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Pathophysiological mechanisms in Parkinson's disease related dementia

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Parkinson's disease (PD) is a true multisystem disorder, characterized by degenerative changes in many neurotransmitter systems and brain areas, including the cerebral cortex, and leading to the classical motor as well as a variety of non-motor symptoms, such as olfactory disturbances, autonomic dysfunction, depression, sleep disorders and importantly also cognitive deficits and dementia, often accompanied by psychotic symptoms.¹ This thesis aims to contribute to our knowledge of the pathophysiology of cognitive dysfunction and especially dementia in PD, using magnetoencephalography (MEG) as a research tool.

In **chapter 2**, a review is given of cognitive dysfunction and dementia in PD and the possible pathophysiological mechanisms involved. A recent study has confirmed that impairments on neuropsychological tests are present in most PD patients in the earliest stages of disease, especially disturbances in executive function.² In about 20 percent of patients, impairment is more prominent in at least one cognitive domain, which some authors refer to as mild cognitive impairment in PD (PD-MCI), defined as a deficit of at least 1.5 standard deviations below the expected age corrected mean score on a neuropsychological test loading on a specific domain.^{3,4} In a considerable number of patients dementia develops, generally consisting of a prominent dysexecutive syndrome with attentional deficits, fluctuating cognition and memory disturbances, often accompanied by psychotic symptoms, mainly visual hallucinations.⁵ At the time of publication of our review, dementia was thought to occur in 25 to 40% of PD patients. These figures were based on cross-sectional data. More recent publications based upon studies with extensive follow up periods, have provided data on the cumulative incidence of dementia in PD. Buter et al found that 60% of PD patients had become demented after 12 years of follow up.⁶ In a study with a follow up period of 20 years, Hely et al established that dementia had developed in 75% of patients before they died.⁷

In early stage PD, disease-specific pathology is concentrated in the brain stem involving among others the locus coeruleus, dorsal raphe nuclei and substantia nigra. Hence, dopaminergic, noradrenergic and serotonergic ascending cortical (and striatal) projections degenerate and the loss of these projections might be involved in the subtle cognitive dysfunction present in the early clinical stages of PD. In advanced stage PD patients, monoaminergic corticopetal projection systems continue to degenerate but other systems are also prominently involved, including the cholinergic system as well as the cerebral cortex. Local cortical Lewy body-pathology and concomitant tau-pathology have been demonstrated in PD.⁸ The exact pathophysiological mechanisms that contribute to the development of dementia in PD, however, are still largely unknown and it is still a subject



of debate to what extent PD related dementia results from progression of pathological changes that can already be demonstrated in non-demented patients, and to what extent additional mechanisms are necessary for dementia to develop. Identifying the mechanisms that lead to dementia is important for the development of novel symptomatic treatment and, ideally, treatments that protect patients from developing dementia. Currently, the symptoms of dementia can only be treated to some extent with drugs that enhance cholinergic function, the cholinesterase inhibitors (and the often accompanying psychotic symptoms additionally with atypical neuroleptics).⁹⁻¹⁴

Oscillatory neuronal synchrony, both within as well as between brain areas is considered to be important for normal cognitive function. Therefore, it is likely that cognitive dysfunction and dementia in PD are associated with disturbances of synchronization within and/or between brain areas. To gain insight in the pathophysiological mechanisms involved in the development of cognitive dysfunction and dementia in PD, we studied changes in synchronized oscillatory brain activity in non-demented and demented PD patients, using MEG as a research tool. The results of these studies are described in **chapters 3-5**.

LOCAL NEURONAL SYNCHRONY

First, in **chapter 3.1**, local oscillatory brain activity, measured using MEG, was compared between three groups: 13 healthy subjects, 13 non-demented PD patients and 13 demented PD patients. Relative spectral power was calculated in the delta (0-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-48 Hz) frequency bands.

The first interesting finding, which had not been consistently reported before,¹⁵⁻²¹ was the presence of a diffuse slowing of the background oscillatory brain activity in non-demented PD patients compared to controls, consisting of increased relative theta activity and decreased beta activity. In a subsequent study by our group we were able to establish that these changes are present from the earliest clinical stages of PD onward.²² In the latter study, slowing of oscillatory activity was largely independent of disease duration, disease severity and was hardly influenced by dopaminergic treatment, suggesting that these changes may not be related to degeneration of dopaminergic neurons, but possibly to changes in non-dopaminergic mechanisms for instance involving noradrenergic and serotonergic projections. Cholinergic involvement in these early stage changes seems less likely, since the cholinergic basal nucleus of Meynert is only mildly involved in the early stages of disease.⁸ Furthermore, a lesion of the cholinergic system would more likely be expected to produce an increase of delta activity,^{23,24} which we did not observe in our study.



Consistent with previous data,^{17,18,20,21} demented PD patients had a much more pronounced slowing of brain activity than non-demented PD patients. Furthermore, posterior reactivity of the alpha rhythm to eye opening was much reduced in the demented patients. Interestingly, the pattern of slowing in demented patients relative to the non-demented patients was qualitatively very different from the slowing observed in non-demented patients compared to controls. In addition to a further increase in theta and a decrease in beta activity, we found an additional increase in delta and a decrease in alpha band power in demented PD patients. These qualitative changes in the pattern of slowing going from non-demented to demented PD patients, suggest that the alterations in local oscillatory brain activity in PD related dementia do not merely reflect a progression of the pathological changes that characterize the non-demented stages of PD, i.e. mainly dopaminergic, noradrenergic and serotonergic deficiencies related to brain stem pathology. Instead, different or at least additional mechanisms would seem to be involved. According to the current pathological concept of PD,^{8,25} dementia develops in the advanced stages of PD. In these stages, degeneration of the basal nucleus of Meynert is a prominent pathological feature. Therefore, degeneration of cholinergic cortical projections with resultant diminished cortical cholinergic activity is a likely candidate to explain the changes in local oscillatory MEG activity in PDD. This hypothesis finds support in animal as well as human studies using spectral power analysis, which have shown that degeneration or lesioning of the cholinergic system results in a shift toward slower frequencies in the powerspectrum.^{23,24,26-31} Further support comes from studies in Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), both characterized by prominent cholinergic deficits, in which profound slowing of background activity is reported.^{32,33}

In some of these animal studies and also in several studies in AD, promotion of cholinergic activity produced a shift of the powerspectrum towards higher frequencies.³⁴⁻³⁹ Consequently, one would anticipate a similar change in the powerspectrum in demented PD patients when treated with drugs that enhance cholinergic function. This effect of cholinergic modulation on relative spectral power in PDD could indeed be demonstrated in the study described in **chapter 3.2**. In this study, relative spectral power was calculated from the MEG recordings in eight demented PD patients before and after a period of treatment with the cholinesterase inhibitor rivastigmine (patients participated in a multicenter, randomized, placebo-controlled trial¹¹). After a mean treatment period of 29 weeks, an increase in relative alpha and beta power and a decrease of delta power could be demonstrated. In other words, there was a shift in the powerspectrum towards higher frequencies. When taken together with the results of **chapter 3.1**, the characteristic



slowing of oscillatory activity in demented PD patients could partly be reversed by treatment with rivastigmine. Moreover, in parallel to the changes in recorded brain activity, cognitive function improved in all but one patient after treatment. It is tempting to speculate that responders to treatment might be characterized by a specific pattern of baseline spectral power parameters and that, in this way, neurophysiological measures might help to select patients who could benefit from treatment. Studies including a larger number of patients, both responders and non-responders to treatment, are needed to further address baseline neurophysiological parameters in relation to treatment response. In addition to cholinergic deficits, advanced stage PD is associated with widespread neuropathological changes in the cerebral cortex, involving both cortical Lewy body- and concomitant tau-pathology. Since these changes are often demonstrated to be more pronounced in PDD than PD⁴⁰⁻⁴⁵ and the extent of cortical Lewy body-pathology was the best correlate of the severity of dementia in one study,⁴⁶ it can be hypothesized that Lewy body- and tau-pathology may also contribute to the slowing of resting state local oscillatory activity in PD related dementia.

In summary, the results presented in **chapters 3.1 and 3.2** indicate that it is unlikely that dementia in PD is merely caused by a progression of changes in neurotransmitter systems already affected in non-demented PD, including the dopaminergic system. Instead, it seems plausible that additional mechanisms, notably cholinergic loss and possibly local cortical Lewy body and tau pathology, play an important pathophysiological role.

FUNCTIONAL CONNECTIVITY

In **chapter 4**, the results are described of two studies in which neuronal synchronization between brain areas was studied using the synchronization likelihood (SL). Rather than measuring the average local power at each separate MEG sensor, this technique measures linear as well as non-linear statistical interdependencies between MEG sensors,⁴⁷ which represents a measure of functional connectivity between brain areas. In the first study, described in **chapter 4.1**, SL was calculated in 70 non-demented PD patients in different stages of disease and compared to 21 healthy controls. A diffuse increase of 8-10 Hz alpha1 synchronization was demonstrated in very early stage, drug naive PD patients. In more advanced patients, increases in SL additionally involved the theta and beta frequency bands. In agreement with the results of an EEG study in advanced stage PD patients,⁴⁸ the increases we observed in theta and beta band synchronization in non-demented PD patients were positively correlated with the severity of parkinsonism. Therefore, the increases in functional connectivity in these frequency bands in non-demented patients might especially be related to motor symptoms.



In the subgroup of early stage, untreated PD patients, increased alpha1 synchronization between both hemispheres correlated with increased perseveration, a quite common and early cognitive deficit in PD.⁴⁹⁻⁵¹ Synchronization in the alpha band is thought to be related to cognitive function, in particular attentional processes.⁵² Possibly, the increased alpha1 synchronization in non-demented PD patients reflects a disturbance of the dynamical balance of functional connectivity with a resultant loss of flexibility. Therefore, increased alpha synchronization may well reflect the very early cognitive deficits known to occur in early stage PD.

Chapter 4.2 describes the results of a study in which SL values were compared between 13 demented PD patients and 13 non-demented PD patients (the same patient groups as described in **chapter 3.1**). In contrast to the increases in synchronization demonstrated in **chapter 4.1** for the non-demented PD patients, PD related dementia was associated with reductions in long range intrahemispheric and interhemispheric synchronization in several frequency bands, mainly in fronto-temporal regions. In addition, there were minor increases in posterior alpha2 and beta synchronization. As frontal and temporal regions are known to be important for memory and executive function, it is tempting to speculate that the observed loss of fronto-temporal functional connectivity reflects cognitive dysfunction in PDD, although we were not able to find correlations between reduced synchronization and measures of cognitive function to support this. The reductions in fronto-temporal and intertemporal functional connectivity we observed in PD related dementia are strikingly similar to the changes in functional connectivity found in AD⁵³ and DLB.⁵⁴ Interestingly, an increase in posterior synchronization was also reported in an MEG study in AD.⁵³ These observations in PD and AD may suggest that increased synchronization may also be related to cognitive dysfunction. This would seem to be supported by the fact that worse cognition in the demented PD group was associated with higher levels of synchronization. Alternatively, increases in synchronization may constitute a compensatory mechanism in relatively healthy networks. Considering that increases in SL were also found in non-demented PD patients relative to controls (**chapter 4.1**), the increases in the PDD patients may merely reflect disease progression. The latter possibility is supported by the fact that PDD patients had higher UPDRS motor scores than the non-demented patients.

The resemblance in the pattern of changes in functional connectivity with AD and DLB, disorders characterized by prominent cholinergic deficits, suggests that, much like the changes in spectral power (**chapter 3**), the reductions in functional connectivity in PD may also be related to the degeneration of the cholinergic system. This notion is further supported by the demonstration of reductions of intrahemispheric as well as



interhemispheric functional connectivity after a decrease in cholinergic tone in an animal study⁵⁵ and following the administration of the anticholinergic drug scopolamine to healthy subjects.^{56,57}

In addition to the involvement of the cholinergic system, a loss of structural connections, much the same as in AD and DLB, may also contribute to the reported changes in functional connectivity between brain areas. In AD, an association was found between fMRI coherence and cortical atrophy.⁵⁸ However, since we did not combine MRI and MEG data in our study, this relationship remains to be explored. However, cortical changes including cortical atrophy are more prominent in demented in comparison to non-demented PD patients,⁵⁹⁻⁶⁴ and therefore, a contribution of local cortical changes to the alterations in functional connectivity seems likely.

In summary, in both non-demented and demented PD patients, there are disturbances of functional connectivity between brain areas.⁶⁵ In contrast to the increases in synchronization reported in non-demented PD patients, which may result from degeneration of ascending brainstem monoaminergic projections, a quite different pattern of changes is found in demented patients, mainly consisting of reductions in synchronization. Very much like the changes in spectral power, the loss of functional connectivity may be caused by cholinergic degeneration, possibly together with cortical Lewy body- and/or tau-pathology

LARGE SCALE NETWORK ORGANIZATION

Finally, changes in the large scale spatial organization of brain networks in PD were studied in **chapter 5**. In the study described in this chapter, modern graph theoretical analysis was applied to matrices of synchronization likelihood values. Networks of 13 non-demented and 13 demented PD patients were characterized by the clustering coefficient, a measure of local connectedness, and the path length, a measure of global integration. Compared to non-demented patients, PDD was characterized by a higher clustering coefficient in all frequency bands as well as a longer path length in all but the delta band. Although these differences reached significance only for the theta band, the overall pattern of change in the organization of networks in PDD was a loss of global integrative properties and increased local interconnectedness.

Preliminary results of a comparison between early stage, non-demented PD patients and controls also show increased local interconnectedness in several frequency bands, including the theta band. However, in these non-demented PD patients there were no changes in path length.⁶⁶ Therefore, it is tempting to suggest that the increase in local interconnectedness observed in both demented and non-demented PD patients reflects



the same pathophysiological mechanism. Obviously, loss of dopaminergic tone is the most likely candidate mechanism. Dopamine is thought to reduce unwanted activity during a task and at rest, and also leads to focusing of activity.^{67,68} Based upon these observations, we hypothesize that the degeneration of the dopaminergic system in PD leads to reduced focusing of cortical activity which is expressed in a pathological increase in local connectedness.

The increase in path length appears to be a characteristic of dementia in PD and, therefore, this more likely reflects the pathophysiological mechanisms underlying dementia in PD. Indeed, a recent fMRI study has emphasized the relationship between a longer path length and a lower intelligence quotient.⁶⁹ As discussed above for other changes in brain activity in PDD, this may involve cholinergic dysfunction and/or local cortical pathology. This assumption is supported by resting state PET studies in PD, in which cortical hypometabolism that was independent of motor function or dopaminergic treatment could be demonstrated in a network of brain areas related to cognitive function.⁷⁰⁻⁷² In another PET study, the cholinergic system was more severely affected in demented PD patients than in non-demented patients in approximately the same areas.⁷³ Therefore, the loss of cholinergic projections and/or local cortical changes may lead to the loss of global integrative properties of brain networks we observed in PDD.

Our results are in agreement with structural network data in AD, as measured by the cortical thickness.⁷⁴ In contrast, the clustering coefficient is reported to be lower in an fMRI study.⁷⁵ In a recent MEG study, both a lower clustering coefficient and shorter path length were demonstrated in AD.⁷⁶ Therefore, our results seem to be in contrast with functional network data in AD. It remains to be clarified whether these differences are related to the use of different methodologies in these studies or whether they reflect differences in pathophysiological mechanisms. Future studies directly comparing PDD and AD are needed to clarify the similarities and differences in large scale network organization between these two neurodegenerative conditions.

CONCLUSION

Taken together, the studies in this thesis contribute to a better understanding of changes in brain activity in PD. Our results have shown that resting state brain activity in PD related dementia is characterized by a prominent and diffuse slowing of rhythmic oscillatory brain activity, reductions in fronto-temporal and intertemporal functional connectivity, and a shift in large scale network organization from global integration to more local connectedness. This pattern of changes is qualitatively very different from the pattern of changes that occurs in non-demented PD patients. Based on this qualitative difference,



the development of dementia in PD entails more than a quantitative progression of disease pathology in brain areas already affected in non-demented patients, but rather the involvement of additional pathophysiological mechanisms. Given the effects of cholinergic modulation on brain activity and the fact that the changes in brain activity observed in PDD in many aspects resemble those reported for AD, these pathophysiological mechanisms most likely include the degeneration of the cholinergic system. In addition, local cortical Lewy body- and tau-pathology may play an additional role. In the future, the differential patterns of altered brain activity in demented and non-demented PD patients may prove useful to identify patients at risk for developing dementia.

Our findings also demonstrate that modulatory effects of drugs on resting state brain activity can be measured using MEG. In this way, studying pre- and post-treatment resting state brain activity may prove to be useful as a monitoring instrument of the effects of potential future treatments for dementia.

Based on our results, several recommendations for future research can be made:

LONGITUDINAL DATA

Longitudinal studies in PD patients combining MEG data and neuropsychological follow up may further help to clarify the natural course of changes in resting state brain activity in PD and their relation to cognitive dysfunction and the development of dementia. In this way, patients at risk for developing dementia (and possibly also psychosis), may be identified. Furthermore, the modulatory effects of for instance cholinergic and dopaminergic drugs may further clarify the contribution of the different neurotransmitter systems to changes in resting state brain activity.

TASK-RELATED CHANGES IN BRAIN ACTIVITY

The changes in brain activity in our study groups were all demonstrated in the resting state. Possibly, differences between the groups may be even more pronounced when subjects perform a cognitive task during the MEG recording. Therefore, studies applying task-specific conditions may further address the relation of oscillatory brain activity and cognitive function.

ADDITIONAL ANALYSIS TECHNIQUES

To reduce the number of statistical comparisons in our studies, we used fairly general measures of analysis, possibly at the cost of detailed local information. Future research might focus more in detail on specific areas that might be involved in cognitive dysfunction and dementia in PD, possibly in combination with other imaging modalities.



For example co-registration with structural MRI may allow the assessment of the relationship between changes in functional neurophysiological parameters of brain activity and cortical atrophy. Similarly, special techniques such as diffusion tensor imaging (DTI) may provide the link between the loss of connecting fibers and changes in functional connectivity. Studies combining MEG and fMRI may yield important information on the relationship of metabolic changes as a measure of neuronal activity with changes in electromagnetic fields induced by neuronal activity.

Furthermore, different time series analysis techniques may further help to unravel the neurophysiological changes in PD. For instance, techniques that take into account volume conduction in EEG or MEG, such as the phase lag index (PLI) may be useful.

PREDICTION OF RESPONSE TO (CHOLINERGIC) TREATMENT

Finally, by studying differences in baseline neurophysiological parameters in a larger number of both responders and non-responders to treatment, MEG (or EEG) might contribute to the selection of patients who may optimally benefit from cholinergic treatment. Furthermore, MEG or EEG may be useful to monitor the effects of other potential treatment strategies.