The Nucleus Accumbens

Summary

The aim of this thesis was to test the hypothesis that deep brain stimulation (DBS) of the nucleus accumbens (NAc) core and shell modulates impulsive behaviour differently. The impulsive behaviour was studied by the reaction time and delay discounting tasks. Based on the results of previous lesion studies on one hand, and the fact that high frequency stimulation mimics the effects of a lesion on the other, we predicted that DBS of the NAc core would have a minor effect on impulsive action but a large effect on impulsive choice, and that DBS of the NAc shell would have no effect on impulsive behaviour (Bezzina *et al*, 2007; Cardinal *et al*, 2001; Christakou *et al*, 2004; Cole and Robbins, 1989; Murphy *et al*, 2008; Pattij *et al*, 2006; Pezze *et al*, 2006; Pothuizen *et al*, 2005; van Gaalen *et al*, 2006).

Altogether, the results presented in this thesis can be summarized as follows:

In **Chapter 2**, we have provided an overview on the role of the NAc in impulsive processes by reviewing imaging studies in humans, and lesioning studies in animals. The emphasis is put on the neuroanatomy of the NAc, with an attempt to clarify the dichotomy between the two main subdivisions of the NAc, namely the NAc core and shell. From a behavioural point of view, we discussed the multidimensional aspects of impulsivity and tried to correlate them with the different neural substrates. It has to be noted that the difference between the subdivisions of the NAc can only be visualized in animals; the current imaging studies do not allow to specify the different parts of the ventral striatum (which is larger than the NAc itself), let alone the subdivisions of the NAc. From a functional point of view, the NAc core is thought to be involved in various aspects of impulsivity such as impulsive action (in case of errors) and impulsive choice. The NAc shell is clearly less investigated, but the few lesion studies available do not directly support a role in impulsive behaviour. One can argue however that at the neurochemical level (e.g. dopamine transmission) the NAc has indeed an essential role in impulsivity but that this is mainly due to the dorsostriatal loop, which is related to the NAc core. This pathway, which is amongst others interconnected with the subthalamic nucleus, has been shown to play an essential role in the control of inhibition. NAc DBS in animal models has clearly shown that this nucleus modulates impulsivity.

Chapter 3: In Chapter 3 another review is presented on the effects of DBS in animal models of psychiatric disorders, and the behavioural side-effects of DBS in animal models of movement disorders. We conclude that nowadays there is still a lack of good animal models for psychiatric disorders, in contrast to the models nowadays available for movement disorders such as Parkinson's disease and Huntington's disease.

In **Chapter 4**, we have provided the first empirical evidence that NAc DBS affects the control of inhibition as assessed by the reaction time task. The premature responses were recorded as a measure of impulsive control, representing a failure to inhibit prepotent responses. We stimulated naïve rats bilaterally either in the NAc core or shell with a large set of different stimulation parameters with varying frequencies and amplitudes. Our results show a differential effect of DBS of the two subdivisions of the NAc, but only at high frequency stimulation (130 Hz). NAc core

stimulation led to a gradual decrease of impulsive action. In contrast, NAc shell stimulation induced an increase of premature responses with a peak at 30 µA. This study additionally suggests that NAc DBS does not mimic NAc lesions.

Chapter 5: Impulsivity is a multidimensional concept. In this experiment we challenged another facet of impulsivity, named delay discounting. In this paradigm, the rats had to choose between a small but immediate reward and a delayed but large reward. A decrease in the number of choices for the large but delayed reward is an indicator of the so-called impulsive choice. In contrast with lesion studies, we found no effect of NAc core stimulation on the choice for large but delayed rewards. However we showed that DBS of the NAc shell at 150 µA increased the number of choices for the large but delayed reward for long delays (40sec), indicating a decrease in impulsivity. Although the number of animals was small, our results are encouraging and can be a stimulus for further research. This study highlights again the importance of the NAc shell in impulsive processes and the potential difference in effects between lesions and DBS.

In **Chapter 6**, we have performed a similar experiment as in **Chapter 4**, but the electrodes were implanted more ventrally (0.4 mm) and the neurochemical effects of DBS of NAc core and shell were assessed. More specifically, we measured dopamine and serotonin levels and their metabolites in the NAc and prefrontal cortex. With the electrodes positioned deeper within the NAc core, DBS did not lead to the changes in impulsivity seen in our previous study, indicating that this part of the NAc core is not likely to be involved in impulsive action. NAc shell DBS, also implanted further ventrally, led again to a consistent increase of premature responding, suggesting a more consistent role of the medial NAc shell in premature responding. This behavioural effect was accompanied by a decrease of dopamine and serotonin turnover at the level of the NAc, mostly characterized by an increase of both neurotransmitters without modification of their respective degradation products. This study confirms the difference of effect on impulsive action between lesion and stimulation of the NAc.