

Chapter 9

Summary and general discussion

Summary and conclusions

Schizophrenia and autism spectrum disorder (ASD) are severe mental disorders with specific differences. For instance, ASD is often diagnosed in the first few years of life, whereas the first symptoms of schizophrenia usually appear in adolescence. Furthermore, ASD is often accompanied by a learning disability, contrary to schizophrenia. Nevertheless these disorders also have similarities. On a genetic level they share an increased risk due to copy number variations and rare specific loci and alleles (Carroll and Owen 2009). On an intermediate phenotype level they share specific findings in volumetric brain studies (Cheung et al 2010) and impaired stimulus filtering (Perry et al 2007;McAlonan et al 2002;Kumari et al 2008). On a clinical phenotype level they share deficits in social behavior, oddness of speech, unusual responsiveness to the sensory environment, isolated skill areas, and inappropriate affect. Furthermore both disorders have a chronic course in the majority of patients.

Schizophrenia is usually preceded by a prodromal period, with mild positive psychotic and negative symptoms, non-specific symptoms and a decline in psychosocial functioning. Using specific assessment instruments it is possible to diagnose patients at Ultra High Risk (UHR) for developing psychosis, of which 10-40% will indeed eventually develop psychosis (Yung and McGorry 1996;Yung et al 2003;Klosterkotter et al 2001;Miller et al 2003). Similarly, ASD is also associated with an increased risk of 14 – 34% for developing psychosis (Stahlberg et al 2004;Tsakanikos et al 2007;Mouridsen et al 2008), with specific subtypes like multiple complex developmental disorder (McDD) having even higher transition rates (Sprong et al 2008;van Engeland and van der Gaag 1994). One could therefore tentatively state that ASD patients, as UHR patients, are also at clinically or even at ultra high risk to develop psychosis.

We used various in vivo brain imaging techniques to assess brain anatomy and function in these two disorders. With diffusion tensor magnetic resonance imaging (DT-MRI) it is possible to study white matter integrity, and previous studies show that integrity is decreased in schizophrenia subjects (Konrad and Winterer 2008;Friedman et al 2008), and there is evidence that white matter may be abnormal in high risk populations although changes have not been consistent across studies. Similar to schizophrenia, ASD has also been called a connectivity disorder, in which disrupted white matter adds to the symptomatology and pathophysiology of the disorders. DT-MRI studies in children and in mixed children/adults groups with ASD have also shown specific abnormalities in white matter (Barnea-Goraly et al 2004;Keller et al 2007;Alexander et al 2007;Lee et al 2007).

Nuclear imaging studies have shown that dopaminergic neurotransmission is disrupted in schizophrenia (Abi-Dargham et al 2000;Abi-Dargham et al 2009), and recent studies showed evidence for abnormal dopamine synthesis in UHR subjects (Howes et al 2009) and altered relations between hippocampal glutamate and presynaptic dopamine function (Stone et al 2010).

In this thesis we sought to further explore the above mentioned theories. The overall aim of the studies described in this thesis was to increase our knowledge on the brain structure and function of UHR subjects and people with ASD. We focused on these groups of patients as they are thought to be at increased or at ultra high risk for developing psychosis. Specifically we sought to answer the following questions; is there enough evidence for specific treatment of UHR patients? Do UHR subjects who later develop psychosis have specific white matter integrity abnormalities compared to UHR subjects who do not and to controls? What is the current literature on challenge studies using alpha-methyl-*para*-tyrosine (AMPT)? Do UHR subjects have abnormalities in striatal dopaminergic function? Is there a relation between hippocampal glutamatergic function and striatal dopamine in UHR patients and do glutamate levels differ from controls? Is psychosis in ASD associated with specific structural brain differences? Do people with Asperger syndrome have white matter integrity abnormalities?

Chapter 1 contained a general introduction and the outline of the thesis. In **Chapter 2** the current literature on interventions in UHR patients was reviewed. The positive (acute) effect reported in three randomized clinical trials with antipsychotic medication and/or cognitive behavioral therapy disappeared at the end of treatment. This suggests that treatment does not prevent but may delay the transition to psychosis. Other naturalistic studies present a hypothesis about a possible preventive effect of antidepressants. Improved prediction of transition to psychosis and a decrease of the number of false positives are needed. At this time the data concerning the benefits and risks do not justify prodromal intervention as standard clinical practice. In **Chapter 3** we described the results of a DT-MRI study, and report that UHR subjects that later develop psychosis (UHR-P) compared to UHR subjects who do not develop psychosis (UHR-NP) have reduced fractional anisotropy (FA) of white matter (WM) lateral to the right putamen and of the left superior temporal lobe, and higher FA of the left medial temporal lobe. Furthermore UHR-P subjects also have reduced FA compared to healthy controls in medial frontal lobes bilaterally. These regions have been found to be involved in psychosis and are associated with severity of psychotic symptoms in other samples. The putative changes in connectivity that these FA differences represent may play a role in the development of psychosis or its symptomatology, or conversely may be a result of this process. From our

data it appears that, compared to the more extensive frontal differences with healthy controls, relatively subtle differences in WM integrity in temporal and striatal brain regions may influence whether an UHR subject develops psychosis. **Chapter 4** reviewed challenge and therapeutic studies using AMPT in neuropsychiatric disorders. The reviewed studies show that catecholamine depletion induced by AMPT provides an useful paradigm for elucidating the function of catecholaminergic pathways. Furthermore, there is promising evidence that AMPT has some beneficial effects in patients with dyskinesia, Huntington's chorea, Tourette syndrome, mania, substance abuse, 22q11 deletion syndrome and psychosis. Side effects, although seldom severe, are common and it is recommended to limit the dose as much as possible. In **Chapter 5** we combined SPECT imaging of dopamine D_{2/3} receptors with dopamine depletion in UHR subjects and age, gender and intelligence quotient (IQ) matched controls. The data suggests that there may be a subgroup of UHR patients that already has abnormalities in dopaminergic neurotransmission. This subgroup is characterized clinically by high scores on positive symptom scales, and has elevated dopamine receptor occupancy by endogenous dopamine compared to the low positive symptom UHR subgroup and compared to healthy controls. Furthermore the relatively low AMPT dose we used leads to similar dopamine depletion in controls as higher doses used by other groups, but also to significant positive symptom reduction in UHR patients, as has also been shown in schizophrenia. High occupancy of dopamine D_{2/3} receptors by endogenous dopamine predicted good response of positive symptoms to AMPT in UHR patients. In **Chapter 6** we investigated the relation between left hippocampal glutamate levels (measured by Proton Magnetic Resonance Spectroscopy (1H-MRS)) and postsynaptic dopamine D_{2/3} receptor availability and receptor occupancy by endogenous dopamine in UHR subjects and controls. A recent study reported a negative relation between left hippocampal glutamate levels and presynaptic [¹⁸F]DOPA uptake in the left striatum of UHR patients, but not in healthy controls. Additionally this study reported evidence that this relationship may predict later transition to psychosis. We found no evidence that glutamate is also related to postsynaptic dopamine neurotransmission UHR subjects or controls, but found statistically significantly decreased glutamate levels in the left hippocampus of UHR subjects compared to controls. Decreased hippocampal glutamate has also been reported in schizophrenia (Lutkenhoff et al 2010), and our data suggest that altered glutamate levels may influence the development of psychosis. In **Chapter 7** we studied psychosis in (non learning disabled) adult ASD patients by performing a voxel based morphometry analysis between people with autism with comorbid psychosis and people with autism without psychosis. Additionally we also compared the autism groups with age, IQ and gender matched healthy controls. Compared to controls, both ASD groups had statistically significantly less grey matter

bilaterally in the temporal lobes (including the fusiform gyrus) and cerebellum, and reduced white matter in the cerebellum. The ASD groups had increased grey matter in striatal regions. However ASD patients with psychosis also had a significant reduction in grey matter content of frontal and occipital regions. *Within* ASD comparisons revealed that psychosis was associated with a bilateral reduction in grey matter of cerebellum and the fusiform gyrus. We concluded that the pre-existing anatomical differences in brain systems also implicated in psychosis may reduce the additional disease burden required to develop co-morbid psychotic symptoms. Our study also suggests that the biology of psychosis in people with ASD may differ from that in the non-autistic population. In **Chapter 8** we described the results of the first DT-MRI study in Asperger syndrome. As there are indications that brain abnormalities may progress into adulthood we compared adults with Asperger syndrome to age, gender and IQ matched healthy controls. Adults with Asperger syndrome had a significantly lower FA than controls in thirteen clusters. These were largely bilateral and included white matter in the internal capsule, frontal, temporal, parietal and occipital lobes, cingulum and corpus callosum. Our results are in line with studies in children with autism, although we found more extensive (and bilateral) differences. Our results suggest that people with Asperger syndrome have widespread abnormalities in the microstructural integrity of white matter, in regions previously associated with ASD and its symptomatology. Further, these findings add to increasing evidence that people with ASD have differences in long-range (inter-regional) brain connectivity.

CONCLUSIONS

The aim of the studies described in this thesis was to increase our knowledge on the brain structure and function of people with an increased risk for developing psychosis. We focused on two groups; 1) patients with an Ultra High Risk for developing psychosis according to international criteria; 2) patients with an autism spectrum disorder. The main conclusions of this thesis are:

1. Ultra High Risk subjects that later develop psychosis (UHR-P) have reduced fractional anisotropy (FA) of white matter lateral to the right putamen and of the left superior temporal lobe and higher FA of the left medial temporal lobe compared to subjects that do not develop psychosis (UHR-NP).
2. UHR-P subjects have reduced FA in white matter of medial frontal lobes bilaterally compared to healthy controls.

3. A subgroup of UHR subjects has elevated dopamine D_{2/3} receptor occupancy by endogenous dopamine. This subgroup is characterized by more severe positive symptoms.
4. Positive symptoms decrease following dopamine depletion (induced pharmacologically by AMPT) in UHR subjects, comparable to observations in schizophrenia, suggesting a similar mechanism.
5. In UHR subjects, higher dopamine D_{2/3} receptor occupancy is associated with more positive symptoms and with a greater decrease of positive symptoms after acute dopamine depletion.
6. Glutamate in the left hippocampus of UHR subjects is not related to postsynaptic striatal dopamine D_{2/3} receptor availability or occupancy by endogenous dopamine.
7. UHR subjects have decreased left hippocampal glutamate levels compared to healthy controls, comparable to observations in schizophrenia.
8. Psychosis in autism is associated with reductions of grey matter in cerebellum and fusiform gyrus compared to non psychotic people with autism.
9. Adults with Asperger syndrome have widespread reductions in FA of white matter.

Discussion

This thesis contains various studies that study possible biomarkers for psychiatric disorders. A biomarker suggests that the disorder is an objective and value free concept. This is interesting as mental disorders are probably most value-laden of all medical conditions. To explore this paradox thoroughly is beyond the scope of this thesis, but it is interesting to take a closer look at what we are actually measuring, and at what point in the disease process.

We conducted two studies which looked at the quality or integrity of WM tracts. WM bundles that are used frequently are restructured to work more efficiently, and for instance become more myelinated, which leads to lower FA values in DT-MRI imaging (Basser 1995). WM bundles that are not much used are less myelinated and even get pruned with time (Giorgio et al 2010). It seems thus that WM structure follows its usage (excluding certain disorders that have WM degeneration as core feature, which does not apply to schizophrenia or autism). This implies that structural changes in WM can inherently only

be of limited value in prediction of, for instance, transition to psychosis as these changes are occurring in response to altered patterns of usage. So when we look at WM integrity changes, we are looking at something that is the result of the disease, much like the symptoms a patient is experiencing. So what makes WM interesting then? It may very well be that WM changes occur before symptoms actually increase to psychotic intensity in patients, and thus WM abnormalities may still predict who will develop frank psychosis. Further, although we are not likely looking at the core of the disease, what we are looking at is a roadmap of the brain and its usage. Therefore the changes in WM connections tell us that something is happening differently or abnormally in the grey matter regions they are connecting and hence may direct us to the cause of the WM abnormalities.

Striatal dopamine dysfunction also seems to occur at the etiological end of the symptoms of schizophrenia, and is thought to be the final common pathway. It may however be one step closer than WM changes, as abnormal striatal dopamine function may cause symptoms but may also cause WM integrity changes close to the striatum as we reported in Chapter 4. For dopamine it has already been more defined what it is we are measuring, given the dopamine hypothesis and Kapur's interpretation of its importance in salience (Kapur 2003). As we reported in Chapter 5 positive symptoms are also related to dopamine receptor occupancy by its natural neurotransmitter. Nevertheless there are remarkable things about dopamine. Increasing dopamine does not cause positive symptoms in most people, a view that is strengthened by the amount of recreational use of dopamine boosters like cocaine, amphetamines and cannabis, although increased salience is likely to be what drives (initial) use of these drugs. A regular dopamine challenge with amphetamine increases extracellular dopamine in the striatum by around 400% (Breier et al 1997) and does not necessarily cause psychotic symptoms. So if increased dopamine is not enough in most people to cause psychosis, something else must be mediating its effect. This is in line with the fact that we find only modest increases in dopaminergic transmission in schizophrenia, which often partly overlap with control groups (Abi-Dargham et al 2000; Abi-Dargham et al 2009; Laruelle et al 1996), although our methods to measure these differences are still quite crude. Neuroanatomically, positive symptoms like hallucinations and delusions are probably not formed in the striatum but in the cortex, so hypothetically the cortex could differ in dopaminergic sensitivity, either inherently or mediated by another agent. This hypothesis is supported by recent evidence for separate regulation of striatal and extrastriatal dopaminergic systems (Cervenka et al 2010). For instance there is increased scientific interest in the role of dopamine in cognition. Perhaps difficulties in performing cognitive tasks that occur in schizophrenia, which are cortical processes, could influence or moderate cortical dopaminergic sensitivity, or influence this indirectly via the thalamus (de Manzano et al 2010). It is postulated that dopamine

influence on cognition follows an inverted U-curve, and thus dopamine has an optimum level for successful cognitive functioning (Williams and Goldman-Rakic 1995). However, one could conversely hypothesize that cognitive problems, as for instance formal thought disorders, could disinhibit delusional logic and thought in susceptible patients.

Our research has focused to some extent on the dimensional model of mental disease, and has looked at for instance psychosis (or positive symptoms) within UHR and ASD subjects. As already mentioned in the introduction, one could therefore tentatively state that ASD patients, as UHR patients, are at increased risk to develop psychosis. Nevertheless the mechanism of psychosis in autism may be different from schizophrenia, as results from Chapter 6 also suggest; psychosis in autism is associated with other grey matter abnormalities than are usually associated with psychosis in schizophrenia. However, it is interesting to see that both UHR and ASD subjects appear to have only subtle brain differences associated with the occurrence of psychosis. What may be trivial for UHR subjects, might be interesting (but tentative) for autism; they are associated with increased risk for psychosis and are neuroanatomically quite similar to people with the same diagnosis who also developed psychosis.

LIMITATIONS

This thesis and the experiments in it have certain limitations. The specific limitations have been discussed in the relevant chapters, nevertheless a few that may have general implications are summarized here. As a whole, imaging studies and the recruitment of specific complex patient groups as UHR patients and patients with Asperger syndrome is very time consuming. Consequently some of the experiments in this thesis have a limited sample size, which could lead to type 2 errors. Nevertheless we were able to detect statistically significant differences with large effect sizes. It is possible that future larger studies may find additional subtle differences. Also, in some experiments only males were included, which limits the generalizability, but at the same time this increases specificity as results are not confounded by gender differences. We used SPECT imaging which has a limited spatial and temporal resolution. Future studies could use PET as this technique has a higher spatial resolution and sensitivity than SPECT. This offers the opportunity to study the different *subregions* of the striatum, as it is mostly the ventral part that is hypothesized to be important for psychosis and schizophrenia. Studying schizophrenia is inherently difficult as the disorder is very heterogeneous and probably encompasses multiple different diseases. The UHR concept does not unambiguously lead to schizophrenia and thus this increases heterogeneity of the sample even more. This is an inherent problem of the classification systems, but this makes the findings in subgroups of the sample interesting and scientifically plausible, as we see in Chapter 5.

STRENGTHS

This thesis also has specific strengths. In this thesis highly original studies were reported. For instance the first DT-MRI study of psychosis in UHR was conducted, as well as the first imaging study of psychosis in autism, both with interesting results. Also the first DT-MRI study in Asperger was reported, a relatively under researched patient group. Furthermore we conducted the first dopamine depletion SPECT study in UHR patients. All but one (chapter 7) of the clinical studies were conducted in patients who did not take anti-psychotics and lastly the control groups were always matched for IQ, age and gender.

FUTURE DIRECTIONS

We plan to complete follow-up of the SPECT study described in chapter 5 to elucidate which UHR patients will develop psychosis and what the relation is to pre-psychosis striatal dopaminergic neurotransmission. However, due to the relatively low sample size, it is unlikely that we will come up with definitive conclusions about changes in receptor occupancy after transition to psychosis.

Seeing the ongoing discussion about dopamine and its relation to schizophrenia, but probably more specifically to positive symptoms, it would be very interesting to design a study which could provide more clarity in this relationship. For instance a longitudinal study in schizophrenia where a depletion PET (which has a higher spatial resolution than SPECT and can therefore identify subregions of the striatum adequately) will be performed at the time of active non-medicated first episode psychosis, followed by a retest when positive symptoms are normalized and medication has been stopped, and in turn followed by a second retest when symptoms have increased again but medication has not yet commenced. Notwithstanding the ethical difficulties in this design (which could be overcome) this design could answer interesting questions, for instance; is increase in symptoms individually accompanied by increase in dopamine? How much increase in dopamine causes how much increase in symptoms? What is the variance? Can symptoms increase while dopamine does not or decreases? In general; how closely is dopamine related to symptoms? This is interesting as these studies have until now always been done non-longitudinally, which limits what can be concluded.

Another field which has received little attention is dopaminergic neurotransmission in ASD and more attention has gone towards serotonin abnormalities and function (Posey et al 2008). It is hypothesized that a hyperdopaminergic functioning of the brain might explain overactivity and stereotyped movements in autism, and it is known that dopamine agonists worsen these symptoms. Also it is known that blockage of dopaminergic receptors

decrease stereotyped and hyperactive behavior in ASD. Moreover, some dopamine receptor antagonists like the antipsychotic drug risperidone are quite commonly used to treat these symptoms, and the few clinical trials that have been done in these subjects showed at least temporary effect on behavior. Although dopaminergic neurotransmission has not been thoroughly researched in ASD, there is preliminary evidence of abnormalities. One [¹⁸F]-DOPA PET study was done which showed a decrease by 39% of regional [¹⁸F]-DOPA accumulation in the anterior medial prefrontal cortex (Ernst et al 1997). Another showed increased dopamine D_{2/3} receptor binding in the caudate nucleus and putamen as a whole (Fernell et al 1997). Both these studies were done in children and there is no literature on dopaminergic neurotransmission in adults with ASD. Therefore it would be very interesting to conduct a dopamine depletion study with PET or SPECT to look at striatal dopamine D_{2/3} receptor occupancy in ASD patients, as this is the target for antipsychotic drugs used to treat some of the symptoms in ASD. The striatal dopaminergic neurotransmission could be related to autistic symptomatology (especially hyperactive and stereotyped behavior) but also to measures of psychotic symptoms in these patients. This could give much needed understanding of why (often off-label prescribed) use of antipsychotics decrease some of the symptoms associated with ASD.

Overall the combination of techniques appears to be most promising in imaging research, as for instance combining (depletion) SPECT/PET and 1H-MRS, PET and functional MRI (fMRI), SPECT/PET and DT-MRI, or combining multiple tracers in nuclear imaging, but always combined with clinical measures of symptom severity. This enables us to bridge the islands of knowledge already obtained in the separate imaging fields, and to discover what the relationship between them is. This is crucial as each provides information on different aspects of the total function, as the instruments do in music. White and grey matter integrity and density (measured by DT-MRI and MRI) acting as rhythm section providing the basic structure; glutamate and GABA (1H-MRS) as the bass section providing more tonal boundaries for the other instruments by inhibiting and disinhibiting; dopamine receptor availability and occupancy (SPECT and PET) as chords section played by piano which colors the timbre and loudness of the music; and cortical activation (fMRI) acting as the solo trumpet, playing the actual melody and improvising within (and around) the boundaries set by the other instruments. The need to study their interrelationships is the way of the future. As in music, the importance of their acting in concert is greater than the sum of their individual contributions. Nevertheless, in this age of biological psychiatry it must not be forgotten that time, place and audience are the final referees that decide if the music is either brilliant or crazy.

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