Reward system dysfunction as the neural basis of symptomdimensions within the schizophrenia-spectrum

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Reward system dysfunction as the neural basis of symptom dimensions within the schizophrenia-spectrum

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To my parents Ursula and Dr. med. Hanns-Georg Kirschner

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1. Introduction and Background

Schizophrenia is one of the most debilitating psychiatric disorders, characterized by heterogeneous clinical manifestations with positive symptoms (e.g. hallucination, delusion), negative symptoms (e.g. apathy, diminished emotional expressivity) cognitive deficits and affective symptoms (e.g. depression, mania) (1,2). Like most psychiatric disorders, schizophrenia typically emerges in late adolescents or early adulthood and causes immense psychosocial burden for patients, their families and social environment (3,4). Simultaneously, due to unemployment, disability and repeated hospitalizations, schizophrenia causes high socioeconomic costs not only for patients and their families but also for the wider society and health care systems (5,6). Worldwide, about 0.4% to 0.75% of people suffer from schizophrenia (7,8) and despite this low prevalence rates, schizophrenia is one of the top 15 global causes of disability and quality of life (9). Even with evidence-based "best practice" treatment, the majority of patients have a chronic relapsing disease course and only a minority achieve full recovery (13.5%) (10,11). In addition to this, across the whole lifespan patients with schizophrenia have significantly higher mortality rates with a reduced life expectancy of 10 to 20 years compared to the general population (12,13). These findings dramatically illustrate the urgent need to improve diagnosis and treatment outcome in schizophrenia. However, the progress to uncover the underlying pathophysiological mechanisms and translate neurobiological findings into clinical practice has been hampered by the complex and multifactorial etiology of schizophrenia involving multiple environmental, genetic and biological factors (4).

Even 100 years after the descriptions of Emil Kraepelin (1896) and the introduction of the term schizophrenia by Eugen Bleuler (1908, 1911), diagnostic, clinical-decision making and treatment relies almost exclusively on the basis of clinical observations (14,15). In contrast to most other modern medical disciplines, in which biological measures (biomarkers) are routinely and successful used for diagnostics and treatment (e.g. cancer treatment), biomarkers with diagnostic, prognostic or therapeutic value for schizophrenia treatment are still lacking (16).
Since the discovery of chlorpromazine (17,18) and the antipsychotic effects of dopamine receptor blockage (19) in the 50s and 60s pharmacological treatment has not significantly improved and does not allow psychiatrist to adequately tailor treatment based on the individual needs of their patients. Although currently available antipsychotic drugs show modest efficacy for acute psychotic symptoms, they do not sufficiently target negative symptoms and cognitive deficits (20–

24). This would be crucial, given that negative symptoms and cognitive deficits are highly prevalent in early disease stage, tend to persist and become chronic, and ultimately impact long-term social functioning, quality of life and disease burden (25–29). Additionally, current antipsychotic treatment causes major side effects including medication-induced negative symptoms such as lack of drive, amotivation and sedation (22,30), and severe long-term metabolic changes, which dramatically increase the risk for metabolic syndromes and diabetes mellitus (31–34). Taken together, to improve diagnostics, clinical-decision making and to develop a personalized medicine of schizophrenia with treatment tailored to individual clinical profiles, a comprehensive symptom-specific understanding of the underlying neurobiological mechanisms is warranted.

The conceptualization of dimensional models designed to unravel symptom-specific neural mechanisms has emerged only recently (35,36). Over decades, the classic Kraepelinian categorical distinction between schizophrenia and other major psychiatric disorders (e.g. bipolar disorder, depression) dominated the clinical and scientific landscape (35,37,38). As a consequence previous studies have mainly tried to identify neurobiological features differentiating schizophrenia from non-schizophrenia, solely based on diagnostic categories and boundaries defined by clinical consensus (35). Such categorical approaches fail to adequately capture the heterogeneity within the schizophrenia-spectrum and the clinical, biological and genetic overlaps with other disease entities (39–42). In contrast several lines of research support a dimensional scientific approach to examine the fundamental neurobiological mechanisms of dysfunction. Epidemiological and clinical studies repeatedly demonstrated that psychotic symptoms including positive symptoms, negative symptoms and cognitive deficits are not unique to schizophrenia, but are also highly prevalent in other psychiatric disorders such as bipolar disorder and depression and can also be detected in subclinical forms in the general population (2,39,43,44). Additionally, a considerable overlap of structural and functional brain dysfunctions (40,42,45,46) and genetic correlations between schizophrenia and other neuropsychiatric disorders have been reported (47).

To integrate these findings and foster progress in neuroscientific research of schizophrenia and other mental disorders, the National Institute of Mental Health has launched the Research Domain Criteria (RDoC) project (36). RDoC is a fully dimensional approach to research the pathophysiology, based on integrative dimensions of psychopathological, behavioural and neuroimaging measures that cut across current diagnostic categories (48). Within this framework psychiatric disorders are conceptualized as dysfunction of distinct brain circuits, which can be

measured with tools of clinical neuroscience such as functional and structural neuroimaging (49). The RDoC project aimed to identify specific brain-behaviour relationships, which guide the development of new treatment targets, and biomarkers for diagnostic, treatment selection and monitoring (49). Critically, over the last decades, neuroimaging research has made substantial progress raising the unique opportunity to accomplish this goal and reduce the long-lasting health, social and financial burden associated with schizophrenia (5,6). The advent of functional magnetic resonance imaging (fMRI) in the early 1990s (50,51), enabled clinical researchers to non-invasively investigate brain activity related to specific behaviour, cognitive functions and emotions and ultimately bridge the gap between clinical observations and brain function. Simultaneously, decreasing costs and easier availability of magnet resonance imaging (MRI) and computing power accompanied with constant progress in statistical methods and data science have facilitated the use of neuroimaging methods in schizophrenia research.

I have dedicated the last 7 years of my research to advancing our understanding of the neural mechanisms underlying symptom dimensions in schizophrenia combining dimensional neuroscientific frameworks such as the RDoC initiative and modern neuroimaging techniques. To this end, I have integrated clinical and neuropsychological measures with novel neuroimaging methods of structural and functional magnetic resonance imaging (fMRI). We applied these methods in a dimensional way within the schizophrenia-spectrum and trans-diagnostic across disease categories. My work, in particular, centers on the investigation of neural correlates of reward system dysfunction and their relationship to motivational deficits and apathy (52,53). The studies presented in this cumulative habilitation thesis exemplify a selection of my contributions to these research areas.

1.1 Reward system dysfunction in schizophrenia

The reward system is responsible for crucial aspects of daily life and normal human behaviour including motivation (wanting of rewards), reward learning (e.g. reinforcement, goal-directed behaviour) and positive emotions (pleasure as the hedonic impact of rewards) (54,55). Key substrates of the brain reward system are the neurotransmitter dopamine and phasic dopamine signals in the mesolimbic and mesocortical circuit including the midbrain, striatum, amygdala and orbitofrontal cortex (54–57). Phasic dopamine release acts as motivational signal not only for rewards to guide reward seeking, outcome evaluation and reward learning, but also as motivational signal for salient events and relevant information to support attentional orienting,

cognitive processing, and general motivation (58,59). Dysfunctions of the brain reward system have been widely reported across different major psychiatric disorders (41,60). Consequently, the RDoC initiative has defined the reward system (positive-valence-domain) as one of five trans-diagnostic domains to guide research in mental disorders (36,48). Over the last two decades, a growing body of literature supports the view that alterations of the dopaminergic mesolimbic system and reward processing deficits are critically involved in the pathophysiology of schizophrenia (61,62). Studies using positron emission tomography (PET) imaging in patients with schizophrenia repeatedly reported an increase of striatal dopamine function (62,63). In particular, studies found an increase of dopamine synthesis capacity, amphetamine-induced elevated dopamine transmission and increased basal dopamine levels (62,64,65). Based on these findings the salience dysfunction hypothesis assumes that increased striatal dopamine function promotes "chaotic" spontaneous phasic dopamine firing in response to "irrelevant" stimuli or events (58,66). In other words, "irrelevant" external and internal stimuli become "relevant" and meaningful due to an "aberrant phasic dopamine signal" (aberrant valuation and gating of thoughts and perceptions) (58,66,67). As a consequence of this imprecise representation and reduced differentiation between relevant from non-relevant stimuli information about our environment cannot sufficiently processed, which ultimately lead to positive symptoms such as paranoid ideation, thought disorders and disorganized symptoms (61,66,67). At the same time, it has been proposed that decreased phasic dopamine response to "relevant" stimuli causes reduced reward learning, impaired goal-directed behaviour and ultimately lead to negative symptoms (67,68). To examine these functional alterations of the striatum and other brain regions of the reward network, researchers started to apply task-related fMRI and measured blood oxygen-level dependent (BOLD) signal in the striatum during reward processing (58,67,69).

My research contributed to this growing body of knowledge by showing that abnormal striatal activation during reward processing is a fundamental neural mechanism in schizophrenia (52,70). Most of the earlier studies focused on group comparisons between mainly chronic patients and controls, and investigated the relation of abnormal brain function to global symptom severity (69). We extended these findings by investigating striatal dysfunction across different stages of the schizophrenia-spectrum from healthy individuals with subclinical psychotic symptoms, patients with first episode psychosis and chronic schizophrenia and dimensional to specific symptom dimensions (52,53). In line with the transdiagnostic RDoC approach we also examined potential transdiagnostic clinical, behavioral and neural mechanisms comparing patients with schizophrenia and bipolar disorder (71). In addition, we were able to identify specific sub-regions of the

associative and limbic striatum as neural correlates of reduced reward anticipation in schizophrenia (72).

1.2 Neural Correlates of symptom dimensions

The advances in neuroimaging research over the last years informed our understanding of schizophrenia as brain disorder. Large-scale studies and meta-analysis have identified system-wide disruption of functional and structural brain networks, and white matter integrity (73–76). These dysfunction and structural alterations have also been linked to clinical manifestations of positive, negative and cognitive symptoms (61,77–81). Although a global picture of brain abnormalities in schizophrenia has widely demonstrated, conclusive associations to clinical phenotypes and underlying pathological processes are still missing. To achieve this goal and to identify symptom-specific neural substrates, integrative approaches combining innovative neuroimaging techniques and state-of-the art clinical assessments of distinct symptom dimensions are needed (52,70,71).

Neural correlates of global negative symptoms encompass structural and functional alterations of fronto-striatal regions including the orbitofrontal, dorsolateral prefrontal cortex, anterior cingulate and striatum (68,69,77,82). These findings lack clinical specificity due to the fact that negative symptoms comprise a complex set of diverse subdomains, including avolition, anhedonia social withdrawal, alogia and blunted affect (83–85). Progress in the conceptualization of negative symptoms revealed two separate factors: a motivational or apathy factor including avolition, anhedonia, social withdrawal and a diminished expression factor including, alogia and blunted affect (84,86,87). Importantly, both factors should be investigated separately as they show different effects on clinical outcome, and may underlie distinct neurobiological mechanisms (29,86,88,89). To this end, we used novel clinical tools and behavioural measures, such as actigraphy to differentiate both negative symptom factors and examine potential specific neural substrates within the cortico-striatal reward system (52,70–72). In particular, we were able to show a specific relation between apathy and reduced ventral and dorsal striatal activity during reward anticipation (52,72).

Regarding neural substrates of positive symptoms, auditory hallucinations and delusions have been linked to structural and functional alterations of frontal, temporal (e.g. superior temporal gyrus) and subcortical regions (e.g., thalamus, striatum) and disconnection among these regions (90–94). Inspired by the comprehensive conceptualization of the disconnection hypothesis

(90,95,96), diffusion tensor imaging studies started to examine distinct relationships between white matter integrity measured with fractional anisotropy (FA) and positive symptoms (97–100). Although emerging evidence of an association between FA alterations in frontal tracts (e.g. thalamic radiation, superior longitudinal fasciculus, arcuate fasciculus) and positive symptoms has been reported (97–100), the FA measure has limitations in the correct and quantitative interpretation of the underlying tissue structure. In particular, the tensor model derived FA measure is only able to represent one major fiber direction in a white matter (WM) voxel (101,102). Thus, the FA values can be confounded in regions with complex fiber geometries (e.g. crossing fibers), which occur frequently throughout the brain (60%-90% of all WM fiber voxels) (102–104). To improve our understanding how subtle changes in white matter microstructure contribute to the pathophysiology of positive symptoms we compared a novel non-tensor-derived diffusion marker of fiber density with the established FA measure (105,106). These analyses provide important insights on how novel structural imaging methods can be successfully applied to foster progress in the development of neuroimaging-based markers of distinct symptom dimensions in schizophrenia (105).

2. Summary of included papers

Article 1: **Kirschner, M.**, Hager, O.M., Bischof, M., Hartmann, M.N., Kluge, A., Seifritz, E., Tobler, P.N., Kaiser, S. (2016). Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia. Journal of Psychiatry and Neuroscience 41: 152–161. (IF = 4.899)

Apathy is one of the most debilitating symptoms in schizophrenia leading to poor social functioning, diminished quality of life and in general, a poor prognosis (25,29,86). Apathy can be defined as a reduction of motivation, drive and goal-directed behaviour (107,108). Current treatment approaches are relatively ineffective and the underlying behavioral and neural mechanisms are not fully understood. Behavioral studies observed an association of apathy and motivational deficits and multiple aspects of impaired reward learning including effort-based decision-making (109), reinforcement learning and reward anticipation (68,82). Neuroimaging studies found converging evidence for reduced ventral striatal BOLD activity during reward anticipation in patients with schizophrenia, which has also been linked to global negative symptoms (69). However, a specific association of reduced ventral striatal activation during reward processing and apathy remained elusive. In this work, we address this research gap by investigating the specific relation between neural correlates of reward processing and the two negative symptom factors apathy and diminished expression. To measure reward-related BOLD signals in the ventral striatum and orbitofrontal cortex, we acquired event-related fMRI in 27 patients with schizophrenia and 25 control participants during a variant of the monetary incentive delay task. We found that ventral striatal hypoactivation during reward anticipation is specifically correlated with apathy, but not related to diminished expression or any other clinical measure such as cognitive ability, depression, positive symptoms or current medication. These findings provide further evidence for impaired reward learning and striatal dysfunction as underlying mechanism of apathy. Furthermore, the results support the view that the two negative symptom factors apathy and diminished expression can be disentangled on a neural level and are caused by different neural mechanisms. In line with the RDoC framework (48), we were able to show a dimensional association between a specific neural substrate (reduced ventral striatal activity during reward anticipation) and a clinical and behavioural measure (apathy). This blunted reward anticipation signal of the ventral striatum can be further tested as potential biomarker for diagnostics, psychopharmacological and psychological treatment development, and treatment monitoring.

Article 2: **Kirschner, M.**, Hager, O.M., Muff, L., Bischof, M., Hartmann-Riemer, M.N., Kluge, A., Habermeyer, B., Seifritz, E., Tobler, P.N., Kaiser, S. (2016). Ventral Striatal Dysfunction and Symptom Expression in Individuals With Schizotypal Personality Traits and Early Psychosis. Schizophrenia Bulletin 44:147-157. (IF = 7.289)

Current conceptualizations define psychosis as a concept in which psychotic-like experience can be observed in the general population and schizotypy and/or first episode psychoses can be described as at-risk stages for developing chronic schizophrenia (43,44,110–112). While in schizophrenia disturbed striatal function during reward processing is discussed as one core mechanism, it is unclear whether striatal abnormalities and reward system disfunction already occur at earlier stages of the psychosis continuum.

To address this knowledge gap, we examined shared and dissociable features of striatal dysfunction during reward processing in different stages of the psychosis continuum. We examined 26 healthy individuals with high schizotypal personality traits and subclinical psychotic symptoms, 26 patients with non-affective first-episode psychosis (including 13 patients with brief psychotic disorder and 13 patients with first-episode schizophrenia) and 25 healthy control. Participants underwent event-related fMRI while performing a reward processing task to assess ventral striatal BOLD activity during reward anticipation. We observed a dimensional association between increased ventral striatal activation and psychotic symptoms across and within each subgroup of the psychosis continuum. This provides neurobiological evidence for a dimensional concept of psychosis ranging from non-clinical psychotic experiences in the general population to severe psychotic symptoms in schizophrenia at the extreme end. Group comparison revealed, that patients with first episode schizophrenia showed strongest elevation in striatal activation compared to the other subgroups of the psychosis continuum. This result suggests additional categorial differences in striatal dysfunction related to the onset of schizophrenia. Taken together, this study extended the current literature showing that disrupted ventral striatal activity can already be observed in non-medicated healthy individuals with subclinical psychotic symptoms and early stages of psychosis and may serve as transdiagnostic marker across different stages of the psychosis continuum. Therefore, our data demonstrate how transdiagnostic approaches may advance our understanding of neural mechanisms within the schizophrenia-spectrum.

Article 3: Kluge, A.*, **Kirschner, M.***, Hager, OM., Bischof M., Habermeyer B., Seifritz E., Walther S., Kaiser S. (2018). Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. Schizophrenia Research 195:176-182. *Shared first-authorship. (IF = 4.569)

Current measures of symptoms in psychiatry rely almost exclusively on self-reports, interview-based retrospective self-reports, questionnaires and proxy reports (113). These measures might be inaccurate due to cognitive impairments, recall errors and therefore not sufficiently address symptom changes over time and across different contexts during daily life (114). With respect to apathy and other negative symptoms, current retrospective clinical assessments might not be able to capture the motivational states and actual functioning during the time period being assessed (115). Objective behavioral measures of apathy using modern technical devices could provide an efficient and complete real-time assessment of behaviour across different time periods of interest (e.g. from one week to one month). The development of such objective measures would be beneficial for a.) the translation of animal and human research and b.) treatment and outcome monitoring in clinical practice (49,116).

In this work, we compared potential objective measures of apathy with current state-of-the-art interview-based assessments of apathy and previously identified neural correlates of reduced ventral striatal activity during reward anticipation. Based on previous promising results showing an association between motor activity and negative symptoms (117), we collected actigraphy data to assess the specific relation to apathy. Additionally, we monitored real-time daily behavior and activities using ecological momentary assessment, a method, which has been successfully related to different symptom dimensions in schizophrenia (118–120). We found that reduced motor activity is associated with more severe apathy but not diminished expression. In contrast, measures of daily activities were not correlated with apathy or diminished expression. These results provide evidence that motor activity measured with actigraphy could be an objective readout of apathy. BOLD signal during reward anticipation revealed an association of reduced activation of the inferior frontal gyrus and motor activity and an association of blunted ventral striatal activity and apathy. These findings suggest dissociable neural processes within the fronto-striatal reward network for objective measure of apathy (motor activity) and subjective interview-based measures of apathy. Taken together, using a multilevel framework, which combines clinical, behavioral and neural measures of apathy, this study supports the utility of motor activity measures as potential behavioral marker for clinical practice and outcome monitoring in clinical trials.

Article 4: Stepien M, Manoliu A, Kubli R, Schneider K, Tobler PN, Seifritz E, Herdener M, Kaiser S, **Kirschner M.** (2018). Investigating the association of ventral and dorsal striatal dysfunction during reward anticipation with negative symptoms in patients with schizophrenia and healthy individuals". PLoS One. 13(6):e0198215. (IF = 2.776)

Previous work from our own and other groups point towards a specific relation between blunted ventral striatal activity during reward processing and apathy in schizophrenia. This association has also been observed in unaffected siblings and the general population suggesting a dimensional mechanism. However this clear brain-behavior relation between blunted ventral striatum activation and apathy has been challenged by studies observing a stronger correlation between blunted dorsal striatal activity and apathy (121–124). The hypothesis that subdivisions of the striatum are differently involved in the pathophysiology of apathy is supported by a large body of basic science studies linking distinct sub-regions of the striatum to specific aspects of goal directed behavior and reward learning (56,57,125–127). In this reward networks, the ventral striatum with connections to the ventral medial prefrontal cortex and anterior cingulate is involved in motivation and reward (57,125), while the dorsal striatum with connections to the dorsolateral prefrontal cortex is more strongly associated with cognitive control processes and action-outcome selection (126,127).

In this work we investigated the specific role of ventral and dorsal striatal activity during reward anticipation in the pathophysiology of apathy and motivational deficits across patients with schizophrenia. In line with the RDoC approach we applied the same clinical and fMRI measures to the general population to identify potential dimensional associations between striatal dysfunction and subclinical forms of negative symptoms. In patients with schizophrenia, reduced ventral and reduced dorsal striatal activity was associated with apathy suggesting that both sub-regions play a critical role in the development of motivational deficits. In contrast, this association was not observed in healthy participants. However, very low average values for apathy might have hampered the ability to replicate previous findings of a dimensional mechanism. Taken together, the contribution of this work is twofold. First, we were able to replicate our previous findings of blunted ventral striatal activity as neural correlate of apathy in an independent sample. Second, the results of comparable associations between dorsal striatal activity and apathy informed our understanding that both sub-regions of the striatum might be involved in the pathophysiology of apathy.

Article 5: **Kirschner, M.***, Cathomas, F.*, Manoliu, A., Habermeyer, B., Simon, J., Seifritz, E., Tobler, PN, Kaiser, S. (2019). Shared and dissociable features of apathy and reward system dysfunction in bipolar disorder and schizophrenia. Psychological Medicine 17:1-12. (IF = 5.641)

Negative symptoms, such as apathy, are not pathognomic for schizophrenia, but also occur in many other neurological and psychiatric disorders such as bipolar disorder and depression (39). Studies investigating negative symptoms within and across diagnostic categories support the view of a transdiagnostic construct with a continuous distribution from healthy, to affective disorders (bipolar, major depression), to schizophrenia-spectrum (high risk, schizoaffective, schizophrenia) (39). Despite this clinical overlap only few studies have attempted to identify common and distinct neural mechanism, comparing the relationship between negative symptoms and neural correlates (42,128,129). In particular, it would be relevant to elucidate whether negative symptoms across different disease categories share similar neural correlates suggesting a dimensional neurobiological model.

In the present work, we compared clinical levels of negative symptoms and task-related fMRI activity of the fronto-striatal reward network between patients with euthymic bipolar disorder and patients with schizophrenia. We found that severity of apathy was comparable between patients with bipolar disorder and patients with schizophrenia, but were stronger correlated with sub-syndromal depressive symptoms in bipolar disorder. On a neural level, patients with bipolar disorder and patients with schizophrenia showed divergent associations of apathy and neural activation. The association of reduced ventral striatal activity during reward and apathy, which has been repeatedly found in schizophrenia (52,72,123,130,131), was not detectable in patients with euthymic bipolar disorder. In contrast, in patients with bipolar disorder apathy was correlated with reduced extra-striatal activation in the inferior frontal gyrus. Taken together, we found that on a clinical level, severity of apathy is comparable between bipolar disorder and schizophrenia and can be measured with the same clinical assessment tools. The results further support the view of different neural correlates of apathy in these two disorders and suggest that extra-striatal dysfunction may contribute to impaired reward processing and apathy in bipolar disorder. While the present work highlights the relevance and opportunities of transdiagnostic research in psychiatry it also illustrates challenges and difficulties in identifying complex relation between behavior and neural function. Future studies, including larger samples and several diagnostic groups in a longitudinal design, are warranted to elucidate the neural pathways underlying the apathy and other negative symptoms.

Article 6: Stämpfli, P., Sommer, S., Manoliu, A., Burrer, A., Schmidt, A., Herdener, M., Seifritz, E., Kaiser, S., **Kirschner, M.** (2019). Subtle white matter alterations in schizophrenia identified with a new measure of fiber density. Scientific Reports 9: 4636. (IF = 4.011)

System-wide dysconnectivity with functional and structural network alterations have been suggested to play a fundamental role in the development of schizophrenia (73,76,132). Diffusion tensor imaging studies revealed that structural alterations of several white matter tracts connecting frontal, temporal and subcortical regions (e.g. thalamus) including the thalamic radiation, the superior longitudinal fasciculus, uncinate fasciculus and arcuate fasciculus are associated with positive symptoms (94,97–100,133,134). One major issue of the previous structural findings is that the most the common used tensor model derived indices, such as fractional anisotropy, are inadequate to characterize the underlying tissue structure in regions with complex fiber geometries and multiple fiber populations. Therefore, novel more specific measures of white matter alterations are needed to understand the microstructural changes related to the development of positive symptoms in schizophrenia.

In the present work, we applied a recently developed non-tensor model derived measure of fiber density to investigate the association of microstructural changes in frontal white matter tracts of the reward network with positive symptoms. We found reduced fiber density in several fronto-temporal and fronto-thalamic tracts in patients with schizophrenia compared to control participants. Comparing the fiber density of five different frontal tracts, which have been related to positive symptoms, reduced fiber density of the thalamic radiation showed the strongest association to positive symptoms. This provides further evidence that fronto-thalamic dysconnectivity might play a key role in the development of positive symptoms. In contrast, analysis using FA did not reveal any significant group differences or correlational findings with positive symptoms. These results suggest that the novel measure of fiber density may be more sensitive to subtle changes in the white matter microstructure compared to FA and could be beneficial to elucidate pathological white matter processes related to schizophrenia and other neuropsychiatric disorders. Finally, using multimodal approaches by combining this novel fiber density measure with task-related fMRI will enable the simultaneously investigation of structural and functional alterations within the reward circuit.

3. Conclusion

Understanding the neurobiological mechanisms and neural substrates of symptom dimensions in schizophrenia is critical for the identification of diagnostic biomarkers, drug development and treatment monitoring. In this regard, the integration of advanced neuroimaging techniques with state-of-the art psychometric measures of symptoms and behaviour provides a way to uncover pathological processes and to identify neuroimaging-derived biomarkers of distinct symptom domains.

The articles of this cumulative habilitation thesis exemplified this integrative methodological approach and illuminated various aspects of reward system dysfunction as neural basis of symptom dimensions in schizophrenia. Using task-related fMRI, we identified striatal hypoactivation during reward anticipation as specific neural marker of apathy in patients with schizophrenia, examined the role of different striatal sub-region in the pathophysiology of apathy and observed the association of blunted extra-striatal prefrontal activation with apathy induced reduced motor activity. Furthermore, we described a potential dimensional mechanism of striatal dysfunction during reward processing across the schizophrenia-spectrum ranging from non-clinical psychotic experiences in the general population to severe psychotic symptoms in early schizophrenia. In a next step, we followed a transdiagnostic approach and compared clinical and neural findings between schizophrenia and bipolar disorder in order to elucidate shared and divergent neurobiological mechanisms of apathy and motivational deficits. In addition, we applied DTI and examined the sensitivity of a novel fiber density measure in detecting symptom-specific microstructural white matter alterations of connections within the reward network.

The work presented in this cumulative habilitation thesis combines advanced neuroimaging techniques with detailed clinical characterization and demonstrates the successful application of transdiagnostic neuroscience frameworks to identify symptom-specific neuronal correlates. Our results extend the understanding of the fundamental role of aberrant fronto-striatal reward system function in the pathophysiology of apathy and other symptom domains within the schizophrenia-spectrum. Based on these findings, future multimodal imaging and transdiagnostic studies can further elucidate the complex relationship between specific fronto-striatal subsystems and motivational behaviour. In addition, fronto-striatal reward system dysfunction can be tested as potential neuroimaging marker for diagnostics, prognosis and the development of selective

pharmacological treatment of apathy. In conclusion, the presented results contribute to the development of neuroimaging-derived biomarkers for specific symptom domains and the translation from neuroimaging research into clinical practice. Ultimately, this work has the potential to optimize and individualize schizophrenia treatment, to improve clinical outcome and patients' quality of life, and to reduce the high burden associated with this severe psychiatric disorder.

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5. Reprints of discussed publications

1. **Kirschner, M.**, Hager, O.M., Bischof, M., Hartmann, M.N., Kluge, A., Seifritz, E., Tobler, P.N., Kaiser, S. (2016). Ventral striatal hypoactivation is associated with apathy but not diminished expression in patients with schizophrenia.
   Journal of Psychiatry and Neuroscience 41: 152–161, IF = 4.899.

2. **Kirschner, M**., Hager, O.M., Muff, L., Bischof, M., Hartmann-Riemer, M.N., Kluge, A., Habermeyer, B., Seifritz, E., Tobler, P.N., Kaiser, S. (2016). Ventral Striatal Dysfunction and Symptom Expression in Individuals With Schizotypal Personality Traits and Early Psychosis.
   Schizophrenia Bulletin 44:147-157, IF = 7.289.

3. Kluge, A.*, **Kirschner, M.***, Hager, OM., Bischof, M., Habermeyer, B., Seifritz, E., Walther S., Kaiser S. (2018). Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. *equal contribution
   Schizophrenia Research 195:176-182, IF = 4.569.

4. Stepien, M., Manoliu, A., Kubli, R., Schneider, K., Tobler, PN., Seifritz, E., Herdener, M., Kaiser S., **Kirschner M.** (2018). Investigating the association of ventral and dorsal striatal dysfunction during reward anticipation with negative symptoms in patients with schizophrenia and healthy individuals.
   PLoS One. 13(6):e0198215, IF = 2.776.

5. **Kirschner, M.***, Cathomas, F.*, Manoliu, A., Habermeyer, B., Simon, J., Seifritz, E., Tobler, PN, Kaiser, S. (2019). Shared and dissociable features of apathy and reward system dysfunction in bipolar disorder and schizophrenia. *equal contribution
   Psychological Medicine 17:1-12, IF = 5.641.

6. Stämpfli, P., Sommer, S., Manoliu, A., Burrer, A., Schmidt, A., Herdener, M., Seifritz, E., Kaiser, S., **Kirschner, M.** (2019). Subtle white matter alterations in schizophrenia identified with a new measure of fiber density.
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