Neurophysiological correlates of the pathway to the early stages of psychosis
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SUMMARY
AND GENERAL DISCUSSION

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SUMMARY

The overall objective of the studies described in this thesis was to develop an integrative multi-system model of neurophysiologic abnormalities related to information processing associated with a first psychotic episode. Specifically, the aims of our studies were to 1) identify neurophysiological markers of schizophrenia and to investigate whether these markers can contribute to the prediction of a first psychotic episode in subjects that are putatively in an early phase of schizophrenia (i.e. Ultra High Risk (UHR) subjects) and 2) determine the course of neurophysiological abnormalities from before until shortly after transition to a first psychotic episode.

AIM I To identify neurophysiological markers of schizophrenia and to investigate whether these markers can contribute to the prediction of a first psychotic episode

In Chapter 1, a short background was provided on schizophrenia and the UHR concept. Moreover, frequently used neurophysiological paradigms were discussed and the outline and aims of this thesis were presented.

Chapter 2 encompassed an overview of neurophysiological abnormalities in schizophrenia patients. Furthermore, candidate neurophysiological endophenotypes of schizophrenia were discussed. Our review of studies on early information processing yielded that schizophrenia patients often show impairments in the filtering of irrelevant stimuli, reflected by deficits in sensory (motor) gating. However, some questions remain regarding the reliability of these measures. With respect to ERP components related to higher order information processing, we concluded that the P300 might be a reliable biomarker of schizophrenia. Additionally, schizophrenia patients frequently present abnormalities on eye movement paradigms, including tasks of smooth pursuit eye movements as well as antisaccade tests. Although some of the discussed neurophysiological measures may be useful to fill the gap between the gene and the clinical expression of the disease (i.e. phenotype), futures studies are needed to test the stability of these biomarkers across different stages of the disease and to further delineate associated genomic and neuro-anatomic networks.

Chapter 3 focussed on the performance of patients at UHR for developing psychosis on a task of smooth pursuit eye movement (SPEM). Results showed that both the corrective and non-corrective saccadic rates during pursuit were higher in the UHR group compared to a group of healthy controls. There were however no differences in smooth pursuit gain between the two groups. The increased saccadic rate was related to more severe positive UHR symptoms. These findings indicate that abnormalities in SPEM, particularly in the rates of saccades during pursuit, are already present in UHR subjects prior to a first psychotic episode.

In Chapter 4, we sought to investigate whether abnormalities in P300 or other ERPs as derived from the oddball paradigm are present in UHR subjects and if they are helpful in predicting future transition to psychosis. Results showed that subjects who later make a transition to psychosis present smaller parietal P300 amplitudes, compared
AIM II To determine the course of neurophysiological abnormalities from before until shortly after transition to a first psychotic episode

Chapter 7 examined the longitudinal course of auditory ERP components in UHR subjects from prior to until shortly after a first psychotic episode. We found that P300 abnormalities are stable from the prodrome until after psychotic onset. However, N100 amplitudes, an ERP component associated with early auditory sensory processing, were smaller at follow up compared to baseline only in UHR subjects with transition to psychosis. These findings suggest that discernable ERP components behave differently during progression from the prodromal phase to the first psychotic episode.

Chapter 8 focused on the course of sensory gating abnormalities from the prodrome until after psychotic onset. Results showed that the N100 difference score contributed modestly to the prediction of a first psychotic episode. However, we also found alterations in N100 and P200 components between the prodromal phase and the first psychosis, suggesting that these changes may relate to the onset of a frank psychotic episode.

In the final chapter of Part II of this thesis (Chapter 9) we aimed to determine a profile of information processing deficits, using complementary neurophysiological markers, in UHR subjects as well as patients with a first episode of schizophrenia psychosis. We found that abnormalities in higher order feedback dependent measures, including
P300 and antisaccade, show temporal stability from the prodromal phase until after the onset of a first psychosis and may thus be viewed as trait factors of schizophrenia. In contrast, deficits in automatic, feedforward processing (e.g. N100 components) seem to be related to the onset of psychosis and may reflect state markers of the disease.

CONCLUSIONS

The central objective of the studies described in this thesis was to develop an integrative multi-system model of neurophysiologic abnormalities related to information processing associated with a first psychotic episode. To this aim, several neurophysiological paradigms were administered to subjects at clinical high risk for a first psychotic episode. In addition, groups of healthy controls and patients with a first episode of schizophrenia were included as comparison groups. Finally, interrelationships of information processing (dis)abilities with severity of (sub threshold) psychotic symptoms as well as functional outcome scales were investigated, herewith providing insights into the associations between neurophysiological parameters and levels of functioning in daily life. The main conclusions of this thesis are:

1. UHR subjects show increased saccadic rates on a task of smooth pursuit eye movement and this is related to the severity of positive UHR symptoms
2. Reduced parietal P300 amplitudes may be helpful in the prediction of future transition to a first psychotic episode in UHR subjects.
3. P300 amplitude reductions are related to increased social anhedonia and withdrawal and a lower global assessment of social functioning and social personal adjustment.
4. Resting state QEEG parameters, including increased power in theta and delta ranges and decreased individual alpha peak frequencies contribute to the short-term prediction of a first psychotic episode. Additionally, QEEG parameters, particularly alpha and theta spectral power, show some potential in predicting functional outcome.
5. Otherwise healthy cannabis users and UHR subjects show similar abnormalities in P300 abnormalities. In contrast, reduced information processing speed, as reflected by prolonged ERP latencies, seems to be specifically associated with cannabis use.
6. In UHR subjects as well as otherwise healthy cannabis users, more severe information processing deficits are related to more severe clinical UHR symptoms
7. Abnormalities in higher order feedback dependent measures, including P300 and antisaccade, show temporal stability from the prodromal phase until after the onset of a first psychosis and may thus be viewed as trait factors of schizophrenia. In contrast, deficits in automatic, feedforward processing (e.g. N100 components) seem to be related to the onset of psychosis and may reflect state markers of the disease.

In conclusion, our results indicate that in help-seeking individuals who meet the criteria for ‘at risk mental state’, particular neurophysiological paradigms (i.e. parietal P300 amplitudes and resting state QEEG theta and delta power and individual alpha peak frequency) can contribute to the differentiation between subjects who do or do not convert to psychosis.
In contrast, neurophysiological components associated with early processing, including N100 and SPEM parameters, showed changes with psychotic onset. These findings suggest that discernable neurophysiological components behave differently during progression from the prodromal phase to the first psychotic episode. Furthermore, as we found several associations between neurophysiological parameters and severity of UHR symptoms and functional disability, our findings provide further insights into the associations between information processing impairments and clinical as well as functional outcome.

DISCUSSION

During the past few decades, early intervention strategies, including the Ultra High Risk approach, have gained much popularity worldwide. However, up to now, validity and reliability of these strategies remain questionable. Specifically, the high rate of subjects included using the high risk criteria who eventually do not make a transition to psychosis (i.e. false positives) have led to a worldwide debate about clinical and ethical justification of indicated prevention (Ruhrmann, 2010). Nevertheless, as recent studies have yielded that early intervention methods, including integrated psychological intervention (e.g. cognitive behavioural therapy), may delay the onset of psychosis (Bechdolf et al., 2012; van der Gaag et al., 2012), these methods might be one of the few useful tools to influence the generally poor course of the disease. However, in the absence of reliable markers for the later development of the disease, early intervention and prevention remain difficult.

One of the aims of the studies included in this thesis was therefore to identify biological markers of (future transition to) schizophrenia. Quantitative biological markers can provide unique information on the nature and extent of cognitive and brain dysfunction in schizophrenia. Additionally, these markers may provide valuable complementary insights into the basic mechanisms of cognitive and higher brain functions, such as perception, attention and memory (van der Stelt & Belger, 2007). This thesis contains various studies investigating the usefulness of neurophysiological parameters in predicting future transition to psychosis. Results showed that reductions of parietal P300 amplitudes as elicited with the oddball paradigm may be an independent predictor of psychosis. Additionally, N100 difference scores as derived from the paired click paradigm showed some potential in identifying future converters, although prediction models with additional neurophysiological parameters yielded that N100 components are not an independent predictor of transition. Finally, results of our multi-centre study indicate that the inclusion of resting state QEEG parameters in prediction models may result in a more reliable risk estimation. Following these results, we advocate the use of a ‘close-in’ strategy in early intervention studies, i.e. prediction strategies in which various factors are combined to improve predictive accuracy. Combining UHR criteria with neurophysiological parameters, but also sociodemographic factors (Dragt et al., 2011), social withdrawal (Velthorst et al., 2009) and neuropsychological data (Becker et al., 2010) may provide the clinician with a more individualized risk estimation.
As discussed in chapter 5, the distinction between transition and non-transition as defined by a (conventional) threshold of positive symptoms can sometimes be arbitrary. That is, positive symptoms meeting psychosis threshold are not always necessarily associated with poor functional outcome. In contrast, subjects who are now being classified as ‘non-transitions’ may still present with neurocognitive impairments, poor functional outcome and high levels of negative symptoms at follow-up (Fusar-Poli et al., 2012). These findings led us to investigate the relationship between QEEG parameters and functional outcome, e.g. impairments in social and occupational functioning. Interestingly, these analyses yielded that resting state QEEG parameters contributed to the prediction of the general level of functioning at follow up. Specifically, we found that more pathology in alpha and theta bands predicted lower levels of functioning in the domains understand and interact with the world and to get along with people. One might therefore hypothesize that QEEG abnormalities, i.e. a measure of basic mechanisms of brain functions (van der Stelt & Belger, 2007), reflect a trait marker of schizophrenia, associated with poor functioning in life. Indeed, oscillations in theta as well as alpha bands have been associated with cognitive function, including memory and attention (e.g. Uhlhaas et al., 2008), and impairments in cognitive functions have frequently been associated with functional outcome. Herewith, our findings provide some insights into the relationship between the pathophysiology of schizophrenia and one of its core features, i.e. a poor level of functioning.

The studies described in the second part of this thesis investigated the longitudinal course of neurophysiological abnormalities from before until shortly after transition to a first psychotic episode. Herewith, we aimed to distinguish neurophysiological antecedents of first psychosis from its correlates and/or consequences. Results showed temporal instability of ‘early’ ERP components (i.e. N100 and P200 amplitudes) and SPEM performance, that is, UHR subjects with transition to psychosis showed more impairments in these components at follow up compared to baseline. These findings suggest that early ERP components and SPEM parameters are related to the onset of frank psychotic symptoms and may thus be labelled as state factors of the disease. In contrast, abnormalities in higher order feedback dependent measures, including P300 and antisaccade, show temporal stability from the prodromal phase until after the onset of a first psychosis and may thus be viewed as trait factors of schizophrenia.

Clinical implications
The results of the studies presented in this thesis cautiously support the usefulness of neurophysiological parameters in clinical interventions in subjects at high risk for a first psychosis. Specifically, combined with other techniques, including MRI neuroimaging or neuropsychological assessments, these measures may provide the clinician with a more individualized risk estimation for future transition to psychosis. Moreover, we suggest that neurophysiological parameters could play a helpful role in the development of effective therapeutic treatment interventions that are focused on specific pathophysiological mechanisms and cognitive dysfunctions rather than on the clinical symptoms of
schizophrenia. The results of our studies provide further evidence that abnormal EEG/ERP and eye movements are related to positive and negative symptoms of schizophrenia as well as impairments in daily life functioning. We therefore hypothesize that interventions that aim at ameliorating neurophysiological deficits might result in improvements in other core symptoms of schizophrenia. Indeed, recent studies have shown some evidence for the effectiveness of transcranial magnetic stimulation (TMS), i.e. a non-invasive method of inducing electrical activation of the brain, in the treatment of schizophrenia (Dlabac-de Lange et al., 2011; Jin et al., 2006). Specifically, TMS may have some effects on the negative symptoms of schizophrenia and this improvement was strongly related to alpha EEG enhancement in the frontal areas. Additionally, results of another study suggest that positive and general psychotic symptoms may improve after TMS. Until further replications, the use of TMS in the treatment of schizophrenia will however remain controversial. Another potentially useful technique is neurofeedback, i.e. an operant conditioning paradigm in which patients are given contingent audio/visual rewards for producing specific patterns of brain wave activity (Surmeli et al., 2012). For instance, a recent study in healthy subjects yielded that neurofeedback may result in stable inhibition of theta activity (de Zambotti et al., 2012). Nevertheless, as with TMS, the reliability of neurofeedback in modifying the electroencephalographic pattern is still limited.

Strengths
To the best of our knowledge, the studies included in this thesis were the first to investigate the neurophysiological profile of subjects at clinical risk for a first psychosis. Herewith, our studies add to the findings of other studies, advocating the importance of including additional markers in prediction models. Hopefully, the findings of the studies in this thesis contribute to the world wide search for valid methods to reduce the number of false positives included using the UHR criteria. In addition, we are the first to report on the longitudinal course of neurophysiological components from the prodrome until after the onset of a first psychotic episode, hereby contributing to the literature on state and trait markers of schizophrenia. Furthermore, following results of recent studies that implicate functional outcome as a valid measure in high risk subjects, we investigated the potential of neurophysiological parameters in predicting disability at follow up. Additionally, by consistently investigating the relationship between neurophysiological parameters and clinical UHR symptoms, we aimed to provide some new insights into the interrelations of the pathophysiology of psychosis with its clinical symptoms as well as demonstrate the usefulness of including neurophysiological paradigms in psychosis research.

Limitations
Our results should be considered in the context of several limitations. Specific limitations of each study were discussed in the relevant chapters, but some may have general implications and will hence be discussed here. The first and most important caveat of the studies was the relatively small sample size. Only one of the studies in this thesis presents the results of a multi-centre study with a larger sample size. Therefore, all of our results
warrant replication in future, preferably multi-centre, studies. A second limitation that is important to consider in the interpretation of our findings is medication use. Although we attempted to correct for the effects of medication use, in particular neuroleptics, in all of the studies included in this thesis, we can not rule out that medication use may have biased our results. Future studies should therefore aim at including medication naïve subjects. Although this choice will probably have negative practical implications and possibly will also effect the willingness of patients and their relatives to participate in studies, including only medication naïve subjects will enable a more valid interpretation of the findings. Another limitation concerns the follow up period. The longest follow-up period of the studies in this thesis was 3 years. Although most transitions take place within the first 3 years (Fusar-Poli, 2012), or even the first (Yung et al., 2011), of clinical presentation, transitions to psychosis are reported even up to 10 years (Yung et al., 2011). We can therefore not exclude the possibility that some of the subjects classified as ‘non-transition’ in our study in fact made a transition after the follow-up period.

Fortunately, during the past decades, multi-centre collaborations have developed to enable the investigation of a larger number of subjects, herewith improving the statistical power but also generalizability of the results. Importantly, these multi-centre approaches should aim at using comparable neurophysiological paradigms and apparatus as well as artefact correction methods. Additionally, as there is increasing evidence that transition rates vary greatly between centres, depending for instance on the age of the patient, the nature of the treatment provided and the manner in which the syndrome and transition to psychosis are defined (Fusar-Poli, 2012), attempts should be made to enhance comparability between centres with regard to these aspects.

**Future directions**

Neurophysiological paradigms can make an important contribution to the identification of biological markers of schizophrenia that provide valuable insights into the basic mechanisms of cognitive and higher brain functions (van der Stelt & Belger, 2007). These markers may help to unravel the pathophysiological mechanisms of schizophrenia, herewith hopefully creating possibilities for new treatment options (Gottesman & Gould, 2003). However, until the associations between neurophysiological activity and clinical phenomena including thoughts and beliefs are better understood, psychophysiological studies remain correlational and not causal. Thus, future studies should aim at further exploring the associations between neuropsychological parameters and clinical symptoms.

Second, it is not yet clear whether any of the biological markers discussed in this thesis are specific to schizophrenia. Although P300 and MMN amplitudes have most consistently been associated with schizophrenia, abnormalities in these components have also been reported in other psychiatric diseases (e.g. bipolar disorder). It is likely that EEG/ERP as well as eye movement abnormalities reflect a more general biological and cognitive risk factor that cuts across current psychiatric diagnostic categories. Although these findings imply that biological markers can not (yet) be used for diagnostic purposes, biological markers related to information processing may aid in
developing more valid classificatory systems. Indeed, DSM–5 and ICD–11 committees are aiming to create a meta-structure for psychiatric disorders based on aetiological and pathophysiological grounds. Until diagnostic categories are more valid, it might be more valuable to investigate neurophysiological parameters in relation to symptom dimensions instead of diagnostic constructs.

Third, although research groups around the world have aimed to identify neuropsychological and neurophysiological markers of schizophrenia, not much is known about treatment options to ameliorate cognitive and information processing deficits in at risk subjects or schizophrenia patients. Future studies should aim to investigate whether specific interventions, including cognitive remediation therapies or neurofeedback and TMS, may improve information processing abilities and consequently reduce (subclinical) psychotic symptoms and disability.
REFERENCE LIST


