to be associated to bradykinesia, however its causal relationship to slowing movements is debated [6, 49–54]. Although deep brain stimulation at beta frequencies potentiates bradykinesia in patients [55], beta frequency stimulation of the STN in healthy rodents and primates does not induce brady-, or akinesia [56]. In line with the latter findings, targeted optogenetic modulation of STN neurons does not induce behavioural changes [57], suggesting that altered STN activity per se does not lead to changes in motor behaviour. The findings in this thesis support this view by demonstrating the involvement of multiple cortical areas in the neurophysiological changes induced by experimental parkinsonism. Moreover, the early appearance of increased interhemispheric synchronization during the development of nigrostriatal dopaminergic degeneration (chapter 2) suggests that dynamic interactions between (relatively) distant areas might be an early adaptive mechanism in response to the induced pathology. To take it one step further, Figure 4 in chapter 3 depicts the lesion-induced changes over multiple brain areas: a widespread increase in beta band synchronization in the lesioned animals at rest, in combination with increased directional influences from the non-lesioned towards the lesioned hemisphere. This stands in contrast to the less prevalent increases in functional connectivity [44, 58] and more widespread increases in directionality in the walking condition. Based upon our observations, it seems reasonable to hypothesize that beta activity, which arises after nigrostriatal dopaminergic cell loss, is not exclusively malignant, and that the changes in directional influences might be necessary or even beneficial for the execution of complex motor activity (walking). Still, whether the observed patterns are

related to a compensatory mechanism or pathological disinhibition remains to be determined.

Methodological considerations

For the studies described in the present thesis we developed an awake, unrestrained behaving rat model of PD enabling multisite chronic neurophysiological recordings over the course of the development of dopaminergic degeneration. The model was based on the classic hemiparkinsonian rat model, where the neurotoxin 6-OHDA is injected unilaterally into the medial forebrain bundle to induce nigrostriatal dopaminergic cell degeneration [59]. A limitation of the 6-OHDA rat model of PD is that it is restricted to nigrostriatal dopaminergic cell loss, which is a key, but not the only neuropathological characteristic of PD. Therefore, the model should be considered as a tool to shed light on the dopamine-dependent features of pathological oscillations in PD. Another limitation is that serial recordings were carried out over several weeks from the same animal; therefore it was impossible to determine the extent of the dopaminergic cell loss at different time points. Although we obtained a general estimate of the behavioural correlates of the dopaminergic cell loss, more specific tests might allow a better clinical estimate of the extent of the underlying dopamine depletion: using a behavioural test [60, 61] or testing with pharmacological agents [62]. Furthermore, the fixed placement of the electrodes did not allow the systematic acquisition of single unit activity over the course of the experiments. Since the aim of the study was to record from the same brain area (same cortical layer, etc.), the recording device was specifically designed to fix the location of electrodes. These experimental conditions allowed us to record only sporadic spikes, which could only be recorded for a limited time period and were not present simultaneously in all recorded channels, thus analysis on the single unit level was not attainable.

An important strength of our study is the chronic serial character of our recordings. This type of experiment offers the possibility to compare states with or without experimental intervention (neurotoxin injection) in the same animal. Furthermore, the fixed placement of electrodes allowing serial recordings over time was of particular significance, since recording from deep and small brain structures such as the STN that have functional subdivisions [63–65] might be challenging over subjects. Another advantage of our recording setup was that it enabled recording LFPs simultaneously from multiple brain regions through the same type of electrodes. This strengthens the reliability of the functional connectivity data, which can be compromised by using a combination of different recording systems, i.e. deep brain stimulation electrodes and MEG or by volume conduction in non-invasive recordings [66, 67].

It is important to mention the specific traits of the behavioural paradigm applied in the present studies. In our experiments, we aimed to record LFPs during self-induced

locomotor behaviour that would come as close as possible to physiological movement patterns. Therefore, the animals were exposed to an environment where food was offered and no action was taken to pressure the rats into collecting the food pellets. This setup enabled us to collect LFPs related to self-induced, self-paced locomotor behaviour that is known to activate different brain areas than externally guided behaviours [68]. By choosing this approach we could measure oscillatory brain activity related to natural movement patterns of the animals. However, this choice also had its disadvantages. The fact that the animals were allowed to initiate movement freely, reduced the amount of movement-related signal available, especially after the 6-OHDA lesions, when the animals developed a tendency to walk less. Alternatively, it would be possible to obtain longer movement related intervals from hemiparkinsonian rats [69] by facilitating motor activity (e.g. a treadmill). However results obtained with this method might differ from the ones presented in this thesis as some parameters of self-induced and self-paced movements might be altered and the continuous locomotor behaviour may lead to a modulation of local oscillatory brain activity over time [9]. The ‘resting state’ condition in the present experiments also needs to be considered. In our experiments, we recorded from sitting rats without any apparent gross movement or any sensory stimulation. Since inattentive and attentive rest are associated with considerably different basal ganglia signals in the hemiparkinsonian rat [9], it is important to try and exclude fluctuations in the alertness of the animals. Although we did not measure the level of arousal specifically, we did not observe any sleep spindles in our resting-state registrations. Moreover, considering the presence of head movements and whisking we are convinced that we recorded brain activity in an alert resting condition.

Another methodological consideration worth mentioning is the comparison of LFPs recorded from cortical and subcortical brain regions. One could question the validity of comparing signals derived from different brain regions that are anatomically different, the cortex being a strictly organized, layered structure, quite unlike the STN. However, it has been demonstrated that subthalamic LFPs are a good indicator of synchronized population activity of local neurons in human and experimental parkinsonism [70, 71].

Future directions

The animal model presented in this thesis offers numerous possibilities to investigate the dopamine-dependent component of parkinsonism. For instance, the effects of acute or chronic medication on brain activity could well be investigated in this model, including the neurophysiological correlates of levodopa-induced dyskinesias. In addition, as dopaminergic medication and deep brain stimulation are believed to have some common but also some divergent effects, it would be interesting to assess the interaction of the modulatory effects of both treatment options on the patterns of neuronal synchrony in PD. The recording device we used also provides the opportunity to analyse how other causes of

experimental parkinsonism may alter oscillatory brain activity, e.g. alpha synuclein-mediated nigrostriatal degeneration [72]. Future studies may also use optogenetics to silence and /or stimulate particular components of the basal ganglia in combination with recordings of cortical brain activity to map the changes in the dynamic interactions between distant brain areas. The multisite recording device presented in this thesis can also be used to study changes in basal ganglia cortical circuits related to other brain diseases, i.e. the limbic cortico-striatal-thalamocortical circuit [73].

By adaptations to the recording device, the brain regions of interest could be more closely matched to the cortical brain areas most affected in PD to further improve the comparison between data that originate from the rodent model and data recorded in PD patients. Furthermore, movement-related oscillatory brain activity could be investigated in more detail. As suggested recently, characterization of specific movement parameters, such as the alteration of kinematic or muscle activity, would enable comparisons across species [74]. Furthermore, to increase the translational value of the results presented in this thesis, it would be interesting to perform non-invasive measurements in PD patients during complex movement patterns, such as walking.

Conclusions

As part of this thesis work, we developed a recording device that allows the simultaneous and chronic recording from multiple cortical and basal ganglia regions in freely moving rats. This device was used in a rat model of PD to study the effects of a unilateral 6-OHDA lesion and shed more light on the neurophysiological parameters associated with the development of nigrostriatal dopaminergic degeneration.

The results of the experiments in the present thesis describe novel traits of the neurophysiological changes in experimental parkinsonism in the rat using three methodological approaches: 1) analysis of changes in local oscillatory brain activity; 2) analysis of changes in synchronization between distributed brain regions, i.e. functional connectivity; and 3) the analysis of directional connectivity. In addition to widespread increases in local synchronized beta band activity, we detected increased functional connectivity in the beta frequency range over a multiple brain regions, connecting the two hemispheres with asymmetric dopamine content. Moreover, directionality analysis made clear that in the hemiparkinsonian rat model directional influences are increased in a bidirectional fashion between cortex and the STN, and that the dopamine-depleted hemisphere becomes a receiver of influences from the non-lesioned side of the brain. The results presented also underline the significance of the functional segregation of the various frequency bands that might be associated with different behaviours: nigrostriatal dopaminergic degeneration seemed to affect local oscillatory activity, symmetrical and

directional connectivity at different frequencies in the two investigated behavioural states (resting and walking).

The experiments presented in this thesis highlight the potential benefits of multiple methodological approaches: the directionality analysis revealed a novel trait of interregional beta dynamics. We were able to demonstrate that despite the highly asymmetric dopamine content of the two hemispheres in the hemiparkinsonian rat, long-distance symmetric and directional interactions between the two sides of the brain are a principal component of the brain's response to experimental parkinsonism. This suggests that the dynamic long-distance connections between the two hemispheres are essential in preserving some functions in the parkinsonian state.

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