The subthalamic nucleus : a novel motor-associative-limbic interface

Chapter 10

Conclusion
Conclusie

Conclusion

In the present study, we tested the hypothesis that the subthalamic nucleus (STN) is a strong regulator of associative and limbic functions and that modulation of the STN by electrical stimulation causes marked changes in these functions. The results of the set of experiments as outlined in this study show that the STN is indeed a strong regulator of associative and limbic functions and that modulation of STN's neuronal activity by deep brain stimulation (DBS) results in affective and cognitive changes. Anatomically, it was already known that STN received input from associative and limbic regions within the basal ganglia such as the anterior part of the globus pallidus externus (GPe) and the ventral pallidum (VP) and also from outside the basal ganglia such as the frontal parts of the cortex[1]. However, the functionality of these projections remained elusive. Our clinical and preclinical experiments revealed that the connections of the STN with the associative and limbic regions are clinically very relevant. Furthermore, we discovered a novel functional connection between the STN and the most important serotonergic nucleus in the brain, the dorsal raphe nucleus (DRN).

In the clinical studies, we demonstrated that STN DBS has long-lasting beneficial effects on motor disability in patients suffering from advanced PD (**Chapter 2**). Concerning non-motor behaviour, our results showed that STN DBS had substantial but differential effects on cognitive performance of PD patients (**Chapter 3**). Stimulation of the STN improved response preparation but impaired the speed of mental processing. In the same study, we evaluated the effects of dopaminergic medication. Dopaminergic medication improved the motor disability, but had no effect on the cognitive performance. Besides changing cognitive performance, STN DBS also changed emotional performance. In our meta-analysis, we showed that PD patients can experience substantial changes in their emotional functions (**Chapter 4**).

The mechanisms underlying these non-motor effects of STN DBS remained unknown. Therefore we carried out a set of preclinical experiments to investigate the neuronal mechanisms entailed in this procedure. In our first preclinical experiment, we faced the problem of correct stimulation settings to perform STN DBS in rat models. We observed substantial amount of histological damage when applying previously published stimulation parameters (**Chapter 5**). We found out that this was due to the difference in polarity which was responsible for the occurrence of histological damage. We adjusted the stimulation parameters in order to have a more comparable stimulation setting to the clinical situation and prevented histological damage in our rat models. In the next study, we introduced and validated the bilateral STN DBS paradigm in freely moving rats (**Chapter 6**). In this study, we found a profound effect of STN DBS on a measure of impulsivity, premature responding. This effect was frequency-, and amplitude-dependent, occurring at high frequency and low amplitude. As reported before in a rat model with STN lesions (**Chapter 8**), a change in premature responding is the most sensitive sign of STN modulation. Subsequently, we applied bilateral STN DBS

in Parkinsonian rats (**Chapter 7**). Again we found that when using specific stimulation parameters, it was possible to modulate different behavioural outputs in different ways. We could change motor and cognitive performance acutely and separately by using specific stimulation amplitudes. These findings suggest that basal ganglia-thalamocortical motor and associative circuits responsible for specific motor and cognitive performance have unique physiological properties that can be modulated by specific electrical stimuli.

With respect to the affective changes, we studied the effects of bilateral STN DBS on the activity of 5–HT neurons in the rat dorsal raphe nucleus (DRN) since some of the psychiatric effects of STN stimulation such as low mood and increased impulsivity have long been associated with reduced 5–HT function. We found that STN stimulation at parameters used clinically exerts a powerful, specific, reproducible, reversible and inhibitory effect on 5–HT neurons (**Chapter 9**). These findings strongly suggest that reduced 5–HT output contributes to the psychiatric disturbances induced by STN stimulation, and provide an basis for their clinical management. The data also demonstrate an unsuspected link between the STN and the 5–HT system, which we see as the first critical step towards establishing the existence of a novel 'motor-limbic interface' in the brain.

Altogether, the data presented in this thesis suggest that the STN serves as an interface between the brain's motor and non-motor (cognitive and limbic) circuits. Modulation of the activity of the STN by electrical currents has immediate and substantial effect on motor and non-motor parameters in preclinical and clinical experiments. However, one could argue that postoperative reduction of dopaminergic medication might underlie the psychiatric effects of following DBS. It is usually possible to achieve an average reduction of approximately 60% of dopaminergic medication after surgery. Some transient changes in mood and psychotic symptoms can occur when the reduction is performed fast. However, in the majority of the cases, the medication reduction has been performed slowly. Furthermore, the reduction of dopaminergic medication is usually fully achieved in the first 2–3 months after surgery, whereas the behavioural symptoms were generally also observed at longer follow-up time points. Secondly, in some studies like in chapter 3, STN stimulation was switched off to investigate the effects of only stimulation and medication on motor and cognitive parameters[2–5]. Results show that it is actually the modulation of the STN and not medication or surgery that has a substantial effect on behavioural parameters.

Furthermore, it can also be argued that current spread to surrounding regions might be responsible for the generation of behavioural changes in the case of STN DBS. Even though that we cannot totally exclude the involvement of surrounding regions in the generation of these behavioral effects of STN modulation, currently only one case report supports this hypothesis. In a brief report, Bejjani and co-workers described a patient who developed transient acute depression when the most distal electrode contact, probably at the level of the substantia nigra, was stimulated[6]. This patient had no

beneficial effects on her motor disability when this contact was stimulated. On the other hand, various clinical reports[7–23], found depression in patients who had clear beneficial effects of STN DBS on their PD signs. From an anatomical point of view, the substantia nigra pars reticulata (SNr) serves as one of the output nuclei for the limbic circuit. Hypothetically, modulation of SNr activity could therefore also result in changes in affective behavior. In experimental studies, changes in premature responses were only seen following lesions and stimulations of the STN in that anatomical region. Baunez and colleagues stated that changes in premature responding were the most sensitive sign of STN modulation in rats[24]. In chapter 9, we performed a trajectory stimulation to evaluate the specificity of the effects of STN DBS. Only stimulation at the level of the STN inhibited 5–HT neuronal firing rate. Therefore, the current data are in favor of the hypothesis that STN itself and not neighboring structures are responsible for the behavioural consequences of STN DBS.

From a mechanistic point of view, our findings identify the STN as an important interface between brain's motor and non-motor (cognitive and limbic) circuits. Modulation of the activity of the STN by electrical currents has immediate and substantial effect on motor and non-motor parameters in preclinical and clinical studies.

From a clinical point of view, the DBS of STN is a very effective therapy in alleviating PD symptoms, but can be associated by behavioural changes of which cognitive dysfunctions and emotional changes are the most frequent. Our recent finding suggests that this may be due to a striking inhibition of 5–HT neuronal activity. This effect on the 5–HT system may contribute to the psychiatric disturbances observed in STN-stimulated PD patients, and provide an experimental basis for their clinical management.

Conclusie

In deze studie hebben we de hypothese getest dat de nucleus subthalamicus (STN), een hersenkern gelocaliseerd in de middenhersenen, de associatieve en limbische functies reguleert en dat modulatie van de STN door middel van elektrische stimulatie een sterke verandering veroorzaakt van deze functies. Onze resultaten, zoals beschreven in deze studie, bevestigen deze hypothese. Anatomische studies hebben reeds aangetoond dat associative en limbische gebieden binnen de basale kernen, zoals het anterieure deel van de globus pallidus externus (GPe) en het ventrale pallidum (VP), en buiten de basale kernen, zoals de prefrontale cortex, naar de STN projecteren[1]. Echter de relevantie van deze projecties waren grotendeels onbekend. Uit onze preklinische en klinische experimenten komt naar voren dat deze projecties zeer relevant zijn. Verder hebben we een nieuwe functionele verbinding ontdekt tussen de STN en de meest relevante serotonerge kern in de hersenen, de dorsale raphe nucleus (DRN).

In de klinische studies hebben we aangetoond dat bilaterale subthalamische stimulatie (STN DBS) langdurige gunstige effecten heeft op de motorische symptomen van patiënten met de ziekte van Parkinson (**Hoofdstuk 2**). We hebben ook aangetoond dat STN DBS effecten heeft op non-motorische functies, zoals de cognitie (**Hoofdstuk 3**). Stimulatie van de STN verbeterde respons preparatie maar vertraagde de mentale snelheid. Behoudens effecten op cognitieve functies, vonden we ook dat STN DBS effecten heeft op affectieve parameters. In het systematische overzichtsartikel hebben we dit laten zien (**Hoofdstuk 4**).

De onderliggende mechanismen van de non-motorische effecten van STN DBS waren grotendeel onbekend. We hebben een aantal preklinische experimenten uitgevoerd om deze mechanismen te onderzoeken. In onze eerste experiment, zijn we het probleem tegengekomen van de te gebruiken stimulatieparameters. Namelijk, we vonden substantiële histologische schade bij het gebruik van eerder gepubliceerde stimulatieparameters (**Hoofdstuk 5**). We zijn erachter gekomen dat dat dit te maken heeft met het verschil in polariteit. We hebben de stimulatieparameters aangepast in onze preklinische experimenten om klinisch relevant te stimuleren. Hiermee hebben we histologische schade voorkomen. In de volgende studie, hebben we het eerste bilaterale STN DBS model in vrij bewegende ratten geïntroduceerd en gevalideerd (**Hoofdstuk 6**). In deze studie, vonden we een sterke effect van STN DBS op een maat voor impulsiviteit, premature responsen. Dit effect was frequentie-, en amplitude-afhankelijk. Vervolgens hebben we bilaterale STN DBS toegepast in een ratmodel voor de ziekte van Parkinson (**Hoofdstuk 7**). We vonden dat het mogelijk was om een specifiek gedrag te moduleren door gebruik te maken van speficieke stimulatieparemeters. We hebben motorische en cognitieve parameters acuut en onafhankelijk kunnen veranderen door gebruik te maken van specifieke stimulatieamplitudes. Deze bevindingen suggereren dat basale kernen-thalamocorticale motorische en associatieve circuits verantwoordelijk zijn voor specifieke motorische en cognitieve functies en

dat ze unieke elektrofysiologische karakteristieken hebben die gemoduleerd kunnen worden door specifieke elektrische stimuli.

Met betrekking tot de affectieve veranderingen, hebben we de effecten van bilaterale STN DBS op de activiteit van 5–HT neuronen in de DRN onderzocht omdat symptomen zoals veranderde gemoedstoestand of verhoogde impulsiviteit geruime tijd geassocieerd zijn met verlaagde 5-hydroxytryptamine (5–HT = serotonine) functie. We hebben gevonden dat STN stimulatie met parameters die klinisch effectief zijn, een sterke, specifieke, reproduceerbare, reversibele en inhibitoire effect heeft op 5–HT neuronen (**Hoofdstuk 9**). Deze resultaten suggereren dat een verlaagde 5–HT functie bijdraagt aan de psychiatrische symptomen geïnduceerd door STN DBS. Deze bevindingen demonstreren tevens voor het eerst het bestaan van een potente link tussen de STN en het 5–HT systeem.

De bevindingen zoals gepresenteerd in dit proefschrift suggereren dat de STN als een interface fungeert tussen de motorische en de non-motorische (cognitieve en limbische) circuits van de hersenen. Modulatie van de STN door middel van elektrische stimulatie moduleert direkt motorische en non-motorische functies in klinische en preklinische condities.

References

1. Temel Y, Blokland A, Steinbusch HW, Visser-Vandewalle V. The functional role of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol. 2005;76:393–413
2. Hershey T, Revilla FJ, Wernle A *et al.* Stimulation of STN impairs aspects of cognitive control in PD. Neurology. 2004;62:1110–1114
3. Witt K, Pulkowski U, Herzog J *et al.* Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. Arch Neurol. 2004;61:697–700
4. Hälbig TD, Gruber D, Kopp UA *et al.* Subthalamic stimulation differentially modulates declarative and non-declarative memory. Neuroreport. 2004;15:539–543
5. Temel Y, Blokland A, Ackermans L *et al.* Differential effects of subthalamic nucleus stimulation in advanced Parkinson disease on reaction time performance. Exp Brain Res. 2006;169:389–399
6. Bejjani BP, Damier P, Arnulf I *et al.* Transient acute depression induced by high-frequency deep-brain stimulation. N Engl J Med. 1999;340:1476–1480
7. Rodriguez MC, Guridi OJ, Alvarez L *et al.* The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord. 1998;13 Suppl 3:111–118
8. Kumar R, Lozano AM, Sime E *et al.* Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology. 1999;53:561–566
9. Moro E, Scerrati M, Romito LM *et al.* Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology. 1999;53:85–90
10. Houeto JL, Damier P, Bejjani PB *et al.* Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. Arch Neurol. 2000;57:461–465

11. Molinuevo JL, Valldeoriola F, Tolosa E *et al.* Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. Arch Neurol. 2000;57:983–988
12. Volkmann J, Allert N, Voges J *et al.* Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology. 2001;56:548–551
13. Dujardin K, Defebvre L, Krystkowiak P *et al.* Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. J Neurol. 2001;248:603–611
14. Valldeoriola F, Pilleri M, Tolosa E *et al.* Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: long-term follow-up of patients. Mov Disord. 2002;17:125–132
15. Houeto JL, Mesnage V, Mallet L *et al.* Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry. 2002;72:701–707
16. Ostergaard K, Sunde N, Dupont E. Effects of bilateral stimulation of the subthalamic nucleus in patients with severe Parkinson's disease and motor fluctuations. Mov Disord. 2002;17:693–700
17. Vingerhoets FJ, Villemure JG, Temperli P *et al.* Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology. 2002;58:396–401
18. Martinez-Martin P, Valldeoriola F, Tolosa E *et al.* Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. Mov Disord. 2002;17:372–377
19. Berney A, Vingerhoets F, Perrin A *et al.* Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. Neurology. 2002;59:1427–1429
20. Doshi PK, Chhaya N, Bhatt MH. Depression leading to attempted suicide after bilateral subthalamic nucleus stimulation for Parkinson's disease. Mov Disord. 2002;17:1084–1085
21. Thobois S, Mertens P, Guenot M *et al.* Subthalamic nucleus stimulation in Parkinson's disease: clinical evaluation of 18 patients. J Neurol. 2002;249:529–534
22. Romito LM, Scerrati M, Contarino MF *et al.* Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease. Neurology. 2002;58:1546–1550
23. Krack P, Batir A, Van Blercom N *et al.* Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003;349:1925–1934
24. Baunez C, Humby T, Eagle DM *et al.* Effects of STN lesions on simple vs choice reaction time tasks in the rat: preserved motor readiness, but impaired response selection. Eur J Neurosci. 2001;13:1609–1616