Pharmacological MRI in the assessment of monoaminergic function
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CHAPTER 11
SUMMARY AND DISCUSSION
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SUMMARY

The goal of this thesis is to assess whether phMRI is able to detect monoamine (dys)function in humans. To achieve this, we performed several imaging studies, both in healthy subjects and in individuals that intermittently use psychotropic drugs in a recreational setting. Previously, SPECT and MRI studies demonstrated that the recreational use of MDMA presumably leads to damage of the 5-HT system (de Win et al., 2004; de Win et al., 2008b; Reneman et al., 2000; Reneman et al., 2001; Reneman et al., 2002), as evidenced by reduction in SERT availability. Evidence for similar damage to the DA system in users of dAMPH also exists, in addition to preclinical work showing DAergic damage even after clinical dosages of dAMPH (Reneman et al., 2002; Ricaurte et al., 2005). Therefore, by comparing healthy individuals to individuals frequently exposed to psychotropic drugs, we were able to determine whether ASL-based phMRI is a useful tool to detect the changes in neurotransmitter function we expected to be present in these specific groups of drug users.

First, we examined whether the administration of i.v. dAMPH would lead to a significant hemodynamic response in healthy individuals (chapter 2). We hypothesised that such a response is linked to DAergic function, as dAMPH causes a considerable rise in intrasynaptic DA levels (Kahlig et al., 2005; Kuczenski et al., 1995; Laruelle et al., 1995). We also hypothesised that the size of the response would be related to D_{2/3} receptor availability, as the amplitude of D_{2/3} binding also correlates to the subjective response to dAMPH (Abi-Dargham et al., 2003). After dAMPH administration, we observed a large decrease in CBF in the entire brain in response to the infusion of dAMPH. Due to the fact that brain microvasculature also contains a significant amount of D_2 receptors, we assumed that this response was mainly attributable to vascular effects. To date, no generally approved method of correction for ASL-based phMRI exists (Khalili-Mahani et al., 2012; Saad et al., 2012). We therefore corrected for this vascular effect, using an internal reference relatively low in D_2 (the occipital cortex) as is common practice in PET/SPECT imaging (Booij et al., 1997a; Lidow et al., 1991). We found a relative increase in CBF in several key DAergic areas such as putamen bilaterally, ACC and cerebellum. However, part from one ICA component, no correlations were found with sCBF changes and D_{2/3} receptor availability and behavioural measures. This study demonstrates that phMRI with an i.v. dAMPH challenge elicits a hemodynamic response that is most likely attributable to an increase in DAergic signalling.

These results are expanded upon in chapter 3, where we collected BOLD based resting state data using an i.v. dAMPH challenge and used several data analysis techniques to further substantiate our hypothesis that phMRI is able to detect alterations in monoaminergic function. Also using BOLD, we observed an increase in brain hemodynamics using independent component analysis (ICA), providing additional proof using a data-driven rather than a hypothesis-driven technique, that dAMPH causes an increase in the BOLD
signal. Furthermore, using a seed-based analysis we first replicated a functional connectivity pattern as reported in previous work by DiMartino and colleagues and subsequently showed that this pattern is affected by dAMPH (Di Martino et al., 2008). We also showed that two known functional connectivity networks (one of the frontoparietal networks and the fronto-executive network) are affected by dAMPH. Taken together, these findings provide further proof that dAMPH alters DAergic signalling and that this can be detected using different, relatively non-invasive MRI techniques.

In order to assess the DAergic system in a fully non-invasive manner (without venous puncture), we performed a series of experiments, the first discussed in chapter 4, involving an oral challenge with a commonly available DAT-blocking psychotropic drug: MPH. In order to detect alterations in the DAergic system, we compared healthy subjects with subjects that used dAMPH recreationally. Preclinical and clinical studies indicate that dAMPH users are likely to have less available DAT than healthy controls. Unfortunately, we were not able to replicate these results with our FP-CIT SPECT study. Although we showed that DAT binding ratios were on average lower in dAMPH users, this result was only trend significant, most likely due to sample size issues. However, ASL-based phMRI with an oral MPH challenge demonstrated a significant difference between controls and dAMPH users (chapter 4). Healthy controls showed a significant decrease in CBF in key DAergic areas such as striatum, thalamus and hippocampus in response to an oral MPH challenge, in line with earlier research. However, in dAMPH users this response was (severely) blunted, only showing a slight decrease in the orbitofrontal PFC and hippocampus. We interpreted this to be the effect of repeated exposure to dAMPH, causing neurotoxic damage to the DAergic system, although alternative hypotheses involving drug addiction theories and sensitisation mechanisms may also be involved.

The results were confirmed in a second series of experiments (chapters 5, 6 and 7) involving fMRI imaging. For the first task we looked at all the healthy subjects from the studies described in chapters 2, 3 and 4. These subjects performing a DAergic task that addressed executive function, the Go/NoGo task both before and after respectively oral MPH or i.v. dAMPH administration (chapter 5). Interestingly, oral MPH decreased task activation in the frontostriatal system, where dAMPH increased task activation in the sensorimotor cortex. The explanation for this apparently counterintuitive result must be sought in the type of challenge used, where oral MPH causes a relatively slow rise in DA by blocking DAT and i.v. dAMPH causes a quick increase in DA by both blocking DAT and actively releasing DA.

The second experiment, examining both healthy subjects and dAMPH users, involved a task targeting anticipation of reward (chapter 6), which mainly induces ventral striatal activation, which is thought to be dependent on DAergic signalling (Knutson et al., 2001). At baseline, dAMPH users showed less activation in the ventral striatum, a key area in reward processing, compared to control subjects. After MPH challenge healthy controls
again showed a decreased activation in the striatum, whereas in dAMPH users no such response was observed. Indeed, when investigating larger groups it would be likely that the reward processing is normalised by MPH, moving activation from the dorsal to the ventral striatum. This is substantiated by the fact that in the emotional faces task (chapter 7), again dAMPH users showed lower activation levels compared to healthy controls, which normalised after MPH administration. This is an indication that the effects of MPH may also be indirect, as the emotional faces task has been found to activate 5-HT-ergic areas, rather than the DAergic areas (Hariri et al., 2002).

We performed similar, though much less extensive work on the role of phMRI in assessing 5-HT (dys)function, again comparing an altered 5-HT system to a normally functioning one (chapter 8). This was an elaboration on previous work in users of MDMA, a substance which is known to affect the 5-HT system, as reflected for instance by a reduction in SERT binding ratios. We replicated this earlier work, using the validated SERT label β-CIT, demonstrating that the 5-HT system in the occipital cortex of our MDMA users was indeed affected, as this brain region contained lower SERT binding ratios compared to healthy controls. We examined the usefulness of phMRI in detecting similar dysfunction, using an i.v. SSRI challenge using a slightly different ASL-based phMRI sequence. MDMA users responded significantly different to this challenge than healthy controls, mainly in the thalamus and occipital cortex, suggesting that phMRI may be even more sensitive in assessing 5-HT dysfunction than SPECT. Arguing against this, is the fact that our healthy controls showed no significant response to the challenge, where other studies did show such an effect (Del-Ben et al., 2005; McKie et al., 2005). This may be explained by the fact that the acquisition method we used was less sensitive to signal changes than the one used in the studies involving dAMPH and MPH challenges. An added finding in the same group of MDMA users (chapter 9) was that they were found to have smaller hippocampal volumes compared to healthy controls, although this finding needs to be replicated in larger samples in order to draw definite conclusions.

These studies taken together suggest that ASL-based phMRI is able to differentiate between monoamine systems in healthy subjects and those whose monoamine systems are affected by psychotropic drugs. Thus, this technique may be applied to groups of subjects whose monoamine systems are expected to be altered either by disease, such as ADHD and Parkinson’s, or by the use of psychotropic medications. The findings of the present thesis paved the way for the studies we describe in chapter 10 of this thesis, which are currently being executed. We designed two randomized controlled trials to investigate the effects of psychotropic medications on the developing brain. Children and adults with ADHD and MDD are recruited to determine the age dependency of the effects of MPH and SSRI treatment on the developing brain. This is based on the hypothesis that the treatment with psychotropic drugs during brain development may lead to a different outgrowth of monoamine systems.
causing lasting effects of treatment, whereas the developed brain will only be temporarily affected during the use of these medications. This is combined with a cross-sectional medical prescription cohort based study in which we determine whether long-term effects of early treatment with psychotropic drugs on the developing brain are still detectable in adulthood. This will provide a wealth of knowledge in order that both medical professionals and parents are able to make a more informed decision regarding medical treatment of children suffering from these disorders.

In conclusion, we demonstrated that both users of dAMPH and users of MDMA have detectable differences in monoaminergic function when compared to healthy controls. The fact that differences in monoaminergic systems were found using several imaging techniques and behavioural tests, shows that phMRI is a valuable added tool in the imaging of monoaminergic function. This gives a clear basis for the further use of ASL-based and fMRI-based phMRI in the assessment of dysfunctioning monoamine systems both in patients suffering from neuropsychiatric disorders, as groups being treated for those disorders with psychotropic medications.

DEVELOPING BRAIN ASSESSMENT

Research in younger populations is pivotal to understanding the effects of psychotropic drugs on brain development. For example, 5-HT seems to be a promoter of the growth of 5-HTergic neurons (Azmitia et al., 1990; Shemer et al., 1991; Won et al., 2002). Consequently, treatment with SSRI’s would be expected to raise 5-HT levels en thereby influence the development and possibly function of the system which may lead to distinct differences in adult outcome. Much less is known on the development and outgrowth of the DAergic and NAergic systems and the influences psychotropic drugs can have on these processes. However, treatment of ADHD with the DAT blocker MPH seems to lead to a reduced chance of developing a substance use disorder and conduct disorder, though possibly increasing chances of developing depression and anxiety disorders (Andersen et al., 2002; Molina et al., 2009). The mechanisms behind these possible behavioural adjustments induced by a DAergic treatment remain to be investigated.

PROSPECTIVE RESEARCH

An important potential limitation of above mentioned studies is the causality of the findings, as the reported studies in this thesis all were cross-sectional studies. Clearly, prospective studies are the best way to investigate the effects of psychotropic drugs on brain development. The information they yield can be combined with existing knowledge to create a more comprehensive picture of the effects of drug treatments, such as has been done in MDMA research (de Win et al., 2006; Reneman et al., 2001; Reneman et al.,
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2002). Information from behavioural, anatomical and functional brain imaging together may shed light on the differences in development and the effects on functional outcome. Ideally, one would design an experiment whereby drug-naive children and adults, both with and without ADHD are treated randomly with either MPH or placebo for several years, with extensive neuropsychological testing and MRI scanning before, during and after treatment, with regular follow-up intervals (for example one year, three years and eight years after medical treatment). However, this is logistically and financially next to impossible.

The next best option would be to combine a short randomized controlled trial with cross-sectional retrospective studies involving subjects that have received psychotropic medications during a similar period of brain development. Recently databases have been developed, registering all manner of patient data. When an objectifiable source of pharmacological medical history exists, this facilitates generating research into the long-term effects of drug treatments, especially in the developing brain. Hopefully, future work in this field will allow us to make more founded statements regarding the effects of psychotropic treatments on the development of neurotransmitter systems, allowing for both physicians and parents to make more informed choices for their patients and children.

A STEP INTO THE FUTURE OF MONOAMINERGIC IMAGING

One of the exciting new directions in assessment of neurotransmitter function comes from the fields of neurosurgery and psychiatry. Deep brain stimulation (DBS) uses a surgically placed electrode in the brain to manipulate neurotransmitter release and is used in the treatment of Parkinson’s disease, obsessive compulsive disorder and depression (for review (Fige et al., 2013)). Recently, preclinical work has led to the development of electrodes that can not only stimulate brain tissue, but also measure neurotransmitter levels (Diczfalusy et al., 2012). This allows the detection of effects of neurostimulation on neurotransmitter levels in the brain tissue that is targeted. MRI investigation of patients who have received a DBS implant could shed more light on the working mechanisms behind neurostimulation. However, as implants induce artefacts in the MR images and are accompanied with extra safety requirements the technical challenges in setting up such studies may prove to be insurmountable. If successful, further research combining these techniques with phMRI may lead to more knowledge on both DBS as neurotransmitter function in general. However, due to the invasive nature of the surgical procedure, it will be a long time before this preclinical work will lead to results in a human population.

Another recent development in the field of neuroscientific research which allows for the measurement of neuronal function is known as optogenetics (Deisseroth, 2011; Deisseroth, 2012). Hereby, genetic material from light-sensitive micro-organisms is introduced into particular cell populations. By shining light of a specific frequency on the brain tissue, activity of the affected cells can be controlled. Validation of this technique has
shown that specific neuronal activity can be achieved (Deisseroth, 2011; Deisseroth, 2012). This technique has been used to demonstrate the release of DA from the striatum (Bass et al., 2010). By pharmacological manipulation one can register in vivo what the effect is of the administered drug on the light-induced DA release in the striatum. If concurrent ASL-based phMRI is added, the hemodynamic response can be directly related to activity of neurotransmitter specific functional architecture such as the striatum.

CONCLUDING REMARKS
The results of this thesis demonstrate that phMRI is a valuable added tool in the imaging of monoaminergic function. I have shown that the i.v. administration of dAMPH leads to a significant hemodynamic response in DAergic areas, most likely reflecting attenuation of DAergic signalling. In addition, resting state studies demonstrated alterations in functional connectivity networks involved in DAergic signalling. Moreover, altered DAergic responses were also demonstrated using fMRI involving a DAergic task.

A second series of experiments showed that MPH, although giving a different response than i.v. dAMPH, also influences the hemodynamic response in monoaminergically relevant areas. Also with BOLD based fMRI, MPH was shown to greatly affect DAergic function studied using fMRI shows that MPH has a great influence on signalling in adult humans. The assessment of alterations of monoaminergic functions caused by psychotropic drugs has been sufficiently demonstrated in adult populations by comparing healthy adults to dAMPH users. The chronic use of dAMPH demonstrably alters responses to an oral MPH challenge.

Finally, we showed that chronic use of MDMA leads to a difference in the hemodynamic response to a challenge with the SSRI citalopram, which overlapped with the SPECT findings. These experiments taken together implicate that these techniques can be applied in research performed in children in order to safely assess neurodevelopment of monoaminergic systems and variations in this development either physiological or induced by external interventions. In addition, it provides further evidence that dAMPH use alters DAergic function and may indeed lead to neurotoxic alterations of the DAergic system.