Challenges of brain imaging in psychiatry: understanding brain structure and function in schizophrenia

da Silva Alves, F.

Citation for published version (APA):
da Silva Alves, F. (2012). Challenges of brain imaging in psychiatry: understanding brain structure and function in schizophrenia

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Summary, Conclusions, General Discussion
Summary

Schizophrenia is the most severe and highly heterogeneous psychotic disorder characterized by a variety of clinical symptoms including disturbances in perception, cognition, emotion and behavior and a decline in general functioning. Similarly, the genetic disorder 22q11DS has been characterized by psychiatric disorders, cognitive disabilities, behavioural problems and a decline in functioning in a subset of patients. Moreover, people with 22q11DS are at increased risk to develop schizophrenia-like psychosis. This makes 22q11DS a unique model to explore the neural substrates to vulnerability and etiology of schizophrenia.

Current evidence from in vivo brain imaging corroborates earlier speculations about the relation of schizophrenia with brain abnormalities. In fact, altered brain structure and function have been linked to psychosis and cognitive impairments in both schizophrenia and 22q11DS. The overall aim of this thesis was to enhance our understanding of the underlying neural correlates of schizophrenia. We used various MRI methods to investigate aspects of brain structure and function that could be related to the etiology of schizophrenia. We focused on three groups: patients with 22q11DS (with and without schizophrenia), patients with idiopathic schizophrenia and healthy individuals. Because altered white matter structure, glutamate and dopamine neurotransmission have been implicated in schizophrenia, we sought to answer questions such as: do people with 22q11DS who develop schizophrenia have specific white
matter abnormalities compared to 22q11DS without schizophrenia, idiopathic schizophrenia and healthy controls? Is glutamatergic dysfunction also a feature in 22q11DS with schizophrenia? And what are the effects of dopamine depletion to the brain reward circuitry in healthy individuals and in schizophrenia?

Chapter 1 contained a general introduction and outline of the thesis. In chapter 2 we reported the results of the first study of white matter integrity in adults with 22q11DS with and without schizophrenia compared to patients with schizophrenia and to healthy controls. In line with earlier studies in children and adolescents, we show that adults with 22q11DS have decreased white matter volume in posterior and temporal regions of the brain. We present evidence for decreased fractional anisotropy indicating impaired white matter integrity in regions of the frontal cortex in the whole 22q11DS group compared to healthy controls. Furthermore, in the 22q11DS group severity of positive and negative symptoms were associated with reduced fractional anisotropy in areas previously implicated in schizophrenia mainly in frontal, cingulate, insula and temporal areas. Although our direct comparisons did not show significant white matter differences in 22q11DS with schizophrenia compared to 22q11DS without schizophrenia, we found fractional anisotropy reductions encompassing inferior frontal white matter in 22q11DS with schizophrenia vs. healthy individuals. This finding was similar to our fractional anisotropy results of idiopathic schizophrenia vs. healthy controls. In summary we conclude that decreased white matter volume in posterior brain is intrinsic to 22q11DS and independent of schizophrenia. The development of schizophrenia in 22q11DS probably requires disruptions of inferior frontal and temporal white matter fibers. Thus, widespread decreased fractional anisotropy in frontal areas and consequently disrupted neuronal communication via white matter fibers of the inferior frontal and temporal lobes may be related to psychotic symptoms in patients with 22q11DS with schizophrenia.

In chapter 3 we hypothesized that glutamatergic abnormalities may be present in 22q11DS with schizophrenia because glutamate dysfunction has been thought to be partially underlying the psychopathology of schizophrenia. Moreover, people with 22q11DS are vulnerable for genetic haplo-insufficiency of PRODH - a gene coding for an enzyme that is involved in converting proline into glutamate. We employed $^{1}\text{H-MRS}$ and found increased concentration of glutamate and Glx (combined glutamate and glutamine) in the hippocampal region of 22q11DS with
Schizophrenia compared to 22q11DS without schizophrenia and compared to healthy controls. This suggests that glutamatergic disturbances may be underlying psychotic symptoms in 22q11DS with schizophrenia. Increased hippocampal glutamate could also explain cognitive impairments in 22q11DS with schizophrenia since hippocampus is crucial in learning and memory function. In addition to glutamate, myo-inositol was another neurometabolite that was increased in 22q11DS with schizophrenia compared to 22q11DS without schizophrenia. Changes in myo-inositol levels are thought to reflect abnormalities in intracellular signalling mechanisms and neuronal development. High concentrations of myo-inositol have been associated with reduced cognitive ability in Alzheimer and Down syndrome. We speculate that disrupted hippocampal neurometabolism has a role in the psychopathology and development of schizophrenia in 22q11DS. We found no evidence for altered metabolism in the prefrontal cortex in our sample. We speculate that antipsychotic drugs could have affected metabolite concentrations in frontal brain regions in 22q11DS with schizophrenia. In fact, in the prefrontal cortex, unlike in the hippocampus, we found a significant association between dosage of medication and metabolite concentration in 22q11DS patients with schizophrenia. We conclude that altered glutamate and myo-inositol metabolism may explain part of psychotic symptoms and cognitive impairments associated with 22q11DS.

In chapter 4 we reviewed studies of pharmacological MRI (PhMRI) that investigated the effect of atypical drugs on prefrontal and striatal brain activity in schizophrenia. Most of the studies reported enhanced prefrontal activity and regulation of striatal functioning following treatment with atypical antipsychotics. These PhMRI findings support the revised dopamine hypothesis of schizophrenia by confirming hypoactivity of the prefrontal cortex and following treatment with atypical antipsychotics, improvement of prefrontal and subcortical function reflecting normalized dopaminergic activity.

In chapter 5 we combined fMRI with a pharmacological challenge using α-methylparatyrosine (AMPT) to investigate the effects of dopamine depletion on neuronal pathways underlying reward-related brain activity in the normal human brain. We found increased brain activation in the striatum and cingulate gyrus during anticipation of monetary reward in the placebo condition. The comparison of placebo vs. AMPT showed increased activation in the cingulate gyrus during anticipation of reward and the medial frontal gyrus during anticipation of loss. Fol-
following dopamine depletion we found no significant brain activation in
the dopamine related areas that were activated in the placebo condi-
tion. Healthy controls showed the recruitment of the insula, frontal and
parietal cortices during anticipation of reward compared to anticipation
loss in the AMPT condition. This could suggest a compensatory role of
these brain areas when dopamine transmission was reduced. Reduced
dopaminergic transmission and brain activation after dopamine deple-
tion were also indirectly supported by measurements of prolactine and
peripheral dopamine markers. In summary, our findings supports the hy-
pothesis that dopaminergic neurotransmission in frontal and striatal ar-
 eas plays an important role in anticipation of monetary reward in healthy
humans.

In chapter 6 we investigated the effects of dopamine depletion in
patients with schizophrenia and how it would interfere with striatal acti-
vation and activation of the brain reward system compared to healthy
controls. Pharmacological challenge with AMPT blunted overall brain
activation in patients during anticipation of monetary reward and loss.
In placebo vs. AMPT condition during anticipation of reward, brain ac-
tivity in patients was mainly concentrated in frontal areas and insular
cortex. This suggests dopamine imbalance and disrupted activity in the
striato-cortical circuitry of our group of medicated schizophrenia pa-
tients. In patients vs. controls we observed reduced activation in the su-
 perior temporal gyrus and posterior cingulate in the placebo condition
and anticipation of reward. In placebo and anticipation of loss, patients
had reduced activation in the ventral striatum, frontal and cingulate cor-
tex. This is in contrast to earlier studies of reward which have shown
normalized striatal responses in medicated schizophrenia patients. Thus
our results indicate that dopaminergic neurotransmission in subcortical
regions of the brain reward system was possibly not normalized by med-
ication. Following AMPT we found reduced activation in several regions
during anticipation of reward and loss in patients vs. controls including
areas of the striatum and the inferior and middle frontal, insular and
cingulate cortex. These results indicate sensitivity of the dopaminergic
striato-cortical reward circuitry to dopamine depletion in schizophrenia
patients. Although patients had low scores on the three subscales of the
PANSS, demonstrating that antipsychotic medication probably stabilized
the symptoms, we could not detect its normalizing effects in brain activ-
ity. In summary this study provided insight in the impairment of frontal
and striatal dopamine-related reward system in schizophrenia.
Conclusions

The aim of the studies of this thesis was to increase our knowledge on aspects of brain structure and function that may be crucial for the etiology of schizophrenia. The main conclusions are:

1. Fractional anisotropy reductions encompassing inferior frontal white matter in 22q11DS with schizophrenia vs. healthy controls are similar to our comparisons between schizophrenia vs. healthy controls.
2. Decreased white matter volume in posterior brain regions is intrinsic to 22q11DS and independent of schizophrenia. The development of schizophrenia in 22q11DS probably involves disruptions of inferior frontal and temporal white matter fibers.
3. In the whole 22q11DS group, positive and negative symptoms were associated with reduced fractional anisotropy in areas previously implicated in schizophrenia mainly in frontal, cingulate, insula and temporal areas.
4. People with 22q11DS with schizophrenia have increased hippocampal glutamate and myo-inositol concentration. Altered glutamate and myo-inositol may be underlying psychotic symptoms and cognitive impairments in 22q11DS with schizophrenia.
5. Dopaminergic neurotransmission is involved in monetary reward prediction in healthy controls. Dopamine depletion induced by AMPT blunted overall brain activation during anticipation of reward and loss.
6. Reduced dopaminergic transmission and brain activation after dopamine depletion are indirectly supported by measurements of prolactin and peripheral dopamine markers showing dopamine decrease in the AMPT condition.
7. Pharmacological challenge with AMPT reduced overall brain activation in patients with schizophrenia during anticipation of monetary reward and loss.
8. In the placebo vs. AMPT condition brain activity in schizophrenia patients was mainly concentrated in frontal areas and insular cortex during anticipation of reward. This suggests
dopamine imbalance and disrupted activity in the cortico-striatal circuitry.

9. Following dopamine depletion schizophrenia patients vs. healthy controls had less activation in the ventral striatum, inferior and middle frontal gyrus during anticipation of reward. During anticipation of loss patients had reduced activation in the ventral striatum, frontal and cingulate cortex.

**General Discussion**

In this thesis we addressed challenges of brain imaging in psychiatry employing magnetic resonance imaging aiming to enhance our understanding of several aspects of brain structure and function related to schizophrenia. We found that neural correlates of schizophrenia in people with 22q11DS possibly include impaired white matter integrity in inferior frontal areas and hippocampal glutamatergic dysfunction. Furthermore we found that in healthy people dopamine modulates brain activation in the cortico-striatal reward system. This dopamine-related reward activation is impaired in schizophrenia. Implications of these findings to schizophrenia are discussed below.

Abnormal white matter volume and fractional anisotropy reductions as well as myelin-related gene abnormalities have been well documented in the schizophrenia literature (Karlsgodt et al., 2012; Walterfang et al., 2011). One of the key processes in white matter maturation is myelination, which occurs in phasic periods during the lifespan. Interestingly, final and optimal myelination of the prefrontal cortex and hippocampus occurs during late adolescence (Benes et al., 1994). This period is notable because it coincides with the emergence of psychotic symptoms and prodomal cognitive deficits. In fact, schizophrenia is currently viewed as a neurodevelopmental disorder and a disorder of disrupted brain connectivity.

Several altered brain networks have been suggested to be involved in schizophrenia including prefrontal and temporal connections (Crossley
et al., 2009; Friston and Frith, 1995; Meyer-Lindenberg et al., 2005). Indeed, the results of this thesis point to disruptions in the inferior frontal and fronto-temporal white matter fibers in schizophrenia. We found that these white matter networks earlier implicated in schizophrenia were related to schizophrenia in people with 22q11DS. In addition, our findings of disrupted functional cortico-striatal activation in schizophrenia are in line with literature suggesting that interactions of fronto-temporal areas with the ventral striatum are impaired (Buchsbaum, 1990). Thus, disruption of the normal trajectory of white matter development affecting brain connectivity and altered neuronal signaling, could potentially have a causal influence on psychotic symptomatology and cognitive deficits in patients with schizophrenia.

Certainly a cascade of brain changes takes place and the interaction of several potential mechanisms will lead to the development of schizophrenia. For instance, malfunction of genes and factors related to dopamine and glutamate neurotransmitters are implicated in oligodendrocyte and myelin development (Alix and Domingues, 2011; Feng, 2008). Signals from myelinating glial cells may influence the axonal growth which in turn may influence thickness of myelin sheath (Baumann and Pham-Dinh, 2001) with consequent impact on the dynamics of signal transmission information processing. Most likely, dopaminergic signaling in synchronization with other modulatory neurotransmission systems (i.e., glutamate, GABA, serotonin) interacts with environmental cues and cognitive schemes leading to the development of psychotic symptoms.

A strong and specific relationship exists between 22q11 deletion and schizophrenia (Karayiorgou et al., 1995; Xu et al., 2008) making the 22q11 deletion syndrome very relevant model to study vulnerability to schizophrenia. Most of the affected genes in the deleted region are expressed in the brain (Maynard et al., 2003). COMT and PRODH have found to be related to dopaminergic or glutamatergic regulation (Gothelf et al., 2008; Lachman et al., 1996; Li et al., 2004) and consequently may be involved in white matter integrity. Furthermore, haplo-insufficiency of COMT is related to high level of prefrontal dopamine in 22q11DS, which possibly interferes with prefrontal cognitive function contributing to vulnerability to schizophrenia.

Neurodevelopmental aberrations and susceptibility to schizophrenia may manifest at multiple neuronal levels common to 22q11DS and schizophrenia. In fact, the mechanisms of schizophrenia will be better addressed from a system-level with focus on mechanisms of disease
risk (Meyer-Lindenberg, 2010). We have contributed to this system level model providing insights from a multidimensional approach, combining genetic, metabolic, structural and functional aspects.

**Strengths**

In this thesis we conducted original studies with a multidisciplinary character to detect common pathways involved in schizophrenia. In particular, we investigated neural correlates of schizophrenia in people with increased genetic liability to schizophrenia and in people with schizophrenia. We reported the first 1H-MRS in 22q11DS and the first DTI study in adults with 22q11DS. Moreover, we investigated for the first time dopamine related brain activation in healthy individuals and in schizophrenia during baseline dopaminergic state and after dopamine depletion in a randomized double blind placebo approach. We combined brain imaging methods with neuro-endocrine and peripheral dopamine markers. In the MRS study we also measured plasma levels of proline and glutamine. Although the sample was small, they present a valuable approach for future studies.

**Limitations**

The results of the studies in this thesis should be interpreted with some caution. Specific limitations of each study were discussed in the relevant chapters. Here, we summarize limitations that may have general implications. Conducting brain imaging studies in psychiatry is a real challenge. Not only because methodological (quantitative and qualitative) limitations of technology, but also because we are dealing with the human factor. The quality of MRI data can be seriously affected by the subject's behavior in the scanner. Healthy individuals and specially patients often experience anxiety (claustrophobia) and have difficulties to avoid movements during the scan sessions. Consequently, our sample size was reduced after data quality check. Thus, the relatively small sample size increases the risk of type II error and may have limited the power to detect specific alterations. Nevertheless we were able to detect significant differences that were in line with the literature and our hypothesis. Another issue is that patients with schizophrenia were using antipsychotic
medication, which is a potentially confounding factor in brain imaging studies. Ideally, studies exploring the neuropathology of schizophrenia investigate medication naive patients because the properties of medication in modulating brain changes. However, this poses practical as well as ethical objections. In some studies only males were included limiting the generalizability of results, but at the same time increasing specificity as results are not confounded by gender differences. Furthermore, our schizophrenia group patients were younger than healthy controls. Finally, regarding the effects of dopamine depletion in brain activity, we should note that it is a rather indirect measure of neurotransmission, although dopamine agonists and antagonists have been shown to affect the BOLD response in earlier studies.

Future directions

Neuroimaging research has contributed greatly to our knowledge unraveling structural and functional brain correlates of schizophrenia. A promising direction is to approach the mechanisms of schizophrenia from a system level combining different modalities of brain imaging.

We plan to further investigate dopamine-related brain activity with fMRI in 22q11DS. Genetic variation resulting in haplo-insufficiency of the COMT and PRODH gene may expose individuals with 22q11DS to disrupted dopaminergic and glutamatergic metabolism interfering with their cognitive functioning and also contributing to the liability to schizophrenia. Hence, we hope to gain more insight in the involvement of dopamine and glutamate in the development of schizophrenia and its relation with brain function in people with 22q11DS with and without schizophrenia.

Psychotic symptoms have been postulated to result from hyperdopaminergic sensitivity in subcortical regions whereas negative symptoms and cognitive deficits are suggested to result from a prefrontal hypodopaminergic state. However, most likely positive symptoms like hallucinations and delusions are produced in synchrony with disrupted cognition in the prefrontal cortex. It will be of great value to design experimental tasks to investigate aspects of positive, negative and cognitive symptoms of schizophrenia related to the prefrontal cortex. Moreover, studies designed to investigate subcortical (e.g., striatum, hippocampus, amygdala) function related to the positive and negative symptoms are
required to provide a better understanding of brain function and symptomatology in schizophrenia.

Preliminary findings of our 1H-MRS study suggested dysregulation of glutamate in the hippocampus. Further studies with large sample sizes are needed to unravel the role of PRODH haplo-insufficiency, consequent altered proline metabolism and its relation with disrupted glutamatergic dysfunction. Molecular imaging studies (SPECT/PET) in combination with metabolic (1H-MRS) and pharmacological (PhMRI) will provide fruitful insights in the glutamatergic and dopaminergic system in 22q11DS and schizophrenia.

Longitudinal studies comparing cognitive, affective and neural development in 22q11DS who do and do not develop schizophrenia will provide important insights into the trajectory from risk to disorder. In addition, the study of gender specific factors is warranted because the onset of schizophrenia occurs earlier in males and it seems that women may have natural protective factors since the course of the disease is less detrimental in females. In addition, of high importance is also the investigation of the involvement of environmental risk factors linked to brain dysfunction.

Finally, the particular contribution of the different brain imaging techniques and methods will add relevant information to put together the pieces of the schizophrenia puzzle. The challenge for the coming years is to integrate the impact of genetics and deal with the problem from a multimodal, multilevel and multidisciplinary approach. In addition, we look forward to bridge the gap between research and clinic, identifying reliable biomarkers for a more accurate diagnosis and effective treatment.

References

Benes, F.M., Turtle, M., Khan, Y., Farol, P., 1994. Myelination of a key relay zone in the