Psychometric, Cognitive, and Oculomotor Characteristics of Schizotypy and Schizophrenia Spectrum Disorders

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Eliana Faiola

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Zusammensetzung der Prüfungskommission:

Prof. Dr. André Beauducel	*Vorsitzender*
Prof. Dr. Ulrich Ettinger	*Betreuer und Gutachter*
Prof. Dr. Christoph Klein	*Gutachter*
PD Dr. Ina Grau	*weiteres prüfungsberechtigtes Mitglied*

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Abstract

Schizophrenia spectrum disorders are considered to be among the most severe mental health issues. However, the question of their etiological mechanisms is still unsolved and requires further research. One promising approach in this context is the study of schizotypy, defined as a temporally stable set of personality traits that mimic symptoms of schizophrenia in an attenuated, subclinical form. Comparing schizotypy to the full-blown clinical disorder can help identify etiological mechanisms, including both risk and protective factors. In this thesis, I provide a detailed overview of schizotypy, including its psychometric characteristics, introduce cognitive and oculomotor continuities between schizophrenia spectrum disorders and schizotypy, and summarize discontinuities suggesting the operation of protective mechanisms in schizotypy. Subsequently, I present four original studies that build upon previous findings and fill relevant gaps left by prior research: In a psychometric study, network analysis was applied to resolve previously reported inconsistencies in one of the most widely used schizotypy questionnaires. In a behavioral investigation, I examined how schizotypy was related to cognitive functions and whether this was affected by experimentally induced sleep deprivation, a manipulation that is considered to evoke transient schizophrenia-like behaviors and experiences. In two studies combining eye tracking with psychophysical approaches, functional magnetic resonance imaging, and machine learning, I examined the cognitive, perceptual, and neural mechanisms of altered smooth pursuit eye movements (an oculomotor marker of schizophrenia) in schizotypal individuals and schizophrenia spectrum patients. Together, the studies of the present thesis indicate that similarities between schizotypy and schizophrenia spectrum disorders are selective and may be found in basic, specific sub-components of complex, high-level functions rather than in the complex functions themselves. This interpretation corroborates the hypothesis that protective mechanisms operate in schizotypal individuals, suggesting that such mechanisms prevent schizotypes from displaying the full phenotype of schizophrenia spectrum disorders. Additionally, embedding the original studies presented in this thesis into previously published research, it appears that different schizophrenia-like characteristics might develop in a highly differentiated fashion along a continuum from low to high levels of schizotypy. Accordingly, more advanced expressions of schizotypy might be associated with a wider range of schizophrenia-like characteristics compared to less intense expressions.

Zusammenfassung

Schizophrenie-Spektrum-Störungen stellen eines der gravierendsten Probleme psychischer Gesundheit dar. Die Frage nach den ätiologischen Faktoren dieser Störungsgruppe ist jedoch immer noch ungeklärt und bedarf weiterer Forschung. Ein vielversprechender Ansatz ist dabei die Untersuchung der Schizotypie, einer Reihe von zeitstabilen Persönlichkeitsmerkmalen, die in abgeschwächter, subklinischer Form den Symptomen der Schizophrenie ähneln. Der Vergleich zwischen Schizotypie und der vollständig ausgeprägten Erkrankung kann dabei helfen, ätiologische Faktoren (sowohl Risiko- als auch Schutzfaktoren) zu identifizieren. In dieser Arbeit gebe ich zunächst einen ausführlichen Überblick über die Schizotypie, einschließlich ihrer psychometrischen Eigenschaften. Weiterhin stelle ich zum einen Gemeinsamkeiten zwischen Schizotypie und Schizophrenie-Spektrum-Störungen hinsichtlich kognitiver und okulomotorischer Funktionen vor, und präsentiere zum anderen Unterschiede, die darauf hindeuten, dass schizotype Individuen über gewisse Schutzmechanismen verfügen. Im Anschluss daran präsentiere ich vier Originalstudien, die auf vorherigen Befunden aufbauen und relevante Lücken in früherer Forschung füllen: In einer psychometrischen Studie wurde eine Netzwerkanalyse angewendet, um zuvor berichteten Unstimmigkeiten bezüglich eines der am meisten genutzten Schizotypie-Fragebogen auf den Grund zu gehen. Mithilfe einer Verhaltensstudie untersuchte ich den Effekt von Schizotypie auf kognitive Funktionen im Zusammenhang mit experimentell induziertem Schlafentzug, der kurzzeitiges Schizophrenie-ähnliches Verhalten und Erleben hervorruft. In zwei Studien, in denen Eyetracking, psychophysische Methoden, funktionelle Magnetresonanztomographie und maschinelle Lernverfahren kombiniert wurden, untersuchte ich die kognitiven, perzeptuellen und neuronalen Mechanismen von Abweichungen in glatten Augenfolgebewegungen (einem bedeutsamen okulomotorischen Marker der Schizophrenie) bei Schizotypie und Schizophrenie-Spektrum-Störungen. Gemeinsam zeigen die Ergebnisse dieser Studien, dass Ähnlichkeiten zwischen Schizotypie und Schizophrenie-Spektrum-Störungen selektiv sind und eher in spezifischen, basalen Subkomponenten komplexer Funktionen als in den komplexen Funktionen selbst zu finden sind. Die Ergebnisse bestätigen die Annahme, dass Schizotype über Schutzmechanismen verfügen, die sie vor der Entwicklung des vollständigen Phänotyps einer Schizophrenie-Spektrum-Störung bewahren. Betrachtet man die hier vorgestellten Studien im Kontext früherer Forschung, liegt die Annahme nahe, dass sich unterschiedliche Schizophrenie-ähnliche Merkmale entlang eines Kontinuums von niedriger zu hoher Schizotypie entwickeln. Dementsprechend ist denkbar, dass eine höhere Schizotypieausprägung mit einem umfassenderen Spektrum Schizophrenie-ähnlicher Merkmale einhergeht als eine niedrigere Ausprägung.

1 Theoretical Background

1.1 The Schizophrenia Spectrum

1.1.1 Schizophrenia Spectrum Disorders

Schizophrenia and closely related mental disorders, which are typically subsumed under the term *schizophrenia spectrum disorders*, are considered to be among the most relevant mental health issues (e.g., Gaebel et al., 2016; Kane & Correll, 2010; Laursen, Nordentoft, & Mortensen, 2014; see also Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014; Rössler, Joachim Salize, van Os, & Riecher-Rössler, 2005). This is hardly surprising, given that the likelihood of developing one of the schizophrenia spectrum disorders throughout one's lifetime is more than 2% (Perälä et al., 2007), the mortality risk of patients is two to four times higher compared to that of the general population (Olfson, Gerhard, Huang, Crystal, & Stroup, 2015; Saha, Chant, & McGrath, 2007; Suvisaari et al., 2013), and life expectancy of patients is up to 25 years lower compared to that of the general population (Hjorthøj, Stürup, McGrath, & Nordentoft, 2017; Laursen et al., 2014; Tiihonen et al., 2009). Moreover, it has been estimated that 5-13% of all schizophrenia patients commit suicide (Hor & Taylor, 2010; Pompili et al., 2007). Many patients also suffer from physical diseases, such as obesity and Type 2 diabetes (Bradshaw & Mairs, 2014; Stubbs, Vancampfort, De Hert, & Mitchell, 2015; Suvisaari, Keinänen, Eskelinen, & Mantere, 2016; Vancampfort et al., 2016). This makes the group of schizophrenia spectrum disorders one of the most expensive diseases worldwide (Andlin-Sobocki & Rössler, 2005), with a total cost of approximately 93 billion euros per year in Europe (Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012). Most importantly, schizophrenia spectrum disorders lead to numerous adverse consequences for individuals suffering from it, including unemployment, homelessness, and delinquency (Carpenter & Koenig, 2008; Fleischman, Werbeloff, Yoffe, Davidson, & Weiser, 2014; Foster, Gable, & Buckley, 2012; Millier et al., 2014).

Despite these sobering numbers, relatively little is known about the etiology of the disorder as well as the most effective forms of treatment (Insel, 2010; Radua et al., 2018). The most widely used approach is the application of antipsychotic medication (Lally & MacCabe, 2015; Lehman et al., 2004). This type of treatment, however, is only helpful in reducing one class of symptoms (the ones typically referred to as *positive symptoms*), while it is significantly less effective in reducing others (Chou, Twamley, & Swerdlow, 2012; Köster, Carbon, & Correll, 2014; Lally & MacCabe, 2015; Remington et al., 2016). This neatly underscores the fact that further research into the etiology of schizophrenia spectrum disorders and efficient ways of treatment are essentially needed.

A common and highly prominent feature of schizophrenia spectrum disorders is psychosis, which is why they are often referred to as *psychotic disorders* (Sheehan, Fodor-Wynne, & Hassiotis, 2016). Coined in 1845 by Ernst von Feuchtersleben, the term *psychosis* initially referred to a general description of mental disorder (e.g., Beer, 1995, 1996). In the late 19th century, Emil Kraepelin proposed a dichotomy of two forms of psychosis, namely *dementia praecox*, which corresponds to what is now termed schizophrenia, and *manic-depressive insanity*, which is nowadays referred to as affective psychosis (Gaebel & Zielasek, 2015; Kraepelin, 1899). In 1911, Eugen Bleuler emphasized the heterogeneity of various forms of schizophrenia in terms of symptoms, duration, and course, which contributed to the development of a spectrum of schizophrenia-related disorders (Heckers, 2009; see also Hoff, 2017). The spectrum contains various clinical subtypes, all of which share features of psychosis, defined today as a loss of contact with reality (Cardinal & Bullmore, 2011; Moskowitz, Heinimaa, & van der Hart, 2018).

Today, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes a chapter on schizophrenia spectrum disorders, comprising schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified (American Psychiatric Association, 2013) as well as additional diagnoses (e.g., drug-induced psychosis), which are, however, beyond the scope of the present thesis. In addition to features of psychosis (such as delusions and hallucinations), specific symptoms of the respective disorder can occur. This includes disorganized thinking or speech, disorganized or abnormal behavior (e.g., catatonia), and negative symptoms (e.g., blunted affect, apathy, and the inability to feel pleasure). In addition, severe impairments in cognitive functioning are a core feature of schizophrenia spectrum disorders (Elvevåg & Goldberg, 2000; Freudenreich, 2020; Nuechterlein, Ventura, Subotnik, & Bartzokis, 2014; Sheffield, Karcher, & Barch, 2019). Especially for schizophrenia, Liddle (1987) assigned these symptoms to three categories: *reality distortion* (e.g., delusions and hallucinations; also referred to as positive symptoms), *psychomotor poverty* (blunted affect, poverty of speech and spontaneous movement; also referred to as negative symptoms), and *disorganization* (impairments in cognitive functioning; disorganized speech, thinking, and behavior). Among schizophrenia spectrum disorders, schizophrenia is the most frequent disorder, with a lifetime prevalence of around 1% in the population (Perälä et al., 2007). This potentially explains why a large part of the scientific literature deals with schizophrenia rather than other disorders of the spectrum.

As stated above, the question of what causes schizophrenia spectrum disorders is still unsolved (see, e.g., Insel, 2010; Radua et al., 2018). However, there is evidence pointing to a multifactorial etiology, resulting mainly from an interaction of genetic and environmental factors (Haller, Padmanabhan, Lizano, Torous, & Keshavan, 2014; Misiak et al., 2018; Tsuang, Stone, & Faraone, 2001; van Os, Kenis,

& Rutten, 2010; van Os, Rutten, & Poulton, 2008). The importance of genetic factors for the development of schizophrenia spectrum disorders becomes evident in heritability studies: For schizophrenia, concordance rates in twins have been found to be 41–65% in monozygotic and 0–28% in dizygotic twins (Cardno & Gottesman, 2000). Heritability estimates for schizophrenia are approximately 80%, while they are a little lower for other schizophrenia spectrum disorders (Cardno & Gottesman, 2000; Hilker et al., 2017). Environmental risk factors can be certain events in prenatal (e.g., nutritional deficiency, maternal infections, maternal stress, older paternal age; Khandaker, Zimbron, Lewis, & Jones, 2013; Meli, Öttl, Paladini, & Cataldi, 2012; Tandon, Keshavan, & Nasrallah, 2008) and perinatal periods (e.g., low birth weight; Cannon et al., 2000; Larsen, Bendsen, Foldager, & Munk-Jørgensen, 2010), in early and late childhood (e.g., severe trauma, urbanicity, migration; Belbasis et al., 2018; Schäfer & Fisher, 2011; Vassos, Pedersen, Murray, Collier, & Lewis, 2012) as well as in adolescence up to early adulthood (e.g., cannabis use; Casadio, Fernandes, Murray, & Di Forti, 2011; Gage, Hickman, & Zammit, 2018; Semple, McIntosh, & Lawrie, 2005). However, while there is plenty of research on risk factors for schizophrenia spectrum disorders, little is known about how exactly their effects on the disorders are mediated (see Heckers et al., 2013; Radua et al., 2018). Thus, until today, it is not possible to determine the exact mechanisms operating in individuals with schizophrenia spectrum disorders (Gaebel & Zielasek, 2015; Tandon et al., 2008).

Some authors claim that the lack of progress in discovering underlying mechanisms can be attributed to the categorical diagnosis of schizophrenia spectrum disorders, which is still applied in the current version of the DSM (Heckers, 2008; Heckers et al., 2013). The change in nosology in favor of a dimensional approach may be a large step toward a better understanding of etiological factors (Cuthbert & Insel, 2010; Insel, 2010). Indeed, an important approach within the research on etiological factors and underlying mechanisms of psychotic disorders is the *continuum hypothesis of psychosis* (Allardyce, Suppes, & van Os, 2007; see also David, 2010). Positing a multifactorial etiology of psychosis, this theory suggests that different combinations of risk factors result in various phenotypic expressions on a continuum from normal mental health to psychopathology. Accordingly, psychotic disorders are not considered a binary phenotype (present, absent) with a sudden onset but rather a continuum between the general population and patients (Nelson, Seal, Pantelis, & Phillips, 2013).

The continuum hypothesis implicates the presence of a psychosis phenotype in the general population or, more specifically, the existence of not only clinical but also subclinical expressions of psychosis (Allardyce et al., 2007). Evidence for the existence of these subclinical forms of psychosis comes, for example, from studies of the psychosis prodrome and from investigations on high-risk populations (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013). One of these subclinical expressions is *schizotypy*, which can be described as personality traits mirroring the symptoms of schizophrenia in an attenuated form (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014; Nelson et al., 2013; see below for a

more detailed description of schizotypy). The existence of subclinical schizophrenia-like traits enables valuable approaches within the search for etiological factors and underlying mechanisms of schizophrenia spectrum disorders: The investigation of healthy individuals who share a liability toward schizophrenia or related disorders can be useful in discovering (i) developmental pathways of schizophrenia spectrum disorders, and (ii) mechanisms that protect against the disorder (Barrantes-Vidal, Grant, & Kwapil, 2015; Chan et al., 2015; Kwapil & Barrantes-Vidal, 2015). A second benefit of studying schizophrenia-like traits can be to apply them as model systems of psychosis for the evaluation of newly developed antipsychotic medication (Ettinger & Kumari, 2015; Koychev et al., 2011).

1.1.2 Schizotypy: Phenomenology and Psychometric Foundations

In accordance with the suggestion that schizophrenia spectrum disorders are not categorical constructs (Allardyce et al., 2007), psychotic or psychosis-like experiences were discovered to occur not only in clinical populations but in the general population as well (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Psychosis-like experiences in the general population have been found to become manifest in two different ways: *First*, numerous studies show that approximately 8% of the general population report isolated subclinical psychotic experiences, such as paranoid beliefs or feelings of suspiciousness as well as auditory hallucinations (e.g., hearing god's voice or the voice of a dead relative; van Os et al., 2009). *Second*, psychosis-like experiences in the general population occur as part of schizotypy, which is defined as a temporally stable set of personality traits that mimic symptoms of schizophrenia in an attenuated, subclinical form (Chan et al., 2015; Ettinger et al., 2014; Nelson et al., 2013; Venables & Raine, 2015).

Schizotypy is understood as a multidimensional construct (e.g., Kwapil & Barrantes-Vidal, 2015), including positive, negative and disorganized facets, thereby paralleling the positive, negative, and disorganized symptom categories of schizophrenia (Liddle, 1987; Nelson et al., 2013; Raine et al., 1994). While the positive dimension includes characteristics such as magical thinking, unusual perceptional experiences, and paranoid ideas, the negative facet comprises features of anhedonia, such as having no close friends, a flattened affect, and refusal of emotional or physical closeness, and the disorganized dimension refers to attributes such as odd behavior and speech as well as difficulties in attention and decision making (Nelson et al., 2013; Raine et al., 1994). Beside the similar factor structure, schizotypy shows overlaps with schizophrenia spectrum disorders regarding cognitive functions, brain structure and function as well as environmental risk factors (Ettinger et al., 2014, 2015; Nelson et al., 2013).

Schizotypy is usually assessed by means of self-report questionnaires (for an overview, see Fonseca-Pedrero et al., 2008; Vollema & van den Bosch, 1995), of which the Schizotypy Personality Questionnaire (SPQ; A. S. Cohen, Matthews, Najolia, & Brown, 2010; Davidson, Hoffman, & Spaulding, 2016; Raine, 1991; Raine & Benishay, 1995), the Chapman Scales (Chapman, Chapman, & Raulin, 1976, 1978; Eckblad & Chapman, 1983), and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Grant et al., 2013; Mason, Claridge, & Jackson, 1995; Mason & Claridge, 2006; Mason, Linney, & Claridge, 2005) are most frequently used. Despite remarkable correlations between these instruments, suggesting they all measure the same construct (Asai, Sugimori, Bando, & Tanno, 2011; Gross, Mellin, Silvia, Barrantes-Vidal, & Kwapil, 2014; Venables & Raine, 2015), they follow different theoretical approaches of schizotypy (Mason, 2015): The items of the SPQ, for example, were created based on DSM criteria of schizotypal personality *disorder*, which is why their wording resembles clinical questions (see Raine, 1991). The O-LIFE, however, is based on the concept of schizotypy as a personality *trait*, which is why its items resemble those of personality questionnaires (see Mason et al., 1995; Mason et al., 2005). Moreover, the questionnaires differ from each other regarding their subscales: The SPQ follows the classical structure of positive, negative, and disorganized schizotypy (Raine, 1991; Raine et al., 1994), the Chapman scales contain only the positive and negative facets (Chan et al., 2015; Chapman et al., 1976, 1978; Eckblad & Chapman, 1983), and the O-LIFE reflects a four-dimensional model of schizotypy (Mason et al., 1995; Mason et al., 2005). In addition to negative, positive, and disorganized dimensions, the latter model proposes the facet of *impulsive nonconformity*, describing features such as antisocial behavior and lack of self-control (Mason et al., 1995; for an overview of the O-LIFE scales and exemplary items see Table 1). It is subject to debate whether impulsive nonconformity, which is based upon Eysenck's concept of psychoticism (Claridge et al., 1996; Mason, 1995), actually represents a valid aspect of schizotypy and can therefore be considered a distinct factor (Cochrane, Petch, & Pickering, 2010; Mason, 2015). It has been proposed that impulsive nonconformity is associated with temporary affective instability and transient psychotic symptoms rather than with schizophrenia (Lin et al., 2013). Investigations into the factor structure of the O-LIFE yielded inconsistent results, with some studies reporting similar performance for three- and four-dimensional models (Fonseca-Pedrero, Ortuño-Sierra, Mason, & Muñiz, 2015; Sierro, Rossier, Mason, & Mohr, 2016). Another study could not confirm the structure of four factors, as a three-factor model (positive, negative, disorganized) better described empirical O-LIFE data (Lin et al., 2013). Due to these inconsistent findings, it is common in schizotypy research not to consider impulsive nonconformity and to rely instead only on the other three scales to assess schizotypy (Mason & Claridge, 2006). However, as the O-LIFE is a widely applied and empirically grounded measure of schizotypy, the contradictory results on its factor structure should be further addressed by investigating whether impulsive nonconformity can be considered a separate factor, and how it is related to other factors.

Table 1

Exemplary items of the Oxford-Liverpool Inventory of Feelings and Experiences.

Scale	Exemplary items
Unusual experiences	Do you think that you could learn to read other's minds if you wanted to?
	Does your sense of smell sometimes become unusually strong?
Introvertive anhedonia	Are there very few things that you have ever enjoyed doing?
	Have you often felt uncomfortable when your friends touch you?
Cognitive disorganization	Are you easily distracted from work by daydreams?
	When in a crowded room, do you often have difficulty in following a conversation?
Impulsive nonconformity	Do you at times have an urge to do something harmful or shocking?
	Do you often feel the impulse to spend money which you know you can't afford?

Notes. Unusual experiences = positive dimension, introvertive Anhedonia = negative dimension, cognitive disorganization = disorganized dimension

In experimental studies, different approaches are applied to assess schizotypy: One possibility is to identify schizotypal participants based on their overall schizotypy score, that is, by summing up questionnaire scores of the different schizotypy dimensions (e.g., positive, negative, disorganized; see, e.g., Koychev et al., 2016; Meyhöfer et al., 2015; Xavier, Best, Schorr, & Bowie, 2015). The disadvantage of this procedure is that information on the association between single facets and the dependent variables gets lost. To examine potential differences between schizotypy dimensions, it is common to choose participants with high scores on a specific subscale (see, e.g., Gooding, Matts, & Rollmann, 2006; Kerns & Becker, 2008; E. A. Martin, Hua, Straub, & Kerns, 2019; Meyhöfer et al., 2017; Modinos et al., 2017). This way, dependent variables can be clearly associated with single schizotypy dimensions. While cognitive disorganization is correlated quite strongly with both the negative and the positive dimension, the latter two are rather independent from each other (Kwapil, Gross, Silvia, Raulin, & Barrantes-Vidal, 2018; Mason & Claridge, 2006). Therefore, the examination of single schizotypy facets is usually limited to the positive and the negative dimensions.

There are two competing models describing how schizotypy is distributed in the general population (Claridge & Beech, 1995; Nelson et al., 2013). According to the *quasi-dimensional model* (Meehl, 1962, 1990; Lenzenweger, 2006), only a small part of the population (approximately 10%) is schizotypal. These individuals are suggested to have a genetic vulnerability (schizotaxia) that can lead to psychosis

when it is combined with additional risk factors. As long as this hereditary predisposition is not combined with the risk factors, only a schizotypal personality but no psychopathology develops. This model is categorical as it poses that an individual either has the genetic vulnerability or does not (Korfine et al., 1995). It is dimensional, though, in that it proposes that schizotypy can take on the form of various different expressions on the psychosis spectrum (Nelson et al., 2013). The *fully-dimensional model* (Claridge, 1987; Claridge & Beech, 1995) is rooted in personality theory (Mason & Claridge, 2006) and is based upon Eysenck's idea of continuity between normal and abnormal individual differences (Eysenck, 1967). The model proposes that schizotypy lies on a continuum ranging from low to high schizotypy, with high levels of schizotypy potentially resulting in psychosis. In contrast to the quasi-dimensional model, the fully-dimensional model suggests that schizotypy applies to all members of the population. Much like the quasi-dimensional model, it suggests that schizotypy per se is not sufficient for the development of psychosis; only a combination of high levels of schizotypy and other etiological risk factors constitute a risk for psychopathology (Nelson et al., 2013). Although the debate about the validity of these two models is still ongoing (K. V. Everett & Linscott, 2015; Grant, Green, & Mason, 2018; Lenzenweger, 2015; Mason, 2014), several recent findings on schizotypy support the fully-dimensional model (Grant, Munk, Kuepper, Wielpuetz, & Hennig, 2015; Nelson et al., 2013). In addition, the fully-dimensional model is in accordance with the widespread view of a continuum between normal mental health and psychosis (see section 1.1.1).

It is important to study schizotypy in connection with schizophrenia spectrum disorders as well as in its own right for various reasons: *First*, despite its high similarity and liability to schizophrenia spectrum disorders (e.g., Lenzenweger, 2015; Nelson et al., 2013), the transition rate from schizotypy to such a disorder is somewhat low (van Os et al., 2009; see also Lenzenweger, 2015). A longitudinal study (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994) revealed that only 5% of all schizotypal participants developed a psychotic disorder within ten years. This implicates that individuals with schizotypy possess some protective factors or resilience mechanisms, keeping them from developing a full-blown disorder (Barrantes-Vidal et al., 2015; Ettinger et al., 2014; Giakoumaki, 2012; Kwapil & Barrantes-Vidal, 2015). Thus, the comparison between schizotypy and schizophrenia spectrum disorders could help identify etiological factors of schizophrenia spectrum disorders, including both risk and protective factors (Barrantes-Vidal et al., 2015; Chan et al., 2015; Kwapil & Barrantes-Vidal, 2015). *Second*, due to its similarity to schizophrenia spectrum disorders, schizotypy can be applied as a low-cost and ethical model system of psychosis that can be used in quasi-experimental studies to empirically evaluate newly developed antipsychotic medication (Ettinger & Kumari, 2015; Koychev et al., 2011). Although various kinds of model systems have been identified in the past (e.g., animal models and pharmacological interventions; e.g., Bramness et al., 2012; Tseng, Chambers, & Lipska, 2009), they often fail to depict the entire complex phenotype of psychotic disorders (Carhart-Harris, Brugger, Nutt,

& Stone, 2013). Combined with well-validated biomarkers of psychosis, the application of schizotypy as a model system of psychosis might overcome these limitations. *Third*, schizotypy is associated with various adverse behaviors and experiences (A. S. Cohen, Mohr, Ettinger, Chan, & Park, 2015), including substance use (Barrantes-Vidal, Lewandowski, & Kwapil, 2010; Esterberg, Goulding, McClure-Tone, & Compton, 2009), lower quality of life (Chun, Minor, & Cohen, 2013; A. S. Cohen & Davis III, 2009), decreased educational functioning and impaired social adjustment (Barrantes-Vidal et al., 2010; Rössler et al., 2015) as well as stressful experiences (Kocsis-Bogár, Miklósi, & Forintos, 2013; Rössler, Ajdacic-Gross, Rodgers, Haker, & Müller, 2016). Therefore, it is essential to study schizotypy itself in order to further our understanding of these disadvantages as well as the development of adequate forms of intervention (Ettinger et al., 2015).

The study of causes and mechanisms of schizophrenia spectrum disorders with the help of schizotypy has an essential advantage, namely that confounding factors, such as long-term medication and hospitalization, are not an issue in schizotypal individuals (Ettinger et al., 2014; Fonseca-Pedrero et al., 2008; Raine & Lencz, 1995). This makes them the optimal population to advance research on antipsychotic medication and etiological factors of schizophrenia spectrum disorders.

1.1.3 Psychosis-Like States

Although subclinical psychosis-like symptoms as part of schizotypal personality traits constitute the center of the present thesis, it should be noted that psychosis-like experiences may also manifest temporarily and transiently. Such states can be evoked by certain substances, such as ketamine (Javitt, Spencer, Thaker, Winterer, & Hajós, 2008), amphetamine (Rognli & Bramness, 2015), and cannabis (Morrison et al., 2009), but also via methods of deprivation, such as sensory (Daniel, Lovatt, & Mason, 2014; Daniel & Mason, 2015) or sleep deprivation (Ettinger & Kumari, 2015).

Of all causes of psychosis-like states, induction by sleep deprivation might be the most important one to study, as sleep disturbances and sleep deprivation are considered to be remarkably common and to have a series of adverse consequences on mental and physical health (Anderson & Bradley, 2013; Ferrie, Kumari, Salo, Singh-Manoux, & Kivimäki, 2011; Irwin, 2015). Around 30% of adults report having had insomnia problems over the past year, and even chronic insomnia might affect as many as 10% of the general population (Ferrie et al., 2011). Moreover, prolonged sleep deprivation is also known to be a risk factor of premature mortality (Everson, 1997; Parthasarathy et al., 2015). Although these findings are already alarming, they are assumed to worsen over time, with the increasing prevalence of nighttime TV consumption as well as Internet and mobile phone usage causing more sleep problems (Ferrie et al., 2011).

Most importantly, abnormal sleep is a core feature of schizophrenia and other psychotic disorders (Chan, Chung, Yung, & Yeung, 2017; Davies, Haddock, Yung, Mulligan, & Kyle, 2017; Kaskie, Graziano, & Ferrarelli, 2017; Reeve, Sheaves, & Freeman, 2015), with 30-80% of schizophrenia patients displaying disturbances such as insomnia, reduced total sleep time, and disrupted circadian patterning of sleep, including complete reversal of day and night (Cohrs, 2008). Given the obvious link to schizophrenia spectrum disorders, sleep disturbances have been hypothesized to contribute to the onset and maintenance of the disorder and are even considered a target for intervention (D. Freeman et al., 2015; Klingaman, Palmer-Bacon, Bennett, & Rowland, 2015; Waite, Sheaves, Isham, Reeve, & Freeman, 2019).

In fact, sleep disturbances, especially sleep deprivation, have been found to induce symptoms of schizophrenia spectrum disorders: The most familiar case is the experiment of Randy Gardner, who achieved entry into the Guinness Book of Records for staying awake for eleven days. Starting on the second day of his experiment, Gardner experienced symptoms such as hallucinations, delusions, speech disorders, fragmented thinking, and paranoia (Coren, 1998). In addition to this case report, several early studies systematically examined the effect of sleep deprivation for up to 205 hours on schizophrenia-like experiences via descriptive reports from the participants (Berger & Oswald, 1962; Kales et al., 1970; Kollar et al., 1969; Luby, Gottlieb, Cohen, Rosenbaum, & Domino, 1962; Patrick & Gilbert, 1896; West, Janszen, Lester, & Cornelisoon, 1962). These reports included signs of hallucinations (e.g., seeing smoke coming from under the doors), delusions (e.g., the belief that the experimenter put drugs in the participant's coffee), negative (e.g., withdrawal from other participants) and disorganized symptoms (e.g., mumbling speech, temporal disorientation).

Later attempts to examine associations between sleep deprivation and schizophrenia-like symptoms were based on validated psychological questionnaires: D. Freeman, Pugh, Vorontsova, and Southgate (2009) found a positive link between the level of insomnia and the level of persecutory thinking in the general population. In addition, already partial sleep deprivation (i.e., restricting sleep to 4 hours for three consecutive nights) led to an increase of self-reported cognitive disorganization, paranoia, and hallucinations (Reeve, Emsley, Sheaves, & Freeman, 2018). Total sleep deprivation (i.e., experimentally depriving participants from sleep for 24 hours and more) was found to induce perceptual distortion, cognitive disorganization, and anhedonia (Meyhöfer et al., 2017; Petrovsky et al., 2014) as well as signs of paranoia (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Apart from inducing features from the classical symptom categories of schizophrenia, sleep deprivation has been found to disrupt prepulse inhibition of the acoustic startle reflex, a measure of sensorimotor gating, in rodents (Frau et al., 2008) and in healthy humans (Meyhöfer, Ettinger, Faiola, Petrovsky, & Kumari, 2019; Petrovsky et al., 2014). This is somewhat striking, seeing as prepulse inhibition is known to be disrupted in psychosis as well (e.g., Ludewig, Geyer, & Vollenweider, 2003; Parwani et al., 2000). In addition, Meyhöfer et al.

(2017) reported sleep deprivation-induced deficits in several oculomotor measures overlapping with deficits found in schizophrenia (O'Driscoll & Callahan, 2008).

There are two major benefits of studying consequences of sleep deprivation regarding psychosis-like symptoms: *First*, similar to schizotypy, sleep deprivation can be applied as a model system of psychosis (Ettinger & Kumari, 2015; Kumari & Ettinger, 2020) and enable researchers to study the effects of newly developed antipsychotic drugs. It is immensely valuable in this context, as it is easy and inexpensive to apply, and its effects can be completely reversed (Everson, 1997). *Second*, the combination of sleep deprivation with a psychosis-like trait such as schizotypy might provide valuable information on potential interaction effects of trait and state causes of psychosis-like features (Meyhöfer et al., 2017; for further information, see sections 1.2.1.3 and 1.2.2.3).

1.2 Continuities in the Schizophrenia Spectrum: Cognitive and Oculomotor Markers

Studying schizotypy in the context of schizophrenia spectrum disorders and examining potential interaction effects with sleep deprivation requires the investigation of valid markers of psychosis. As the clinical phenotype of psychosis (i.e., the set of symptoms of the disorder) is diverse, the focus has shifted toward smaller but stable characteristics associated with the disorder (e.g., Perkovic et al., 2017). Two of the best established signatures of schizophrenia spectrum disorders are cognitive and oculomotor markers (for meta-analyses, see, e.g., O'Driscoll & Callahan, 2008; Schaefer, Giangrandea, Weinberger, & Dickinson, 2013), which have also been found in schizotypy (e.g., Meyhöfer et al., 2017; Siddi et al., 2017). Impaired cognitive functions are a core feature of schizophrenia spectrum disorders (Elvevåg & Goldberg, 2000; Freudenreich, 2020; Nuechterlein et al., 2014; Sheffield et al., 2019), which means that they are a primary deficit of the disorder and do not emerge from other symptoms (Kern & Horan, 2010). They are not only present in patients but also in patients' unaffected relatives (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Snitz, Macdonald III, & Carter, 2006) and in the prodromal or high-risk state of psychosis (Bora et al., 2014; de Paula, Hallak, Maia-de-Oliveira, Bressan, & Machado-de-Sousa, 2015; Fusar-Poli et al., 2012). Dysfunctions in oculomotor processes, especially in smooth pursuit eye movements (SPEM), are a well-validated and highly robust marker of schizophrenia spectrum disorders, with impaired performance in up to 80% of patients (Holzman, Levy, & Proctor, 1976; Levy, Holzman, Matthysse, & Mendell, 1993; Levy, Sereno, Gooding, & O'Driscoll, 2010; O'Driscoll & Callahan, 2008). Oculomotor measures benefit from being more specific compared to the complexity of cognitive functions (Hill, Bishop, Palumbo, & Sweeney, 2010; Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008). Therefore, they can be a valuable addition to cognitive markers, especially when the aim is to discover subtle, subclinical features in

schizotypy (Chun et al., 2013). Importantly, not only the oculomotor deficit itself but also its underlying perceptual and neural mechanisms can be of great interest for comparisons of schizotypy and schizophrenia spectrum disorder.

1.2.1 Cognitive Markers

Cognitive functions represent one of the most frequently studied fields in schizophrenia spectrum disorders (Kern & Horan, 2010). They refer to one's essential mental abilities to process information and comprise processes such as attention, learning, and memory (e.g., Roy, 2013; Wessinger & Clapham, 2009). In the context of social situations, these cognitive functions constitute the basis of social cognition (i.e., all forms of information processing that enable us to interact socially; Amodio, 2019; Bartholow, 2010; Frith, 2008; Greifeneder, Bless, & Fiedler, 2017), which is also frequently studied in the schizophrenia spectrum (Kern & Horan, 2010). However, as social cognition has been shown to be closely linked to and largely rely on general cognitive functions (Bell, Tsang, Greig, & Bryson, 2009; Deckler et al., 2018; Fanning, Bell, & Fiszdon, 2012), this thesis will subsequently focus on the latter. More specifically, it will concentrate (i) on executive functions, a widely studied aspect of cognitive functions in the schizophrenia spectrum (see, e.g., Aas et al., 2014; Dickinson, Ramsey, & Gold, 2007; Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Schaefer et al., 2013), and (ii) on a composition of domains identified by the *Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)* initiative (Kern et al., 2008; Marder & Fenton, 2004; Nuechterlein et al., 2008).

Executive functions are defined as a set of high-level cognitive processes enabling individuals to control their behavior in order to attain certain goals (Friedman & Miyake, 2017). In particular, three core executive functions have been identified: response inhibition, updating (working memory), and mental set shifting (cognitive flexibility; Diamond, 2013; Miyake et al., 2000). These core functions provide the basis for more complex, higher-level functions, such as problem solving and planning (Collins & Koechlin, 2012; Diamond, 2013).

Inhibition describes the ability to suppress a dominant or automatic response in favor of a more appropriate behavior (Miyake et al., 2000). A typical task used to assess inhibition is the Go/NoGo task, which requires participants to respond when a Go stimulus is presented and to withhold the response when a NoGo stimulus is shown (e.g., Falkenstein, Hoormann, & Hohnsbein, 1999; Verbruggen & Logan, 2008a). As Go stimuli are presented more frequently than NoGo stimuli, the response is made prepotent, while withholding it requires inhibitory control (e.g., Aron & Poldrack, 2005; Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). Further frequently used tasks measuring inhibition are the Stroop task (Stroop, 1935) and the Stop-Signal task (Verbruggen & Logan, 2008b). *Updating* refers to the

ability to hold information in working memory and to replace it when new, more relevant information is presented (Miyake et al., 2000). Working memory abilities are often assessed with the n-back task (Kirchner, 1958): In each trial, participants are required to hold information about a previously presented stimulus in working memory (e.g., its position) and to remember this information one, two or three trials later, while new stimuli are presented (e.g., Coulacoglou & Saklofske, 2018). Beside the n-back task, working memory is often assessed with digit-span tasks (Ramsay & Reynolds, 1995) or letter-number sequencing tests (e.g., Wechsler, 2008). *Mental set shifting*, also referred to as cognitive flexibility, is defined as the process of switching between different tasks or mental states (Miyake et al., 2000). It comprises abilities such as adjusting to changing demands but also shifting between perspectives spatially or "thinking outside the box" (Diamond, 2013). A category of tasks to capture shifting abilities includes letter fluency and category fluency tasks (Diamond, 2013; Rende, 2000), such as the *Regensburger Wortflüssigkeitstest* (Aschenbrenner, Tucha, & Lange, 2000). Here, participants are instructed to name as many words as possible beginning with a certain letter or belonging to a certain category in a given time (Rende, 2000). An additional task that is often used to measure shifting is the Wisconsin Card Sorting Test (Berg, 1948).

Problem solving and *planning*, which are closely linked, refer to the process of achieving a goal when the solution to meeting this goal is uncertain and separate steps have to be carried out in a specific order and thus need to be planned (Unterrainer & Owen, 2006). A frequently used task to measure problem solving abilities is the computerized Tower of London task (Shallice, 1982), requiring participants to relocate balls within three tubes of different lengths with the goal to reach a particular target position. This needs to be done in as few moves as possible and following certain rules (e.g., only one ball at a time is allowed to be moved). Further tasks used to measure problem solving are the Tower of Hanoi task (e.g., Sullivan, Riccio, & Castillo, 2009) as well as different variants of mazes (e.g., Kirsch et al., 2006).

Apart from working memory and cognitive flexibility, the MATRICS initiative proposed four additional domains thought to be particularly affected in schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008): *Verbal learning* (also referred to as verbal memory) is defined as the ability to acquire, store, and recall verbal material (see, e.g., Tatsumi & Watanabe, 2009). In verbal learning tasks, such as the California Verbal Learning Test (Delis, Kramer, Kaplan, Ober, & Fridlund, 1987), participants are required to recall freely or following a cue as many words as possible (both immediately and after a delay) from a list they learned before. *Sustained attention* refers to the ability of focusing on a stimulus or an activity for a long period of time (R. A. Cohen, 2011). A frequently used task to measure sustained attention is the identical pairs version of the Continuous Performance Test (CPT-IP; Cornblatt, Risch, Faris,

Friedman, & Erlenmeyer-Kimling, 1988). During the presentation of a series of four-digit stimuli, participants are required to respond as quickly as possible when two identical stimuli are presented consecutively. *Processing speed* refers to the time needed to perform a task (or to the number of items completed within a given amount of time; Sweet, 2011). Tasks are usually simple and the difficulty emerges from the need to perform them as quickly as possible (see, e.g., Groth-Marnat, 2009). A frequently used test is the Digit-Symbol Substitution Task (Wechsler, 1939), where participants have to repeatedly assign symbols to digits according to a key of digit-symbol pairs.

1.2.1.1 Cognitive Markers in Schizophrenia Spectrum Disorders

It is well established that patients with schizophrenia spectrum disorders display impairments in all of the abovementioned cognitive domains, with effect sizes ranging from medium to large (for meta-analyses, see Aas et al., 2014; Bokat & Goldberg, 2003; Dickinson et al., 2007; Forbes, Carrick, McIntosh, & Lawrie, 2009; Frangou, 2010; Heinrichs & Zakzanis, 1998; Mesholam-Gately et al., 2009; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Piskulic, Olver, Norman, & Maruff, 2007; Schaefer et al., 2013; Wright et al., 2014). Importantly, these impairments seem to be independent of disorder chronicity (Bozikas & Andreou, 2011; Schaefer et al., 2013) and can be found in unaffected first-degree relatives as well (Snitz, Macdonald, & Carter, 2006).

Schizophrenia spectrum patients display deficits in all domains of executive functioning: Impairments in *inhibition* manifest, for example, in higher rates of Go/NoGo commission errors (i.e., increased rates of responses in NoGo trials; e.g., Kiehl, Smith, Hare, & Liddle, 2000; Weisbrod, Kiefer, Marzinzik, & Spitzer, 2000) and slower responses in Go trials in patients compared to controls (Ettinger et al., 2018; Fryer et al., 2019; Thoma, Wiebel, & Daum, 2007; Woolard et al., 2010). Additionally, performance decreases in patients have been found in other tasks measuring inhibition, such as the Stroop task (Westerhausen, Kompus, & Hugdahl, 2011) and the Stop-Signal task (Enticott, Ogloff, & Bradshaw, 2008; Hughes, Fulham, Johnston, & Michie, 2012). Reduced *working memory* abilities in the n-back task have been demonstrated through lower accuracy (e.g., Jansma, Ramsey, Van Der Wee, & Kahn, 2004; Koike et al., 2013; Subramaniam et al., 2014; Üçok et al., 2013) and longer reaction times of correct responses (e.g., Krieger, Lis, Cetin, Gallhofer, & Meyer-Lindenberg, 2005; Zanello, Curtis, Badan Bâ, & Merlo, 2009) in patients compared to controls. Additionally, performance is worse in patients compared to controls in digit-span or letter-number sequencing tests (Heinrichs, Ammari, McDermid Vaz, & Miles, 2008; Horan et al., 2008; Twamley, Palmer, Jeste, Taylor, & Heaton, 2006). Deficits in *mental set shifting* have been found in letter and category fluency tasks, with patients usually generating fewer correct words than controls (e.g., Ehlis, Herrmann, Plichta, & Fallgatter, 2007; Elvevåg, Weinstock, Akil, Kleinman, & Goldberg, 2001; Marumo et al., 2014). In addition, impairments in patients are regularly found in the Wisconsin Card Sorting Test (e.g., Carruthers et al., 2019;

J. Everett, Lavoie, Gagnon, & Gosselin, 2001; Liu et al., 2011). Performance reductions in *problem solving* in patients compared to controls manifest in fewer correct responses (i.e., fewer solutions with the minimum number of moves) in the Tower of London task (e.g., Greenwood, Wykes, Sigmundsson, Landau, & Morris, 2011; Langdon, Coltheart, Ward, & Catts, 2002; Zhu et al., 2010).

Impaired *verbal learning* abilities are indicated by poorer immediate and delayed recall of words (both freely and cued) in patients compared to controls as well as reduced recognition performance (e.g., Altshuler et al., 2004; Hill, Beers, Kmiec, Keshavan, & Sweeney, 2004; Stone et al., 2011). Deficits in *sustained attention* measured with the CPT-IP manifest in an increased rate of misses (i.e., not detecting identical pairs) and false alarms (i.e., erroneously responding to non-identical pairs; e.g., Groom et al., 2008; Nuechterlein et al., 2015). Additionally, patients with schizophrenia spectrum disorders respond more slowly to identical pairs than healthy controls (e.g., Zabala et al., 2010).

Taken together, numerous replications of cognitive deficits in schizophrenia spectrum disorders indicate the appropriateness of cognitive dysfunctions as a marker of the disorder (e.g., Dickinson et al., 2007; Mesholam-Gately et al., 2009; Schaefer et al., 2013). This is strengthened by the findings that cognitive deficits in schizophrenia are temporally stable (e.g., Keshavan et al., 2010) and independent of disorder chronicity (Bozikas & Andreou, 2011; Schaefer et al., 2013).

1.2.1.2 Cognitive Markers in Schizotypy

Impairments in several cognitive functions are not only found in schizophrenia spectrum disorders but also in subclinical expressions, such as schizotypy (for reviews, see Giakoumaki, 2012; Siddi et al., 2017). Deficits in *inhibition,* manifesting in an enhanced rate of commission errors in the Go/NoGo task, have been reported in overall and in positive schizotypy (Kaczorowski, Barrantes-Vidal, & Kwapil, 2009; Zou et al., 2014). In addition, Ettinger et al. (2018) found that higher scores in the positive, negative, and disorganized schizotypy dimension correlated with lower performance on several tasks measuring inhibition. Reduced *working memory* abilities have been found in all schizotypy dimensions, indicated by lower accuracy in the n-back task (Kerns & Becker, 2008; Schmidt-Hansen & Honey, 2010) as well as worse performance in the letter-number sequencing test (Matheson & Langdon, 2008). Further studies reported worse performance in positive, negative, and overall schizotypy in a delayed-response task (Park, Holzman, & Lenzenweger, 1995; Park & McTigue, 1997; Tallent & Gooding, 1999). *Shifting*, measured by the amount of correctly generated words in verbal fluency tasks, is decreased in positive schizotypes (Krabbendam, Myin-Germeys, Hanssen, & van Os, 2005) as well as in negative schizotypes (Cochrane, Petch, & Pickering, 2012). In addition, performance on the Wisconsin Card Sorting Test has repeatedly been found to be impaired in all dimensions of schizotypy (e.g., Cappe, Herzog, Herzig, Brand, & Mohr, 2012; Gooding, Tallent, & Hegyi, 2001; Kim, Oh, Hong, & Choi, 2011). The

association between *problem solving* and schizotypy is unclear, as studies using the Tower of London or similar tasks did not find any differences between schizotypes and controls (Langdon & Coltheart, 1999; Laws, Kondel, Clarke, & Nillo, 2011; Suhr, 1997), whereas Louise et al. (2015) found an association between performance in solving mazes and negative schizotypy. Moreover, problem solving deficits were found in adolescents with a diagnosis of schizotypal personality disorder (Diforio, Walker, & Kestler, 2000).

Verbal learning appears to be reduced in schizotypal individuals, manifesting in a reduced number of correctly learned words (Chan et al., 2011; Palacio et al., 2006). There are, however, some inconsistencies regarding this cognitive function in schizotypy (Aguirre, Sergi, & Levy, 2008; Kim et al., 2011; Lenzenweger & Gold, 2000). *Sustained attention*, operationalized as sensitivity and response speed in the CPT-IP, has repeatedly been found to be poorer in positive schizotypes (Bergida & Lenzenweger, 2006; Gooding et al., 2006; Lenzenweger, Cornblatt, & Putnick, 1991) as well as in negative schizotypes (Gooding et al., 2006) compared to control groups. In addition, higher reaction times for correct responses in the CPT-IP have been reported for the positive schizotypy dimension (Lenzenweger, 2001).

Overall, it is obvious that the same cognitive functions that are impaired in schizophrenia spectrum disorders are also deficient in schizotypy (Giakoumaki, 2012; Siddi et al., 2017). It should be noted, however, that according to two meta-analyses, cognitive impairments in schizotypy are inconsistent and the effects are mostly small (Chun et al., 2013; Steffens, Meyhöfer, Fassbender, Ettinger, & Kambeitz, 2018). More research on this topic is therefore needed to further examine the similarity of schizophrenia spectrum disorders and schizotypy.

1.2.1.3 Cognitive Markers after Sleep Deprivation

Cognitive deficits overlapping with those in schizophrenia spectrum disorders can be observed not only in schizotypy but also in schizophrenia-like states, such as sleep deprivation (for meta-analyses, see Lim & Dinges, 2010; Philibert, 2005; see also Fortier-Brochu, Beaulieu-Bonneau, Ivers, & Morin, 2012): *Inhibition* has been found to be reduced in participants deprived from sleep for 24 up to 55 hours, with sleep deprivation leading to slower responses and a higher percentage of both commission and omission (i.e., not responding in Go trials) errors in the Go/NoGo task (Chuah, Venkatraman, Dinges, & Chee, 2006; Drummond, Paulus, & Tapert, 2006; Sagaspe et al., 2012). Zhao et al. (2019) found impaired inhibition after 24 hours of sleep deprivation, as indicated by slower stop-signal responses in the Stop-Signal task. In addition, partial sleep deprivation (five hours compared to eight hours of sleep per night) reduced Go/NoGo accuracy (van Peer, Gladwin, & Nieuwenhuys, 2018). *Working memory* performance declines after sleep deprivation (Frenda & Fenn, 2016; Killgore, 2010), with lower performance in a spatial span test being registered already after mild cumulative partial sleep deprivation of one hour less

sleep than usual (Santisteban, Brown, Ouimet, & Gruber, 2019). Choo, Lee, Venkatraman, Sheu, and Chee (2005) found a decrease in n-back accuracy after 24 hours of sleep deprivation. In addition, several studies using different working memory tasks (e.g., the Sternberg task; Sternberg, 1966) found impairments after up to 48 hours of sleep deprivation (e.g., Bell-McGinty et al., 2004; Habeck et al., 2004; Mu et al., 2005). Fittingly, several studies have demonstrated the importance of sleep for working memory in children and adolescents (Kopasz et al., 2010). *Shifting* (e.g., assessed with letter and category fluency tests) has been reported to be affected by 36 hours of sleep deprivation (Harrison & Horne, 1997, 1998). However, in a study in which participants were deprived of sleep for 24 hours, performance in a verbal fluency task did not differ compared to participants who slept normally (Holding, Sundelin, Lekander, & Axelsson, 2019). Sleep deprivation of 32 or 44 hours has also been found to have detrimental effects on *problem solving* as assessed by Tower of London and Tower of Hanoi tasks (Horne, 1988; Killgore, Kahn-Greene, Grugle, Killgore, & Balkin, 2009). In addition, it has been shown that poorer problem solving is linked to sleep disturbances in everyday life (e.g., in response to stressful situations; Palmer, Oosterhoff, Bower, Kaplow, & Alfano, 2018).

The effect of sleep deprivation on *verbal learning* is subject to debate: Although impaired recall of learned words after 24 and 35 hours of sleep deprivation has been found (Drummond et al., 2000; Ellenbogen, Hulbert, Jiang, & Stickgold, 2009), the results are inconsistent (Nilsson et al., 2005). In contrast, *sustained attention* clearly declines after sleep deprivation: Reducing sleep time by four hours per night already leads to a higher rate of omission and commission errors in the CPT (Kahn, Fridenson, Lerer, Bar-Haim, & Sadeh, 2014; Sadeh, Dan, & Bar-Haim, 2011), as does sleep deprivation of 40 hours (Ikegami et al., 2009). 24 hours of sleep deprivation lead to fewer correct responses and more errors in the CPT (Joo, Yoon, Koo, Kim, & Hong, 2012). In addition, sleep deprivation between 23 and 85 hours induces deficits in sustained attention as assessed by several different tests, such as the psychomotor vigilance task (Cassé-Perrot et al., 2016; Lim & Dinges, 2008).

The above findings illustrate that a trait subclinical expression of psychosis (schizotypy) and a state subclinical expression of psychosis (sleep deprivation) show remarkable overlap in terms of cognitive deficits (see Giakoumaki, 2012; Lim & Dinges, 2010; Siddi et al., 2017). It is therefore highly interesting whether and how these two schizophrenia-like phenomena interact with regard to cognitive performance. This might elucidate whether transitory states might even worsen the influence of certain predispositions on cognitive functioning. Moreover, according to additive-factors logic (Sternberg, 1969; Sternberg, 2001), if the observable effects of both phenomena interacted, this would indicate that they rely on the same latent process. That is, an interaction effect would suggest that the impact of schizotypy on cognitive performance is based on the same underlying component as the cognitive deficits observed

after sleep deprivation. With this approach, valuable insight into the mechanisms operating in schizotypal individuals might be gained, which then again could provide useful information as to the etiology of schizophrenia spectrum disorders. So far, potential interaction effects have only been examined for oculomotor measures (Meyhöfer et al., 2017; see section 1.2.2.3), which is why further research into the effects on cognitive markers is clearly needed in this context.

1.2.2 Oculomotor Markers and their Perceptual and Neural Mechanisms

There are various oculomotor markers that have been applied in the study of schizophrenia spectrum disorders, including prosaccades and antisaccades (Gooding & Basso, 2009), predictive saccades (Krebs et al., 2001), and SPEM (O'Driscoll & Callahan, 2008). Among all oculomotor markers, SPEM are of particular interest, as abnormalities in SPEM can be found in a great number of patients (Holzman et al., 1976). SPEM tasks are short, easily understandable, and rely on everyday functions, which makes them acceptable even for severely affected patients (Klein & Ettinger, 2008). Moreover, measuring SPEM provides valuable information on underlying mechanisms, such as predictive processes (Barnes, 2008).

SPEM are defined as slow movements of the eye (not faster than 100°/s) that help the observer keep a small, moving stimulus on the fovea centralis, the area on the retina with the greatest acuity (Leigh & Zee, 2015; Lisberger, Morris, & Tychsen, 1987). SPEM are typically measured via short computerized tasks: Participants are instructed to follow a small target (e.g., a white circle) moving horizontally across the screen with their eyes, as accurately as possible, without moving their head. SPEM performance is usually based on an interaction of the pursuit and the saccadic system (Barnes, 2008; Lisberger et al., 1987). Saccades allow the observer to rapidly shift the gaze (with a velocity of up to 900°/s) to bring a new stimulus onto the fovea (Leigh & Zee, 2015). During SPEM, seeing as eye and target velocity usually do not match precisely (Barnes, Donnelly, & Eason, 1987), the evolving position error can be corrected via *compensatory* saccades (catch-up/back-up saccades) that bring the target back on the fovea. In contrast, *intrusive* saccades (square wave jerks, anticipatory saccades, leading saccades) occur when a participant fails to inhibit saccadic eye movements, thus increasing the position error (Abel & Ziegler, 1988).

The SPEM response consists of two separate phases, based on different underlying mechanisms driving pursuit (Lisberger et al., 1987; Rashbass, 1961). When the stimulus begins to move, the pursuit response usually starts after a latency of approximately 100-130 ms (Robinson, 1965) due to a delay in visuomotor processing and required time for pursuit initiation (Wyatt & Pola, 1987). After this latency, the eyes begin to accelerate, and the *initiation* or *open-loop phase* begins and comprises the first 100 ms of the pursuit response. During this time, the motor response of the eye is only driven by motion perception

or, more precisely, by visual motion information from the target moving slowly across the retina (retinal slip velocity; Lencer & Trillenberg, 2008). In this phase, the pursuit response is not influenced by feedback from the retina (Lisberger & Westbrook, 1985), as the retina needs approximately 100 ms to deliver visual information to the brainstem (Krauzlis & Lisberger, 1994).

After 100 ms, information about position and velocity of the target is reported back from the retina to relevant brain structures, thus influencing the motor response (Lencer & Trillenberg, 2008). This is when the *maintenance* or *closed-loop phase* starts (Barnes, 2008). During this phase, pursuit is driven by a combination of retinal feedback about performance quality and extraretinal mechanisms (Levy et al., 2010). The latter include an efference copy of the oculomotor command (Robinson, Gordon, & Gordon, 1986) as well as accumulating experience with target velocity and movement pattern, allowing prediction and anticipation of target position (Barnes & Asselman, 1991; Barnes, 2008).

SPEM performance in the maintenance phase is usually assessed using targets moving in periodic waveforms, following sinusoidal or triangular movement patterns (Lencer & Trillenberg, 2008; for further information, see section 2.3). The parameters assessed in these tasks can be categorized into global and specific measures (O'Driscoll & Callahan, 2008). Specific parameters, such as velocity gain (i.e., the relation of eye velocity to target velocity) or specific types of saccades, provide information about whether a deficit is based on inabilities of the pursuit or the saccadic system (Levy et al., 2010). In contrast, global parameters, such as the root mean square error (RMSE; i.e, a global measure of eye compared to target position) or the total saccade frequency (i.e., the amount of saccades that disrupt pursuit, including both compensatory and intrusive saccades), provide no information on the nature of the deficit (Abel & Ziegler, 1988). Nevertheless, global measures appear to be highly meaningful for quantifying deficits in schizophrenia (Clementz, Iacono, & Grove, 1996).

For a separate examination of predictive processes underlying pursuit, the target can be blanked out for short periods of time (Becker & Fuchs, 1985; Barnes, 2008; for further information, see section 2.3), during which participants are instructed to continue eye movements as if the target was still visible. During these blanking intervals, SPEM can be sustained, though with lower accuracy (Becker & Fuchs, 1985; Lencer & Trillenberg, 2008). When the target is absent, performance can no longer be based on visual motion information. Instead, knowledge on target movement and velocity becomes essential to predict future target positions in order to continue SPEM (Barnes, 2008; Fukushima, Fukushima, Warabi, & Barnes, 2013). This is usually applied to tasks with triangular waveforms, where target movement and velocity are constant and thus highly predictable (see Becker & Fuchs, 1985).

The neural underpinnings of SPEM are well described (for overviews, see Leigh & Zee, 2015; Lencer, Sprenger, & Trillenberg, 2019; Lencer & Trillenberg, 2008; Sharpe, 2008). First, retinal image signals

are projected via the lateral geniculate nucleus to the primary visual cortex. As stated above, the perception of visual motion information is an important mechanism of pursuit (Lencer & Trillenberg, 2008), which makes extrastriate, motion-sensitive area V5, including the middle temporal area and the medial superior temporal area, a key structure for SPEM (e.g., Nagel et al., 2006; Tanabe, Tregellas, Miller, Ross, & Freedman, 2002). Additional relevant structures are the frontal eye fields (FEFs), which are involved in generating the oculomotor command and therefore contribute to predictive processes of pursuit (e.g., Fukushima, Yamanobe, Shinmei, & Fukushima, 2002; Ilg & Thier, 2008; Lencer et al., 2004; Nagel et al., 2006). The supplementary eye fields (SEFs) are suggested to be involved in planning of the motor response as well as in learning of target movement and velocity, thus also being responsible for target prediction and anticipation (Heide, Kurzidim, & Kömpf, 1996; Lencer, Nagel, et al., 2004; Schmid, Rees, Frith, & Barnes, 2001). The parietal eye fields and the dorsolateral prefrontal cortex appear to be responsible for attentional and monitoring processes (Burke & Barnes, 2008; Schmid et al., 2001).

1.2.2.1 SPEM in Schizophrenia Spectrum Disorders

Research on SPEM dysfunctions in the schizophrenia spectrum goes back to the year 1908, when Allen Diefendorf and Raymond Dodge first examined eye movements in patients with what was then still called dementia praecox (Diefendorf & Dodge, 1908). Due to the strong link between SPEM impairments and dementia praecox, they invented the term *praecox pursuit*. However, research in this field was resumed only decades later, when Holzman and colleagues discovered abnormal SPEM in schizophrenia patients and their first-degree relatives (Holzman et al., 1974; Holzman, Proctor, & Hughes, 1973). Since then, SPEM dysfunctions have become one of the most replicated impairments in psychophysiological research on schizophrenia spectrum disorders (for overviews, see Holzman & Levy, 1977; Levy, Holzman, Matthysse, & Mendell, 1993; O'Driscoll & Callahan, 2008). To get an impression of SPEM dysfunctions in schizophrenia patients, Figure 1 displays SPEM data of a patient and a control participant.

A large meta-analysis, including 2107 schizophrenia patients and 1965 controls from studies published between 1993 and 2008 (O'Driscoll & Callahan, 2008), reported impairments in patients in most parameters of SPEM, with the largest effect sizes found for global measures (d = .70 – 1.55). More precisely, schizophrenia patients have repeatedly been found to display lower pursuit quality and higher signal to noise ratio (e.g., Altman, Hedeker, Davis, & Comaty, 1990; Amador et al., 1991; these early measures of SPEM have been replaced by now), a higher total frequency of saccades (e.g., Haraldsson

et al., 2008) as well as an enhanced RMSE (e.g., Iacono, Moreau, Beiser, Fleming, & Lin, 1992; Lee, Williams, Loughland, Davidson, & Gordon, 2001; Sponheim, Iacono, Thuras, Nugent, & Beiser, 2003).

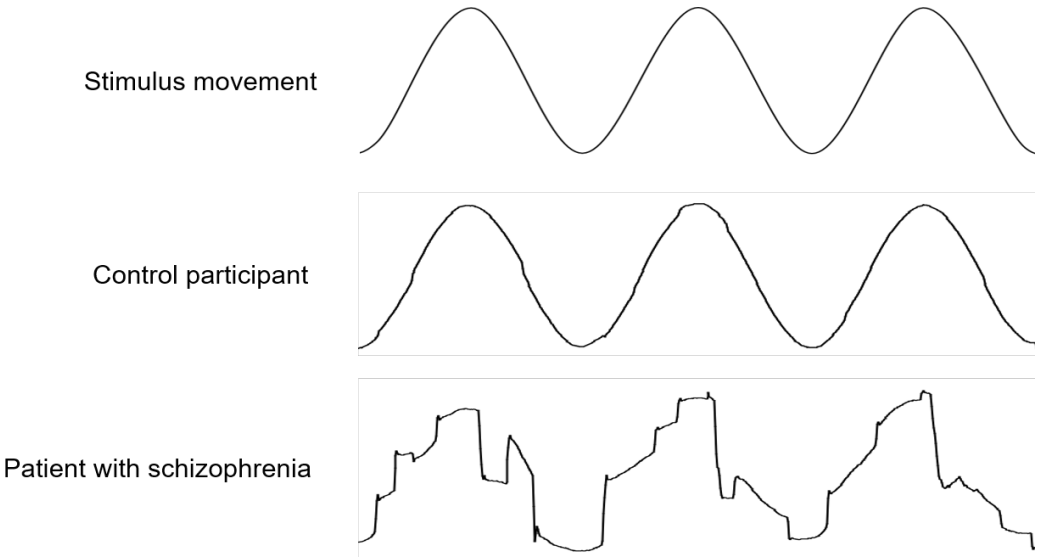

Figure 1. Original data from a sinusoidal smooth pursuit task. The figure shows a stimulus moving with a sinusoidal movement pattern (top panel) as well as the responses to this stimulus by a control participant (middle panel), and a schizophrenia patient (bottom panel). The patient's SPEM response is characterized by numerous saccadic deviations.

As a possible reason for the large effect sizes in global measures, Levy et al. (2010) emphasized that global measures include different types of deficits and can thus identify a higher proportion of individuals with SPEM dysfunctions then specific measures. However, large effect sizes were found for some specific measures as well: A lower gain in patients compared to controls, the most frequently replicated SPEM deficit (see, e.g., Bagary et al., 2004; Haraldsson et al., 2008; Ivleva et al., 2014; Lencer et al., 2015; Lencer, Trillenberg, et al., 2004; Nkam et al., 2001; Nkam et al., 2010; Spengler et al., 2006; Sprenger, Trillenberg, Nagel, Sweeney, & Lencer, 2013; Sweeney et al., 1998), yielded an effect size of d = .87, while an increased rate of leading saccades (e.g., R. G. Ross, Olincy, Harris, Sullivan, & Radant, 2000; R. G. Ross et al., 2002) resulted in an effect size of d = 1.31 (O'Driscoll & Callahan, 2008). Additionally, schizophrenia patients display detriments during the open-loop phase of pursuit (i.e., reduced gain, slower acceleration and increased pursuit latency; e.g., Hong, Avila, Adami, Elliot, & Thaker, 2003; Lencer et al., 2015; Trillenberg et al., 2017). Further SPEM disturbances in schizophrenia include a higher rate and amplitude of catch-up saccades (e.g., Flechtner, Steinacher, Sauer, & Mackert, 1997; Lencer et al., 2008; Sweeney et al., 1994) as well as an increased anticipatory saccade rate (e.g., R. G. Ross et al., 2000; R. G. Ross, Olincy, & Radant, 1999; Spengler et al., 2006). These results demonstrate that both global and specific parameters are valuable in identifying SPEM abnor-

malities in schizophrenia spectrum disorders. In addition, this meta-analysis shows that SPEM dysfunctions in the schizophrenia spectrum seem to rely on impairments of both the pursuit and the saccadic system (O'Driscoll & Callahan, 2008).

SPEM impairments in patients with schizophrenia spectrum disorder have been found regardless of target movement pattern (sinusoidal or constant) and target velocity (O'Driscoll & Callahan, 2008). In addition, the SPEM deficit can be found independent of disorder duration: Abnormalities have been found in patients with recent-onset (Yee, Nuechterlein, & Dawson, 1998), first-episode (Bagary et al., 2004; Hutton, Crawford, Kennard, Barnes, & Joyce, 2000; Iacono et al., 1992; Lencer et al., 2010) as well as chronic schizophrenia (Abel, Friedman, Jesberger, Malki, & Meltzer, 1991; Katsanis & Iacono, 1991). Not only schizophrenia *patients* but also their *relatives* have been found to perform worse in SPEM tasks (Iacono et al., 1992). Also, impairments are similar in both medicated and unmedicated patient groups (Hutton et al., 2001), and the type of antipsychotic medication does not affect the differences between patients and controls (O'Driscoll & Callahan, 2008). In addition, longitudinal studies have confirmed the temporal stability of SPEM impairments in schizophrenia (Gooding, Iacono, & Beiser, 1994; Schlenker & Cohen, 1995; Yee et al., 1998). Although meta-analyses and reviews focus on SPEM dysfunctions in schizophrenia, abnormalities can also be observed in other schizophrenia spectrum disorders, such as schizoaffective disorder (Lencer et al., 2015; L. F. Martin et al., 2007), delusional disorder (Campana, Gambini, & Scarone, 1998; Gambini, Colombo, Cavallaro, & Scarone, 1993), and psychotic disorder not otherwise specified (Kumra et al., 2001). However, the most pronounced deficits seem to be present in schizophrenia patients (Lencer et al., 2015).

The mechanisms underlying abnormal SPEM in schizophrenia spectrum disorders are subject to debate (Levy et al., 2010). One explanation of SPEM dysfunction in schizophrenia spectrum disorders is a deficit in the perception of visual motion (Chen et al., 1999; Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005; Stuve et al., 1997). Motion perception is usually measured with psychophysical velocity or direction discrimination tasks, for example, random dot kinematograms (Newsome & Paré, 1988). Random dot kinematograms require participants to determine the direction of coherently moving dots (left or right) within a proportion of dots moving in random directions. Studies measuring random dot kinematograms in schizophrenia have consistently found lower task performance, that is, reduced motion perception, in patients (Chen, Nakayama, Levy, Matthysse, & Holzman, 2003; Li, 2002; Norton, Mcbain, Öngür, & Chen, 2011; Slaghuis, Holthouse, Hawkes, & Bruno, 2007; Stuve et al., 1997). Fitting evidence comes from velocity and contrast discrimination tasks (for a review, see Chen, 2011). Interestingly, decreased performance in both direction and velocity discrimination tasks has been found to be associated with reduced SPEM performance (Chen et al., 1999; Slaghuis, Bowling, & French, 2005; Slaghuis et al., 2007; Stuve et al., 1997). Taken together, these findings point toward a motion perception deficit in schizophrenia, which is likely to play a major role in SPEM abnormalities.

Another explanation for impaired SPEM in schizophrenia spectrum disorders is a deficit in prediction (e.g., Hong et al., 2003, 2008; Thaker et al., 1996). In blanking tasks, which are used to measure predictive processes during SPEM separately, schizophrenia patients were repeatedly found to perform worse than controls (Hong et al., 2003, 2008; Hong, Avila, & Thaker, 2005; Ivleva et al., 2014; Thaker, Ross, Buchanan, Adami, & Medoff, 1999; Thaker et al., 1996). Converging evidence comes from studies reporting faulty prediction during SPEM in relatives of schizophrenia patients (Hong et al., 2008; Thaker et al., 2003, 1998). Furthermore, prediction during SPEM has been linked to working memory abilities, as information on velocity and movement pattern of the target has to be kept in mind (Fukushima et al., 2013; Thaker et al., 1999), and working memory has been frequently found to be impaired in schizophrenia (e.g., Schaefer et al., 2013).

Studies examining the neural correlates of dysfunctional SPEM in schizophrenia spectrum patients found evidence for deficits in both prediction and motion perception as underlying mechanisms of SPEM performance: Some studies have observed a major contribution of motion-sensitive area V5, responsible for perception of visual motion (Braddick et al., 2001; Newsome & Paré, 1988), as patients displayed reduced activity of this area during SPEM (Hong, Tagamets, et al., 2005; Lencer et al., 2005; Tregellas et al., 2004). Similarly, Nagel et al. (2007) found activity reductions in schizophrenia patients in area V3A, which lies adjacent to area V5 and is also known to be involved in the perception of visual motion (Braddick et al., 2001; Koyama et al., 2005). On the other hand, schizophrenia patients have been found to exhibit reduced activity in the FEFs during SPEM compared to healthy controls (Hong, Tagamets, et al., 2005; Keedy, Ebens, Keshavan, & Sweeney, 2006; Tregellas et al., 2004). These results could be confirmed in first-degree relatives of schizophrenia patients (O'Driscoll et al., 1999). The FEFs are known to be important for predictive processes during SPEM (Fukushima et al., 2002; Ilg & Thier, 2008). Furthermore, activity reductions in patients during SPEM were found in SEFs and cingulate gyrus (Hong, Tagamets, et al., 2005; Tregellas et al., 2004), which are assumed to be involved in learning and predicting the target's movement pattern as well (Lencer, Nagel, et al., 2004; Lencer & Trillenberg, 2008; Schmid et al., 2001).

Interestingly, not only activity reductions but also enhanced activity was found in patients: Two studies reported higher activity in patients compared to controls in thalamus and hippocampus (Tregellas et al., 2004; Nagel et al., 2007). Overactivity in the thalamus has been interpreted as representing alternative SPEM strategies of schizophrenia patients (Nagel et al., 2007). An increase in hippocampal activity, however, has been assumed to be a general characteristic of the disorder rather than a specific indicator of impaired pursuit (Lisman et al., 2009; Tregellas et al., 2004).

Altogether, numerous replications of SPEM deficits in schizophrenia spectrum disorders, along with findings on temporal stability and independence of task or patient characteristics, confirm the benefit of SPEM dysfunctions as a marker of the disorder (O'Driscoll & Callahan, 2008). While the deficit itself is stable, findings on the neural, cognitive, and perceptual mechanisms of the deficit in schizophrenia spectrum disorders are somewhat inconsistent, suggesting that both motion perception and predictive processes play an important role (Levy et al., 2010).

1.2.2.2 SPEM in Schizotypy

There is considerable overlap between individuals with high levels of schizotypy and patients with schizophrenia spectrum disorder regarding SPEM deficits: Lower gain scores have been found in positive (Gooding, Miller, & Kwapil, 2000; Lenzenweger & O'Driscoll, 2006), negative (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Lenzenweger & O'Driscoll, 2006), and disorganized schizotypy (Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007) as well as in participants with high overall schizotypy scores (Koychev et al., 2016; Lenzenweger & O'Driscoll, 2006). A higher total saccade frequency has been reported in negative and disorganized schizotypy (Smyrnis et al., 2007) as well as in elevated overall schizotypy (Meyhöfer et al., 2015). The RMSE has been observed to be impaired in positive (Gooding et al., 2000; Meyhöfer et al., 2015; Smyrnis et al., 2007), negative (Gooding et al., 2000), and overall schizotypy (van Kampen & Deijen, 2009; Kelley & Bakan, 1999). Studies investigating catch-up saccades in schizotypal participants revealed a higher amplitude in positive schizotypes (Meyhöfer et al., 2017) and a higher rate in disorganized schizotypes (Lenzenweger & O'Driscoll, 2006). In addition, pursuit quality has been found to be impaired in positive schizotypes (O'Driscoll, Lenzenweger, & Holzman, 1998), and a higher percentage of poor trackers has been reported for groups of positive and negative schizotypy (Simons & Katkin, 1985). Three additional studies showed elevated scores of positive, negative, and overall schizotypy in poor trackers (Kendler et al., 1991; Siever et al., 1989, 1982). All studies used sinusoidal target movements (with target frequencies ranging from 0.2 to 0.8 Hz) except for three studies using triangular target movements, with velocities of 8 to 30°/s (O'Driscoll et al., 1998; Smyrnis et al., 2007; van Kampen & Deijen, 2009). Only one study found no associations between schizotypy and alterations in SPEM gain or saccadic frequency (Schmechtig et al., 2013); however, this study differed from others in that measures of schizotypy were combined with the administration of various drugs.

While SPEM abnormalities in schizotypy and schizophrenia spectrum disorders clearly overlap on the behavioral level, the mechanisms of the dysfunctions are poorly explored in schizotypy. The only study that examined neural correlates of SPEM in schizotypy reported activity reductions in individuals with high compared to low schizotypy in a part of the middle occipital gyrus near visual area V5, in the fusiform gyrus, and in area V3A (Meyhöfer et al., 2015). Two conclusions can be drawn from these

results: *First*, the neural mechanisms of SPEM in schizotypy seem to partly overlap with those discovered for schizophrenia (Hong, Tagamets, et al., 2005; Lencer et al., 2005; Meyhöfer et al., 2015; Tregellas et al., 2004). However, activity reductions in frontal regions (FEFs, SEFs) repeatedly found in schizophrenia (Hong, Tagamets, et al., 2005; Keedy et al., 2006; Tregellas et al., 2004) could not be discovered in schizotypy. *Second*, as areas V3A and V5 are involved in the perception of visual motion (Braddick et al., 2001; Newsome & Paré, 1988), these findings suggest that SPEM impairments in schizotypy rely on deficient motion perception. However, as no study has examined motion perception performance in schizotypy to date, it is not possible to draw clear conclusions as to the underlying mechanisms of SPEM in schizotypal individuals. Similar to schizophrenia, alternative processes, such as faulty prediction of target movement, may be responsible for the SPEM deficit in schizotypy. This suggestion is supported, again, by impaired working memory in schizotypy (Chun et al., 2013; Steffens et al., 2018). In addition, deficits in predictive pursuit have been discovered in relatives of schizophrenia patients, particularly in those with schizophrenia spectrum personalities (Thaker et al., 1998). However, studies examining predictive processes during SPEM in schizotypy are lacking, which is why further research is needed on this topic.

Overall, SPEM impairments found in all three dimensions of schizotypy overlap with those found in schizophrenia spectrum disorders, with deficits reported primarily for three parameters, namely gain, total frequency of saccades, and RMSE (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Koychev et al., 2016; Lenzenweger & O'Driscoll, 2006; Meyhöfer et al., 2015; Smyrnis et al., 2007; van Kampen & Deijen, 2009). While the underlying neural and cognitive mechanisms have been studied quite intensively in schizophrenia patients (Levy et al., 2010), they are poorly understood in schizotypy. Further research is needed to discover whether faulty motion perception, deficient prediction, or a combination of both processes is responsible for the SPEM deficit in schizotypy. Additionally, the neural mechanisms of SPEM deficits in schizotypy should be further investigated, seeing as this has only been examined once (Meyhöfer et al., 2015). Understanding not only the deficit itself but also its causes, might provide useful information as to potential protective mechanisms operating in schizotypes.

1.2.2.3 SPEM after Sleep Deprivation

Alterations in SPEM after a certain duration of total sleep deprivation resemble deficits displayed in schizophrenia spectrum disorders and schizotypy: Depriving participants of sleep for 24 up to 40 hours evoked lower gain scores compared to performance after nights of sleep (Ferrara, De Gennaro, & Bertini, 2000; Fransson et al., 2009; Gennaro, Ferrara, Urbani, & Bertini, 2000; Meyhöfer, Kumari, Hill, Petrovsky, & Ettinger, 2016; Porcu, Ferrara, Urbani, Bellatreccia, & Casagrande, 1998; Tong, Maruta, Heaton, Maule, & Ghajar, 2014). In addition, rates of catch-up and anticipatory saccades as well as the

total saccade rate were found to be increased after sleep deprivation (Meyhöfer et al., 2016, 2017; Tong et al., 2014). Meyhöfer et al. (2017) reported higher RMSE scores after 24 hours of sleep deprivation compared to normal sleep nights. Most studies used sinusoidal target movements, with target frequencies ranging from 0.2 to 0.7 Hz (Ferrara et al., 2000; Gennaro et al., 2000; Meyhöfer et al., 2016, 2017; Porcu et al., 1998; Tong et al., 2014). Only two studies (Quigley, Green, Morgan, Idzikowski, & King, 2000; van Steveninck et al., 1999) reported no sleep deprivation-induced SPEM impairments at all; this may be due to the choice of parameters, which were, however, not specified by the authors.

Considering the strong overlaps regarding SPEM in schizotypy and after sleep deprivation, Meyhöfer et al. (2017) examined how these two subclinical expressions of psychosis would interact with regard to SPEM performance. The authors applied 24 hours of sleep deprivation to positive schizotypes and low-schizotypy control participants. They found an interaction effect for velocity gain in a sinusoidal SPEM task: After one night of sleep deprivation (but not after a normal sleep night), schizotypal participants displayed lower gain than control participants. This result shows that schizotypes seem to be affected more strongly by sleep deprivation than control participants. It has to be noted, however, that an interaction effect has been found in only one out of several different measures. It is therefore questionable to what extent such interaction effects are valid. This question has to be explored in more depth with additional markers of psychosis.

1.3 Discontinuities between Schizotypy and Schizophrenia Spectrum Disorders

So far, this thesis has mainly focused on similarities or continuities between schizotypy and schizophrenia spectrum disorders. However, it is important to note that there are also mentionable discontinuities in several areas. For example, divergent anomalies of brain structure have been reported for schizotypal individuals and schizophrenia patients: Schizotypy has been linked to *increased* cortical thickness in the frontal lobe (Kühn, Schubert, & Gallinat, 2012) as well as augmented volume in the cingulate cortex and precuneus (Modinos et al., 2010; Modinos et al., 2018; Nenadic et al., 2015). In addition, Wiebels and colleagues discovered *positive* associations between all dimensions of schizotypy and volumes in the parietal and temporal lobe as well as in the putamen and cerebellum (Wiebels, Waldie, Roberts, & Park, 2016). For schizophrenia, in contrast, volume *reductions* have been found in all these regions (e.g., Ballmaier et al., 2008; Borgwardt et al., 2008; Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Kasai et al., 2003; Koo et al., 2008; Laidi et al., 2015; Mitelman, Shihabuddin, Brickman, Hazlett, & Buchsbaum, 2005). Modinos et al. (2018) concluded that while "volumetric changes in the precuneus are present along the psychosis continuum, the discrepancies in directionality indicate that structural characteristics of this region may vary based on the degree of psychosis risk" (p. 1886). This might apply for the other aforementioned brain areas as well. In addition, paralleling findings in depression (Miller et al., 2014),

the authors proposed that greater volumes may operate as resilience mechanisms, in that they protect individuals with an enhanced liability to psychosis from developing the disorder (Modinos et al., 2018). Furthermore, Meller, Ettinger, Grant, and Nenadic (2019) found general intelligence as a moderator of the association between schizotypy and volume in the putamen. They concluded that general intelligence may work as a buffering mechanism, attenuating the risk of developing psychosis in schizotypal individuals.

In addition, discontinuities in brain function have been revealed: As mentioned above, the alterations of frontal cortical activity typically observed in schizophrenia during SPEM have not been found in schizotypal individuals (Meyhöfer et al., 2015). Similarly, despite overlapping deficits in antisaccade performance (Hutton & Ettinger, 2006; Myles, Rossel, Phillipou, Thomas, & Gurvich, 2017), schizotypal individuals did not show frontal activity reductions typical of schizophrenia patients during performance of antisaccades (Aichert, Williams, Möller, Kumari, & Ettinger, 2012).

Moreover, positive schizotypy has been found to be associated with positive experiences (Mohr and Claridge, 2015), such as normal or even elevated subjective well-being (Goulding, 2004; McCreery & Claridge, 2002). In addition, mild expressions of schizophrenia symptoms, such as in schizotypy, have been found to support creativity, while a full expression of the symptoms undermines it (Acar, Chen, & Cayirdag, 2018).

In light of the finding that people with high levels of schizotypy usually do not convert into psychosis (Chapman et al., 1994; see section 1.1.2), the above evidence on discontinuities between schizotypy and schizophrenia spectrum disorders suggests that protective factors or compensatory mechanisms operate in schizotypal individuals, preventing them from developing schizophrenia or a similar disorder (see Barrantes-Vidal et al., 2015; Chan et al., 2015; Kwapil & Barrantes-Vidal, 2015). As Barrantes-Vidal and colleagues (2015) emphasize, "the very concept of resilience relies on identification of individuals with risk factors who remain healthy" (p. S410). Therefore, the existence of both continuities and discontinuities provides an opportunity to further understand the heterogeneity of factors that lead to clinical or subclinical outcomes (Barrantes-Vidal et al., 2015).

To take advantage of this opportunity, a shift in the methods of schizotypy and schizophrenia spectrum research is needed: *First*, schizotypy and schizophrenia spectrum disorders have usually been studied separately, while investigations involving direct comparisons are scarce (Hazlett, Goldstein, & Kolaitis, 2012). *Second*, previous studies have mainly focused on similarities between the two constructs. However, to advance research on protective mechanisms in schizotypy and to gain information on etiological

factors of schizophrenia spectrum disorders, direct comparisons of schizotypy and schizophrenia spectrum disorders as well as examinations of differences between the two constructs are required (Hazlett et al., 2012; Nelson et al., 2013).

1.4 Goals of the Present Thesis

Within the context of the continuum hypothesis of psychosis, schizotypy is considered a useful construct to study developmental paths and potential resilience mechanisms of schizophrenia spectrum disorders (Barrantes-Vidal et al., 2015). Researchers agree upon three dimensions of schizotypy that mirror the positive, negative, and disorganized symptom categories of schizophrenia (Nelson et al., 2013). However, inconsistencies exist regarding the factor structure of important schizotypy questionnaires: In particular, factor analytic results on the O-LIFE, one of the most widely used instruments to identify schizotypal individuals, has yielded inconsistent results, varying between three- and four-factor solutions (Fonseca-Pedrero et al., 2015; Lin et al., 2013; Sierro et al., 2016). More specifically, it is subject to debate whether the subscale *impulsive nonconformity* constitutes a valid aspect of schizotypy and how it relates to other schizotypy facets (Lin et al., 2013; Mason, 2015). Thoroughly investigated questionnaires are, however, inevitable for the study of schizotypy. Based on a psychometric investigation using network structure analysis, the goal of **Study 1** was to further investigate inconsistencies on the O-LIFE.

Subclinical expressions of psychosis can become manifest as transient states, which can be induced, for example, by sleep deprivation (Ettinger & Kumari, 2015). Plenty of research has revealed strong overlaps between schizophrenia spectrum disorders, schizotypy, and sleep deprivation regarding two central markers of psychosis: cognitive and oculomotor functions (Lim & Dinges, 2010; Meyhöfer et al., 2017; O'Driscoll & Callahan, 2008; Schaefer et al., 2013; Siddi et al., 2017). The examination of potential interaction effects of schizotypy and sleep deprivation on these markers might be highly beneficial in providing information on how schizotypal individuals react to additional stressors known to induce psychosis-like states. While interaction effects on oculomotor functions have previously been studied (Meyhöfer et al., 2017), the putative effect on cognitive processes has long remained unclear. Therefore, this issue was examined in an extensive experimental investigation in **Study 2**.

While it is well established that schizotypy and schizophrenia spectrum disorders overlap substantially regarding SPEM dysfunctions (Meyhöfer et al., 2017; O'Driscoll & Callahan, 2008), little is known about the cognitive and neural mechanisms of these dysfunctions in schizotypy. In schizophrenia spectrum disorders, impaired SPEM performance seems to rely mainly on both deficient motion perception and faulty predictive processes (Levy et al., 2010). On the neural level, this manifests in reduced activity in motion-sensitive area V5 as well as the FEFs in schizophrenia patients (Keedy et al., 2006; Lencer et al., 2005). So far, only one study has examined the neural correlates of SPEM in schizotypy (Meyhöfer

et al., 2015), and studies on cognitive and perceptual mechanisms of the deficit in schizotypy are lacking. However, comparing schizotypy and schizophrenia spectrum disorders is important not only regarding the phenotype of the deficit but also concerning its underlying processes. Understanding the causes of SPEM deficits in schizotypy might provide useful information as to potential protective mechanisms. **Study 3**, a registered report, therefore aimed at examining motion perception and predictive processes as potential underlying mechanisms, combining psychophysiological and psychophysical measures. Finally, **Study 4** was designed to fill the gap of missing direct comparisons between schizophrenia spectrum disorders and schizotypy. In a large-scale bicentric functional magnetic resonance imaging (fMRI) investigation, schizotypal participants and schizophrenia spectrum patients were compared regarding SPEM performance as well as its neural underpinnings, applying a novel machine learning approach with clear-cut advantages compared to classical fMRI analyses (Madsen, Krohne, Cai, Wang, & Chan, 2018).

2 Methodology

This chapter provides an overview of the methodological approaches, which are central for the original studies of this thesis. The assessment of schizotypy, which is relevant for all studies, has already been explained in section 1.1.2. Moreover, the relevant approaches include network analysis (Study 1), induction of sleep deprivation (Study 2), recording and analysis of eye movements (Studies 3 and 4), assessment of motion perception (Study 3), fMRI (Study 4), and multivariate pattern classification (Study 4).

2.1 Network Analysis

Traditional theories in psychopathology research follow the view that symptoms are direct consequences of mental disorders and that different symptoms of a certain disorder co-occur and correlate only because they all share a common latent cause, that is, the disorder (*common cause theory*; Borsboom & Cramer, 2013; Bringmann & Eronen, 2018). This view has been intensively discussed (van Bork, van Borkulo, Waldorp, Cramer, & Borsboom, 2018). It has been proposed that for this theory to hold, it has to be possible that causes can be separated from their effects (Borsboom & Cramer, 2013). That is, a cause (i.e., the mental disorder) can occur without its effects (i.e., the symptoms). While this is easily applicable to somatic diseases (e.g., lung cancer can initially be present without any symptoms), it is hardly imaginable for mental disorders (e.g., it is not possible to have a panic disorder without experiencing panic attacks). This is why a new approach has recently developed, relying on the rationale of mental disorders as dynamic network structures (Borsboom, 2008; Cramer, Waldorp, van der Maas, & Borsboom, 2010).

Network structure theory is based on the assumption that the co-occurrence of different symptoms does not rely on a disorder as a common cause but on direct interactions between the symptoms (Fried & Cramer, 2017; Robinaugh, Millner, & Mcnally, 2016). This means that symptoms can cause other symptoms, and these interdependencies constitute the mental disorder (Borsboom & Cramer, 2013; Kendler, Zachar, & Craver, 2011). A highly simplified example in the context of psychotic disorders would be that an adverse life event (e.g., a childhood trauma) causes feelings of worthlessness, which again cause delusions of sin or guilt. This constellation leads to hallucinations manifesting as hearing voices accusing the patient of being stupid. Finally, this chain results in a diagnosis of schizophrenia. In short, network structure analysis is the result of a shift in the conceptualization of mental disorders, away from the common cause theory and toward a focus on symptoms and their interactions as dynamic networks (Fried & Cramer, 2017; Fried et al., 2017; Schmittmann et al., 2013).

A network consists of *nodes*, which are connected by *edges* (or paths) with certain weights, indicating interactions between nodes (van Bork et al., 2018). In network analyses of psychopathology, nodes typically represent symptoms. However, it is also possible to apply this type of analysis to questionnaires, with nodes representing items. Edges represent interactions between symptoms or items. Of specific interest within network analysis is the concept of *centrality*, which describes how strongly a node is connected to other nodes and thus how important this node is within the network (Fried, Epskamp, Nesse, Tuerlinckx, & Borsboom, 2016; van Bork et al., 2018). On the symptom-level, this means that when developing a symptom with high centrality (compared to a peripheral symptom), a person is more likely to develop other symptoms in the network (Fried et al., 2017). There are different frequently used measures to determine centrality (Figure 2): degree, betweenness, and closeness (L. C. Freeman, 1978; Fried & Cramer, 2017; Opsahl, Agneessens, & Skvoretz, 2010). *Degree* specifies the number of connections of one node with other nodes. Thus, the more interconnections a node has with other nodes, the higher its degree centrality. *Closeness* refers to the distance between two nodes, defined as the length of the shortest path connecting them. A node with a high average closeness would have low distances to other nodes of the network. *Betweenness* measures the extent to which a specific node lies on the shortest path between two other nodes. It captures how much information flowing from one part of the network to another has to pass a certain node or, in other words, to what extent one node mediates the association of two other nodes.

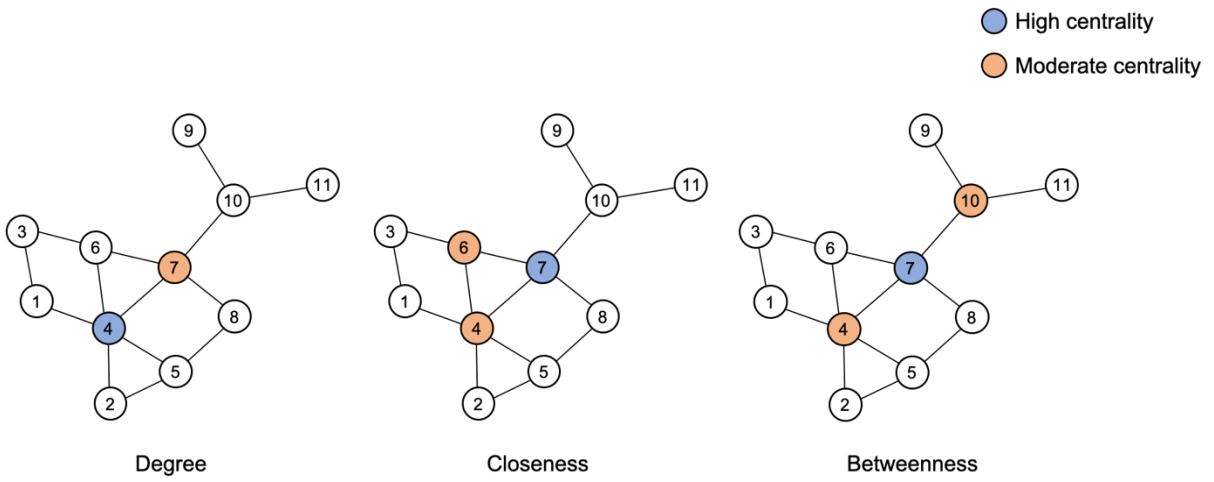

Figure 2. Hypothetical network depicting measures of centrality. Circles represent nodes. Nodes in blue represent high centrality scores, nodes in orange reflect moderate centrality scores. Adapted from "Network models for clinical psychology" by R. van Bork, C. D. van Borkulo, L. J. Waldorp, A. O. J. Cramer, and D. Borsboom, 2018, in J. T. Wixed (Ed.), *Stevens' handbook of experimental psychology and cognitive neuroscience,* p. 18; copyright (2018), with permission from John Wiley & Sons, Inc.

Additional approaches to determine node importance are the calculation of *node strength* as well as a node's *expected influence* within the network (Robinaugh et al., 2016; van Bork et al., 2018). Node strength and expected influence describe how strongly a node is related to its immediate neighbors, as defined by the sum of edge weights coming off this node. When a node has only positive edge weights, node strength and expected influence are identical. However, while node strength treats all edge weights as positive weights, expected influence retains positive and negative weights.

Finally, *node predictability* determines to what extent a node can be predicted by all its neighbors (Haslbeck & Waldorp, 2018). This parameter indicates whether a network (or a part of it) is rather predicted by itself (i.e., by strong associations between nodes) or by different factors that are independent from the network. Moreover, node predictability is an important measure in networks with a large number of observations. Usually, these kinds of networks lead to the detection of multiple small and rather meaningless edge weights. In this case, predictability of a node by these edges is a more appropriate indicator of their importance than edge weights (Haslbeck & Waldorp, 2018).

Networks often exhibit a community structure. Communities are clusters of nodes that are densely interrelated, while they are not or only modestly connected to nodes in different communities (Clauset, Newman, & Moore, 2004; Newman, 2006). Different communities of a network can be compared regarding various parameters (e.g., centrality scores) in order to determine how important a community is within the network. In addition, absolute weights of edges within a community as well as between communities can be calculated, indicating the coherence within and the connections between communities, respectively.

2.2 Induction of Sleep Deprivation

As introduced in Chapter 1, methods to experimentally induce sleep deprivation can take various forms. *First*, one has to differentiate between total and partial sleep deprivation. While total sleep deprivation means that a participant is deprived of sleep for at least one entire night, partial sleep deprivation implies that a participant gets to sleep fewer hours than usual per night, often for several nights. The effects of total sleep deprivation (e.g., on cognitive functions) are often stronger than those of partial sleep deprivation (see, e.g., Basner, Mollicone, & Dinges, 2011; Rowland et al., 2005).

Second, within total sleep deprivation, the duration of sleep deprivation can be varied. A duration that is often selected and has repeatedly led to the induction of cognitive or oculomotor deficits is 24 hours of sleep deprivation (e.g., Choo et al., 2005; Chuah et al., 2006; Joo et al., 2012; Meyhöfer et al., 2016; Petrovsky et al., 2014; Zhao et al., 2019), usually meaning that the participant stays awake for one night and variables of interest are measured in the morning after the night of sleep deprivation, when the

participant has been awake for 24 hours. Longer durations of sleep deprivation, such as 48 hours or even more, have also been employed (e.g., Bell-McGinty et al., 2004; Drummond et al., 2006; Habeck et al., 2004). The longer the sleep deprivation lasts, the more performance impairments are usually found (see, e.g., Drummond et al., 2006; Gennaro et al., 2000). However, the well-being of participants has to be considered, and multiple nights of sleep deprivation can be immensely stressful. In addition, it has been shown that performance can recover again after very long durations of sleep deprivation. For example, Fransson et al. (2009) reported a performance decrease after 24 hours but a performance increase after 36 hours. Altogether, it is safe to assume that 24 hours of total sleep deprivation are usually sufficient to evoke the desired effects.

2.3 Eye Movement Recording and Analysis

Among several different methods for eye movement recordings, video-based eye trackers are the most widely used in research, as they stand out with their high spatial and temporal resolution and a fast setup (Holmqvist et al., 2011). One example is the video-based combined pupil and corneal reflection (VCPCR) tracker. VCPCR trackers use infrared light that produces reflections from the eyes, which can be used to calculate gaze positions and eye movements (Duchowski, 2007). Two parameters are essential to this measurement (Duchowski, 2007): the corneal reflection (first Purkinje image; Crane, 1994), which remains stable during eye movements, and the center of the pupil, which moves according to a person's gaze. Before starting the recording of eye movements, calibration of the eye tracker is essential: This includes the presentation of a set of stimuli that a participant has to fixate in order to map a participant's points of regard to screen coordinates (Hutton, 2019). Combined with the calibration procedure, the relation of corneal reflection and center of the pupil can be used to identify a person's points of regard and convert them to screen positions (usually assessed in pixels; Hutton, 2019).

As mentioned earlier, performance in the maintenance phase of SPEM is usually assessed with tasks involving sinusoidal or triangular movement patterns (Lencer & Trillenberg, 2008). In addition, it is common to adopt different target velocities (or frequencies) to vary task difficulty and examine whether this affects performance in a population of interest (see, e.g., Gennaro et al., 2000; Koychev et al., 2016; Meyhöfer et al., 2017, 2015). A graphic representation of a SPEM task with a sinusoidal target movement of 0.4 Hz is displayed in Figure 3A. A slight modification of regular SPEM tasks allows to directly measure the predictive processes of SPEM. This is done by blanking out the target for short periods of time (Becker & Fuchs, 1985; Barnes, 2008), usually in tasks with constant target movement and velocity (Figure 3B).

To calculate different parameters of oculomotor performance, certain events (such as saccades and blinks) have to be identified in the raw data, which is done using information about eye position, velocity, and acceleration (e.g., Lencer et al., 2019). As mentioned above, the SPEM parameters that have repeatedly found to be affected in schizotypes are maintenance gain, total frequency of saccades, and RMSE, which is why they will be of particular importance in the present thesis.

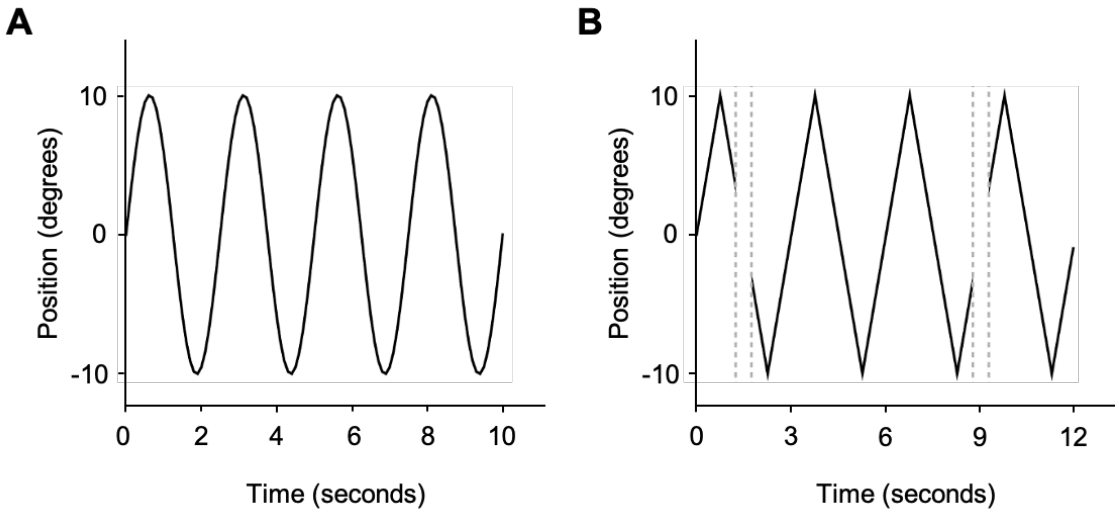

Figure 3. Exemplary smooth pursuit tasks. (A) Common smooth pursuit task with sinusoidal target movement of 0.4 Hz. The stimulus starts to move in the center of the screen (at position 0) and then moves horizontally across the screen in a certain range (here: ±10°) from the center. (B) Blanking task with constant target movement at a velocity of 13°/s. Again, the stimulus starts in the center of the screen and moves horizontally across the screen in a certain range (here: ±10°) from the center. In some of the trials, the target is blanked off in the middle of the half-cycle, which is reflected by the dashed lines. Adapted from "Mechanisms of smooth pursuit eye movements in schizotypy" by E. Faiola, I. Meyhöfer, and U. Ettinger, 2020, *Cortex, 125,* p. 194; copyright (2020), with permission from Elsevier.

Maintenance gain is defined as the relation of eye velocity and target velocity in the maintenance phase of pursuit (Lencer & Trillenberg, 2008). It can be multiplied by 100 to quantify it as a percentage. Thus, a gain of 100% means that the eye velocity exactly matches the target velocity. A gain below 100% indicates that the eyes move more slowly than the target, while a gain above 100% implies that the eyes are faster than the target (see Leigh & Zee, 2015; Lencer & Trillenberg, 2008). Gain is measured only for segments of pursuit, meaning that saccades and blinks have to be excluded (e.g., Lencer et al., 2019). The beginning and the end of each ramp (i.e., the peripheral turnaround points of the stimulus) are usually excluded for gain calculation, as only the performance of following a smoothly moving object is relevant (e.g., Hutton et al., 2000; Meyhöfer et al., 2017). Usually, gain is time-weighted, meaning that gain in longer segments of pursuit is weighted more than gain in shorter segments (Abel et al., 1991; Calkins, Iacono, & Ones, 2008; Friedman, Jesberger, & Meltzer, 1992). A modification of the typical gain measure is the *residual gain*, which is measured in SPEM tasks with target blanking (Becker & Fuchs, 1985) and calculated only within a time window at the end of the blanking interval (Lencer &

Trillenberg, 2008). As a blanking task is composed of alternating blanking and non-blanking trials (i.e., trials with continuous target presentation, see Figure 3B), it is possible to calculate the difference between the residual gain in non-blanking and blanking trials. This measure provides information on how the gain deteriorates when the target is invisible (Meyhöfer et al., 2017) and thus on a participant's predictive abilities.

The *total frequency of saccades* is usually indicated as the number of all types of saccades (both intrusive and compensatory) per second. Saccades can be identified by means of minimum velocity (e.g., 22°/s; Meyhöfer et al., 2017; N. M. Ross, Goettker, Schütz, Braun, & Gegenfurtner, 2017), amplitude (e.g., 1°; Meyhöfer et al., 2016; Olincy, Johnson, & Ross, 2003; R. G. Ross et al., 1999), and acceleration (e.g., 3800°/s^2; Schütz, Lossin, & Gegenfurtner, 2015) criteria.

RMSE is defined as the deviation of eye and target position, including segments of both pursuit and saccades (Clementz et al., 1996). For each point in a segment of SPEM, the squared difference between eye and target position is calculated. These squared differences are then summarized. This sum is averaged by the number of measurement points, and the squared root of this average is taken (Friedman et al., 1995).

2.4 Assessment of Motion Perception

Motion perception can be assessed by several different tasks, most commonly using measures of direction and velocity discrimination. As a direction discrimination task was employed in Study 3, only this method will be described in further detail in this section. Direction discrimination tasks usually include random dot kinematograms, where a high number of dots moves across the screen in various directions (Newsome & Paré, 1988). While a certain proportion of dots moves in the same horizontal direction (i.e., coherently moving dots), the other dots move in random directions (i.e., random dots). Participants are required to determine the direction (left vs. right) of the coherently moving dots (Figure 4). Task difficulty increases as the proportion of coherently moving dots decreases.

There are different approaches to present random dot kinematograms. One possibility is to present a predetermined number of trials for each of several predefined coherence levels (e.g., Norton et al., 2011). An alternative, more accurate approach is to apply a staircase procedure, meaning that the coherence level (i.e., the percentage of coherently moving dots) adapts to the participant's performance (e.g., Slaghuis & Ryan, 2000). In case of a 3:1 staircase, for example, task difficulty increases after three correct responses and decreases after one incorrect response. This continues until a predefined number of staircase reversals (i.e., a shift from task difficulty increase to decrease or vice versa) is reached. The relevant dependent variable in this task is the coherence threshold, which is calculated by averaging the

coherence levels of all staircase reversals. The 3:1 staircase procedure that was used in Study 3 yields a coherence threshold that produces approximately 79% correct responding (Wetherill & Levitt, 1965).

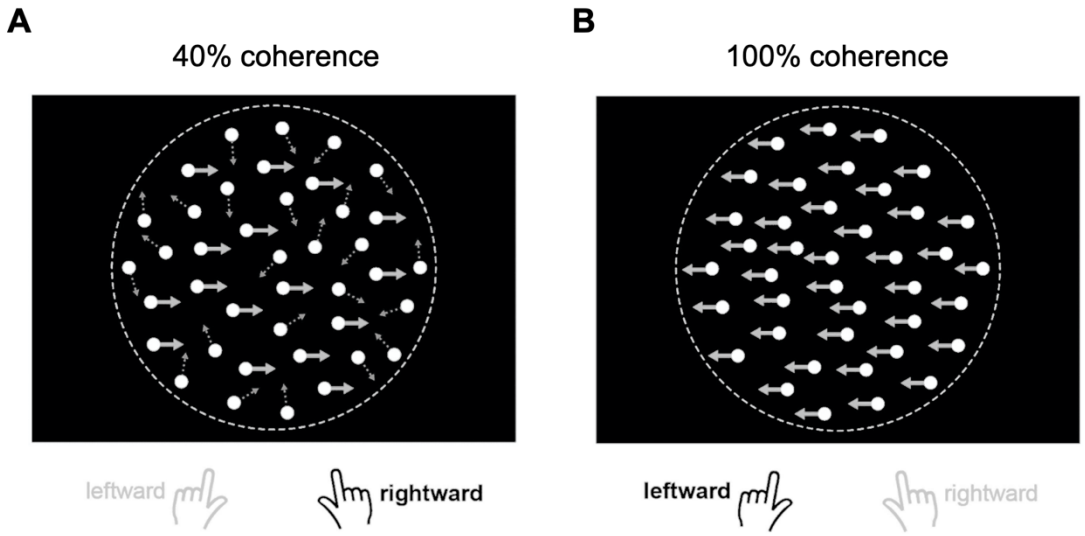

Figure 4. Exemplary random dot kinematograms. Arrows help to indicate direction of dot motion and dashed circles represent the circular window in that dot motion took place, both arrows and circles were not visible in the task. Solid arrows reflect coherent dot motion, dashed arrows indicate random dot motion. Participants indicated whether the coherent dots are moving rightward or leftward. Hands in bold reflect the correct answers. (A) shows a coherence level of 40% and coherent motion to the right, the correct answer is rightward. (B) shows a coherence level of 100% and coherent motion to the left, the correct answer is leftward. Adapted from "Mechanisms of smooth pursuit eye movements in schizotypy" by E. Faiola, I. Meyhöfer, and U. Ettinger, 2020, *Cortex, 125,* p. 19; copyright (2020), with permission from Elsevier.

2.5 Functional Magnetic Resonance Imaging

Developed in the early 1990s (Bandettini, 2012), fMRI has revolutionized the study of the human brain (Ashby, 2015). It allows the assessment of neural activity, for example, during cognitive processes in a noninvasive way and with high spatial resolution (Logothetis, 2008). Of importance for the present thesis, fMRI can be combined with oculographic measurements, providing the possibility to examine the neural mechanisms of eye movements.

fMRI is based on MRI, which makes use of a static magnetic field produced by the MR scanner (Ashby, 2015). This magnetic field causes protons of hydrogen molecules in the human body to align in an identical direction. During an MR measurement, radiofrequency coils that are wrapped around the relevant part of the body generate radio waves, causing the protons to change their orientation. After each radio wave impulse, the protons return to their primary alignment, a process that is called relaxation (Logothetis, 2002). During relaxation, the protons release energy, which is measured by the coils as the MR signal and transferred to images. A distinction is made between longitudinal relaxation (T1) and

transverse relaxation (T2 or T2*). T1 refers to the time that the protons need to return to their previous alignment, while T2 refers to the time until transverse magnetization decays (Logothetis, 2002). An important factor is that different types of tissue (e.g., grey matter, white matter, bone) vary in their density, which leads to differences in relaxation time and subsequently allows to distinguish between different tissues on the images (Logothetis, 2002).

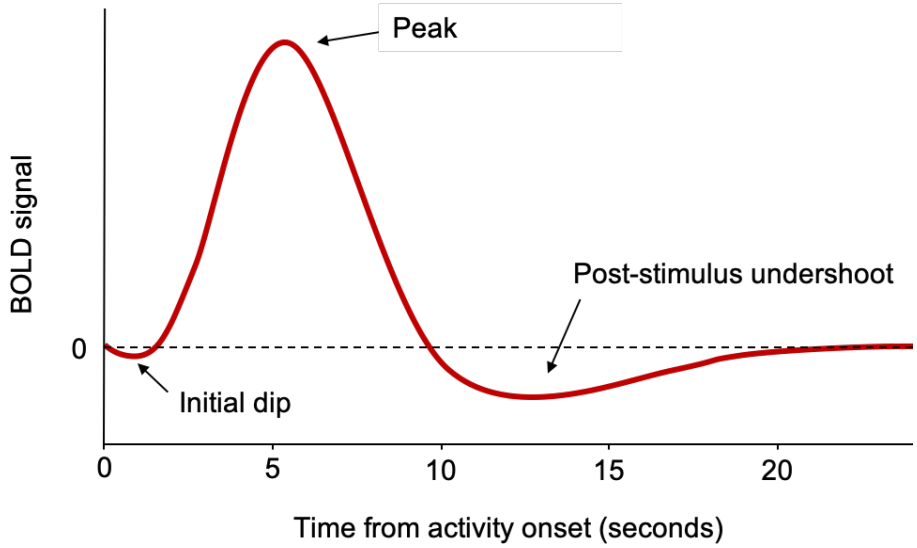

Figure 5. Hypothetical hemodynamic response function. First, the initial oxygen uptake caused by neural activity is thought to lead to a decrease of the BOLD signal (initial dip; Huettel et al., 2014). Then, as a result of increasing oxygenated hemoglobin, the BOLD response reaches its peak approximately 5-6 seconds after the onset of the corresponding neural activity. After the neural activity, the BOLD signal decreases below baseline (i.e., the dashed line), presumably due to a combination of reduced blood flow and elevated blood volume, resulting in an increase of deoxyhemoglobin (post-stimulus undershoot; Huettel et al., 2014). This is followed by a return of the BOLD signal to baseline.

First described by Ogawa and colleagues (Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990), the measurement of the *blood oxygenation level-dependent (BOLD)* signal using T2*-weighted scans became the most common method of fMRI (Logothetis, 2002). The BOLD signal is defined as the ratio of oxygenated and deoxygenated hemoglobin (i.e., the molecule responsible for oxygen transportation; Ashby, 2015). The difference between the magnetic properties of oxygenated (diamagnetic) and deoxygenated (paramagnetic) hemoglobin can be used to detect brain activity (Pauling & Coryell, 1936). The theory is that the more a brain area is activated (e.g., following a cognitive task), the more oxygen it consumes. As a consequence, an increasing amount of blood containing oxygenated hemoglobin is transported to this brain region. Subsequently, the ratio of oxygenated to deoxygenated hemoglobin (i.e., the BOLD signal) rises (Harris, Reynell, & Attwell, 2011), which is referred to as the hemodynamic response (Logothetis & Wandell, 2004; see Figure 5). The BOLD signal reaches its peak approximately 5 to 6 seconds after the onset of the corresponding neural activity, and

the decay toward the baseline is even slower (Glover, 2011). This means that the temporal resolution of fMRI is quite low, which has to be taken into account when designing fMRI tasks. An additional limitation is that the BOLD signal provides an indirect measure of neural activity (Logothetis & Wandell, 2004). However, it has been shown that the BOLD signal is strongly associated with the neural response to a stimulus (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Logothetis & Wandell, 2004), which is why fMRI is widely accepted as a reliable measure of neural activity (Ashby, 2015; Glover, 2011).

2.6 Multivariate Pattern Classification

Classical fMRI analyses focus on differences between groups regarding certain voxels. This often leads to the problem of between-group overlap, meaning that although two groups differ from each other regarding their brain activity, they show substantial overlap at certain voxels, reducing the likelihood of detecting the differences (Davatzikos, 2004; Fu et al., 2008). This problem is addressed by machine-learning approaches, in that they concentrate on individuals rather than on group differences (Fu et al., 2008; Koutsouleris et al., 2009). This means that instead of examining whether two groups differ regarding certain voxels, machine-learning algorithms allow to predict whether an individual belongs to group A or group B based on the pattern of brain activity.

Machine learning is understood as "a computational strategy that automatically determines (i.e., learns) methods and parameters to reach an optimal solution to a problem rather than being programmed by a human a priori to deliver a fixed solution" (Dwyer, Falkai, & Koutsouleris, 2018, p. 94). In psychiatry research, machine-learning approaches have become popular due to their benefit in prognosis, diagnosis, and the prediction of treatment success (Dwyer et al., 2018). The central process in machine learning is reinforcement learning, that is, statistical models are trained reiteratively and with feedback on a present data set, attempting to recognize certain patterns in the data (e.g., patterns of brain activity) and to predict an individual's group membership based on these patterns.

A key concept in machine-learning approaches is generalizability, that is, "the extent to which a statistical model generated in one group performs accurately in new groups or individuals" (Dwyer et al., 2018, p. 96). In psychiatric contexts, generalizability is usually estimated by training the statistical models in one sample and then testing (or validating) them in another sample (Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012). This can be done with a method called *cross-validation (CV)*. While there are different kinds of CV approaches, a widely used method is *k*-fold CV (Dwyer et al., 2018). Here, a sample is divided into *k* folds (by recommendation, five or ten; Breiman & Spector, 1992), that is, separate subsets of individuals. Subsequently, following an iterative process, a certain percentage of these folds are used to train the statistical models, while the remaining folds are left out

for the testing phase. Adaptations to this method, such as *nested CV*, lead to an even higher generalizability and accuracy (Filzmoser, Liebmann, & Varmuza, 2009). Nested CV includes two separate CV cycles, an inner cycle (called CV1) and an outer cycle (called CV2). While in CV1, models are trained and tested as described above, the best performing models are then validated in CV2, by being applied to individuals who had previously been held out completely.

To perform classification with machine learning, an algorithm is needed. While there are various kinds of machine-learning algorithms, the *support vector machine (SVM)* is the most widely used algorithm in neuroimaging research (Arbabshirani, Plis, Sui, & Calhoun, 2017; Orrù et al., 2012). The SVM discovers regularities or patterns in the data (e.g., patterns of brain activity) and classifies individuals into separate groups based on these patterns (Dwyer et al., 2018). Classification with SVMs is based on a maximal-margin approach (James, Witten, Hastie, & Tibshirani, 2015): An SVM is trained using the data of two groups (e.g., patients and controls) with known group membership of the cases. The goal of the training is to find a decision function that best distinguishes these two groups (Orrù et al., 2012). This decision function is called a *hyperplane*. To define the hyperplane, the SVM identifies the cases that lie closest to the opposite group distribution (i.e., the support vectors), which are then used to create a margin that maximizes the distance between these support vectors (Dwyer et al., 2018; Koutsouleris et al., 2009; see Figure 6 for a graphic representation). Thus, an SVM uses only those cases that are most

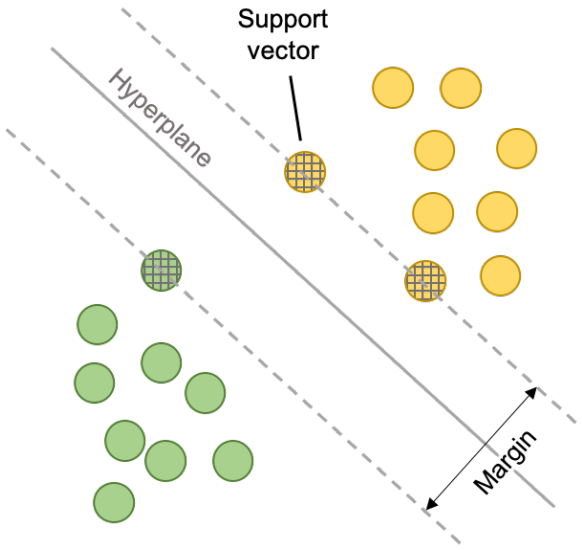

Figure 6. Hypothetical Support Vector Machine classification. Dots represent cases of two groups A (green) and B (yellow). Shaded dots are the support vectors, which are used to determine the hyperplane (i.e., the decision function that classifies the two groups) by maximizing the margin between these support vectors. Republished (in adapted form) with permission of Annual Reviews, Inc., from "Machine learning approaches for clinical psychology and psychiatry" by D. B. Dwyer, P. Falkai, and N. Koutsouleris, 2018, *Annual Review of Clinical Psychology*, *14*(1), p. 101; copyright (2018), permission conveyed through Copyright Clearance Center, Inc.

difficult to classify. This method ensures that subtle rather than easily detectable differences are taken into account for classification (Koutsouleris et al., 2009).

Importantly, it is possible to manipulate the size of the margin as well as the degree of allowed misclassification (Dwyer et al., 2018). If a hard margin is selected in the training phase, allowing no misclassification at all, the algorithm will lead to a perfect classification of the groups. However, this would lead to an overfitting of the algorithm, and the generalizability of such an algorithm when applied to new data would be low. In contrast, a soft margin allowing misclassification to some degree leads to a higher generalizability (Cortes & Vapnik, 1995).

Various parameters are important when estimating the accuracy of a classification (Dwyer et al., 2018): *Sensitivity* is defined as the proportion of true positive cases, that is, for example, cases that belong to the control group and have been correctly classified as controls. *Specificity* includes the proportion of true negative cases, that is, cases that belong to the patient group and have been correctly classified as patients. *Accuracy* is the proportion of correctly predicted cases. *Balanced accuracy* [(sensitivity + specificity) / 2] takes the sample size of the positive and negative groups into account and is used instead of accuracy in case of unequal sample sizes (as it is the case for the patient and control groups of Study 4).

3 Summaries of Original Studies

In this chapter, the original studies included in the present thesis (see Table 2) will be summarized. Given that the overall theoretical background of the studies has already been presented in detail in Chapter 1 and the relevant methodological approaches in Chapter 2, the original studies will be summarized here primarily with regards to design, key findings, and major conclusions.

Table 2

Original studies included in the present thesis.

Reference	Citation	Status
Study 1	Polner, B., **Faiola, E.**, Urquijo, M. F., Meyhöfer, I., Steffens, M., Rónai, L., Koutsouleris, N., & Ettinger, U. (2019). The network structure of schizotypy in the general population. *European Archives of Psychiatry and Clinical Neuroscience.* doi: 10.1007/s00406-019-01078-x	Published
Study 2	**Faiola, E.**, Meyhöfer, I., Steffens, M., Kasparbauer, A., Kumari, V., & Ettinger, U. (2018). Combining trait and state model systems of psychosis: The effect of sleep deprivation on cognitive functions in schizotypal individuals. *Psychiatry Research, 270,* 639-648. doi: 10.1016/j.psychres.2018.10.033	Published
Study 3	**Faiola, E.**, Meyhöfer, I., & Ettinger, U. (2020). Mechanisms of smooth pursuit eye movements in schizotypy. *Cortex, 125,* 190-202. doi: 10.1016/j.cortex.2019.12.008	Published
Study 4	**Faiola, E.**, Urquijo, M. F., Bey, K., Meyhöfer, I., Steffens, M., Kasparbauer, A., Ruef, A., Högenauer, H., Hurlemann, R., Kambeitz, J., Philipsen, A., Wagner, M., Koutsouleris, N., & Ettinger, U. Neural correlates of smooth pursuit eye movements in schizotypy and recent onset psychosis: A multivariate pattern classification approach. *Under review at Schizophrenia Bulletin Open.*	Under review

Note. The studies are sorted according to the order in which they are presented in this thesis. To avoid violations of copyright, the original articles have not been included in this thesis. They can be found online via the respective reference.

3.1 Network Analysis of the O-LIFE

The O-LIFE (Grant et al., 2013; Mason et al., 1995; Mason & Claridge, 2006; Mason et al., 2005) is one of the most widely used questionnaires to measure schizotypy (Fonseca-Pedrero et al., 2015). Three of its scales refer to the three dimensions repeatedly reported for schizotypy (Nelson et al., 2013): *unusual experiences* (measuring positive schizotypy), *cognitive disorganization* (measuring disorganized schizotypy), and *introverted anhedonia* (measuring negative schizotypy). A fourth scale, *impulsive nonconformity*, assesses aspects such as lack of self-control and antisocial behavior (Mason et al., 1995).

The validity of impulsive nonconformity as a distinct dimension of schizotypy is subject to debate (Cochrane et al., 2010; Fonseca-Pedrero et al., 2015; Lin et al., 2013; Sierro et al., 2016). While some factor analyses of the O-LIFE reported similar performance for both three- (without impulsive nonconformity) and four-dimensional models (Fonseca-Pedrero et al., 2015; Sierro et al., 2016), others found that three-factor models (positive, negative, disorganized) better described empirical O-LIFE data (Lin et al., 2013). Due to these inconsistencies, further research on the O-LIFE is clearly needed, as thoroughly investigated questionnaires are highly important for the study of schizotypy.

In addition, relatively little is known about the network structure of schizotypy (and especially the O-LIFE). This is important, however, as network analysis provides more information on the importance of specific items or domains compared to factor analysis (see section 2.1). Previous studies that examined the network structure of schizotypy (Christensen, Kenett, Aste, Silvia, & Kwapil, 2018; Dodell-Feder, Saxena, Rutter, & Germine, 2019; Fonseca-Pedrero et al., 2018) used questionnaires that differ from the O-LIFE in terms of their wording (i.e., clinical vs. personality focus) and subscales. In the present study, we therefore applied network analysis to the O-LIFE, aiming to detect network structural dynamics of schizotypy and examine the role of impulsive nonconformity within this network.

For this purpose, 11,807 participants from the general population filled out a short version of the German O-LIFE (Grant et al., 2013; Mason et al., 2005) online. Using network analysis, we determined communities within the network and compared them regarding centrality (closeness and betweenness), expected influence as well as predictability. In addition, we examined weights of edges (i.e., the sum of node strengths) within and between communities.

Four communities were detected (Figure 7), showing a substantial overlap of 93% with the subscales of the O-LIFE. The four communities were positive, negative, and disorganized domains as well as a domain identified as impulsive nonconformity. Closeness of nodes as well as node predictability were significantly higher in the disorganization community than in all other communities. The communities did not differ regarding node betweenness and expected influence. A comparison of within-community edge weights revealed larger edge weights within the disorganization community than within all other communities. Comparisons of between-community edge weights revealed significantly lower edge weights between the positive and the negative community compared to weights of edges between all the other community pairs. In addition, edge weights connecting impulsive nonconformity and disorganization were larger than edge weights between disorganization and the positive domain.

The community structure revealed by the network analysis replicates the three classical dimensions (positive, negative, and disorganized) of schizotypy. In addition, impulsive nonconformity was identi-

fied as a distinct community, with only one of this scale's items emerging as part of a different community. In addition, impulsive nonconformity did not differ from the positive or the negative domain regarding measures of centrality and edge weights. Therefore, it may be assumed that it represents a legitimate community in its own right. Whether or not this aspect of schizotypy is included in one's measurement, does, however, still depend on the theoretical understanding (or definition) of schizotypy, which typically does not involve the concept of impulsive nonconformity (see, e.g., Nelson et al., 2013).

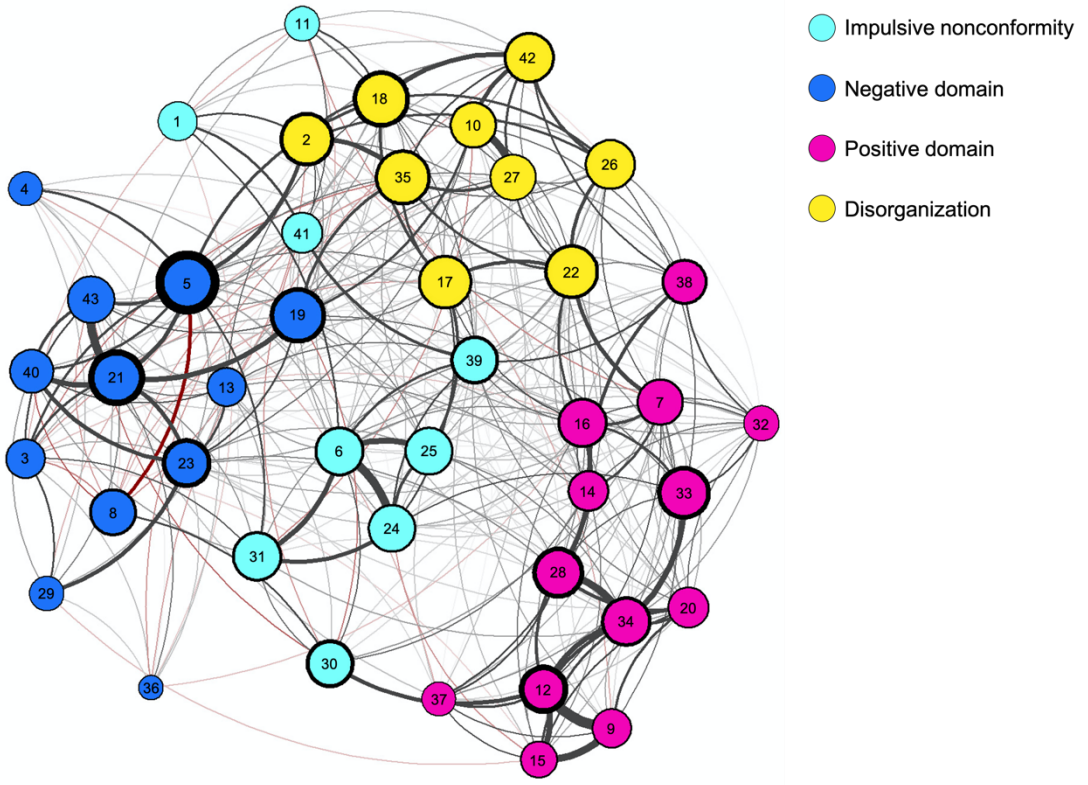

Figure 7. Key findings of Study 1. Network structure of the German Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE), short form. Circles represent nodes, that is, O-LIFE items. Node colors reflect communities. Node size represents closeness, node border width represents betweenness. Node numbers correspond to the position of the specific item in the O-LIFE. Connections between nodes represent edges, that is, relationships between items. Grey edges indicate positive relationships, red edges indicate negative relationships. Edge width represents edge weight. Adapted from "The network structure of schizotypy in the general population" by B. Polner, E. Faiola, M. F. Urquijo, I. Meyhöfer, M. Steffens, L. Rónai, N. Koutsouleris, and U. Ettinger, 2019, *European Archives of Psychiatry and Clinical Neuroscience* (article can be found here: https://link.springer.com/article/10.1007/s00406-019-01078-x). Material has been modified (different node colors). Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0).

Comparisons of predictability and within-community edge weights suggest that features in the disorganization domain are more strongly interrelated compared to features in other communities. An explanation for this might be that the content of the disorganization items is more homogeneous compared to the set of items of all other communities, especially the negative domain, which covers aspects of both social and physical anhedonia.

As mentioned earlier, when developing a symptom with high centrality (compared to a peripheral symptom), a person is more likely to develop other symptoms in the network. Transferring this to the present results, the increased closeness centrality of the disorganized domain suggests that disorganized features highly co-occur with features from the other dimensions. This finding has implications for the importance of cognitive disorganization in the study of high-risk individuals and fits the assumption that cognitive impairments are a core feature of the schizophrenic phenotype (Freudenreich, 2020; Nuechterlein et al., 2014; Sheffield et al., 2019). However, due to its strong association with features from other communities, disorganization is probably not suited to be examined as a separate schizotypy dimension within experimental studies. For this purpose, it might be better, as stated before, to consider an overall schizotypy score or the positive and the negative dimensions, which do not interrelate much (as indicated by the comparisons of between-community edge weights).

3.2 Schizotypy, Sleep Deprivation, and Cognitive Functioning

Both schizotypy and sleep deprivation are associated with features typically found in schizophrenia spectrum disorders: Individuals deprived of sleep for more than 24 hours as well as schizotypal individuals have been found to display experiences similar to the positive, negative, and disorganized symptoms of schizophrenia, albeit in an attenuated form (Ettinger et al., 2014; Kahn-Greene et al., 2007; Meyhöfer et al., 2017; Nelson et al., 2013; Petrovsky et al., 2014). In addition, schizotypy and sleep deprivation are associated with impairments in SPEM resembling those found in schizophrenia spectrum disorders (e.g., Meyhöfer et al., 2017). Further overlaps concern brain function as well as alterations in prepulse inhibition (Ettinger et al., 2014, 2012; Meyhöfer et al., 2019; Petrovsky et al., 2014). Due to these similarities and overlaps, schizotypy and sleep deprivation can be seen as trait and state model systems of psychosis, respectively (Barrantes-Vidal et al., 2015; Ettinger & Kumari, 2015). Such model systems are highly important, *first*, to further elucidate mechanisms of the disorder, and *second*, to evaluate newly developed antipsychotic medication (Ettinger & Kumari, 2015; Koychev et al., 2011).

Model systems are usually validated by examining whether their effect on a valid signature of psychosis is comparable to the expression of the signature in the disorder. One of the most important markers of psychosis is cognitive functioning, with patients reliably exhibiting deficits in inhibition, working memory, sustained attention, verbal learning, problem solving, and verbal fluency (Freudenreich, 2020; Nuechterlein et al., 2014; Schaefer et al., 2013). Such deficits have been found in schizotypy (Giakoumaki, 2012; Siddi et al., 2017) and in sleep deprived individuals (Lim & Dinges, 2010) as well, albeit at lesser severity. Up to now, effects on cognitive functioning have only been examined for schizotypy and sleep deprivation separately. However, it might be of great benefit to study potential interaction effects of schizotypy and sleep deprivation on cognitive markers of psychosis in order to draw conclusions on whether these two model systems share similar underlying mechanisms (Meyhöfer et al., 2017).

Therefore, this study had two aims: *First,* to replicate the schizotypy and sleep deprivation model systems using well-validated cognitive markers of psychosis, and *second*, to explore potential interaction effects of schizotypy and sleep deprivation on these cognitive markers.

Applying a within-subjects design, 17 schizotypes with primarily positive schizotypy traits and 19 control participants spent one night of sleep deprivation (i.e., 24 hours without sleep) and one night of normal sleep in a laboratory. On the morning after the night of sleep (deprivation), participants worked on a cognitive test battery measuring inhibition (Go/NoGo task), working memory (n-back task), sustained attention (CPT-IP), verbal learning (California Verbal Learning Test), problem solving (Tower of London task), and verbal fluency (Regensburger Wortflüssigkeitstest).

An effect of sleep deprivation was found in the Go/NoGo task, with participants showing a higher rate of commission errors after sleep deprivation than after normal sleep (Figure 8A). In addition, performance on the n-back task was worse after sleep deprivation compared to performance after normal sleep, in that sleep deprivation reduced the rate of correct responses (Figure 8B). The other tasks revealed no effects of sleep deprivation. In addition, no effects of schizotypy and no interaction effects of schizotypy and sleep deprivation on cognitive performance were found.

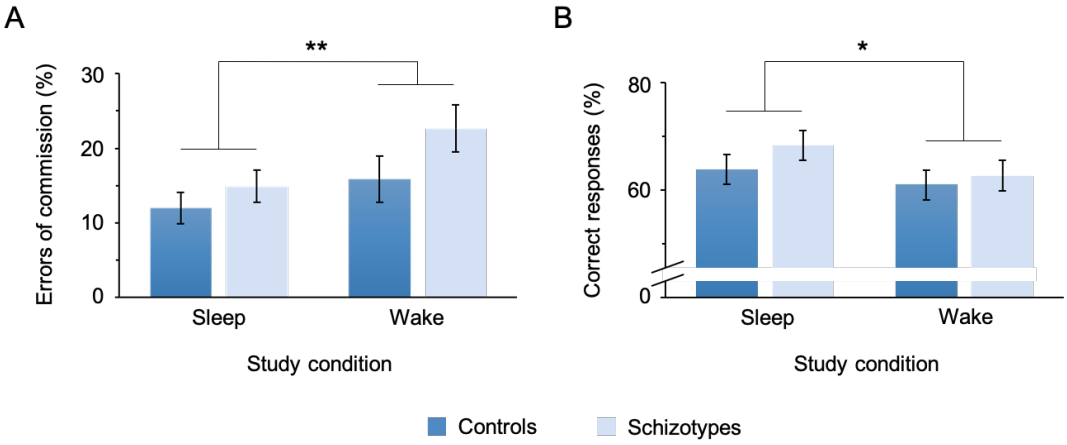

Figure 8. Key findings of Study 2. Compared to normal sleep nights (Sleep), sleep deprivation (Wake) increased the commission error rate in the Go/NoGo task (A) and decreased the rate of correct responses in the n-back task (B). $^{**}p < .01$, $^{*}p < .05$. Error bars indicate standard errors. Adapted from "Combining trait and state model systems of psychosis: The effect of sleep deprivation on cognitive functions in schizotypal individuals" by E. Faiola, I. Meyhöfer, M. Steffens, A. Kasparbauer, V. Kumari, and U. Ettinger, 2018, *Psychiatry Research, 270,* p. 644; copyright (2018), with permission from Elsevier.

The results support the validity of sleep deprivation as a model system of psychosis, particularly when combined with measures of inhibition and working memory. We were, however, not able to replicate findings on cognitive deficits in schizotypy, and the two proposed model systems did not interact with

each other. Both results were somewhat surprising as numerous earlier studies had found cognitive dysfunctions in schizotypal individuals (Giakoumaki, 2012; Siddi et al., 2017), and interaction effects had been found before, albeit not for cognitive but for oculomotor markers (Meyhöfer et al., 2017). It is, however, conceivable that complex, higher-level cognitive markers are not entirely appropriate for the validation of the schizotypy model system and that more basal (e.g., perceptual or motor) functions are better suited to detect subtle deficits in schizotypal individuals (Chun et al., 2013). This suggestion is supported by two meta-analyses, showing that associations between schizotypy and cognitive impairments are weak and, at least concerning certain functions, not stable (Chun et al., 2013; Steffens et al., 2018). Therefore, and considering that the similarity between schizotypy and psychosis has been shown in several various areas, the validity of schizotypy as a model system of psychosis should not be questioned based on the present results. Rather, the results indicate that the markers used to test model systems have to be chosen carefully and the selection of basal instead of complex markers should be considered, at least when it comes to examining schizotypy.

3.3 Mechanisms of SPEM in Schizotypy

While schizotypal individuals display SPEM dysfunctions resembling, in an attenuated form, those found in schizophrenia patients (Meyhöfer et al., 2017; O'Driscoll & Callahan, 2008), it is unclear whether the mechanisms that drive this deficit are identical for schizotypy and schizophrenia (Meyhöfer et al., 2015). This is, however, important to discover, as it can help obtain a better understanding of impairments in schizotypy.

In schizophrenia, the SPEM deficit is thought to be primarily driven by impairments in motion perception (Chen et al., 1999; Lencer et al., 2005; Stuve et al., 1997). Evidence comes from fMRI studies reporting reduced activity in schizophrenia patients during SPEM in area V5 (Hong, Tagamets, et al., 2005; Lencer et al., 2005; Tregellas et al., 2004), which plays a major role for the perception of visual motion (Braddick et al., 2001; Newsome & Paré, 1988). In addition, motion perception dysfunctions in schizophrenia patients have repeatedly been shown using psychophysical direction or velocity discrimination tasks (Chen, 2011; Norton et al., 2011), such as random dot kinematograms (Newsome & Paré, 1988). Compared to controls, patients usually show enhanced coherence thresholds (and thus worse performance; Chen et al., 2003; Li, 2002; Norton et al., 2011; Slaghuis et al., 2007; Stuve et al., 1997). Importantly, higher coherence thresholds in both direction and velocity discrimination tasks have been linked to SPEM dysfunctions in schizophrenia patients (Chen et al., 1999; Slaghuis et al., 2005, 2007; Stuve et al., 1997). However, not only motion perception but also predictive processes are assumed to contribute to the SPEM deficit in schizophrenia spectrum disorders (Levy et al., 2010). When performing SPEM, brain activity in the FEFs, which are important for predictive processes (Fukushima et al., 2002; Ilg & Thier, 2008), is reduced in schizophrenia patients compared to controls (Hong, Tagamets,

et al., 2005; Keedy et al., 2006; Tregellas et al., 2004). In addition, schizophrenia patients perform worse in SPEM tasks with target blanking (Hong et al., 2003, 2008; Hong, Avila, et al., 2005; Ivleva et al., 2014; Thaker et al., 1999, 1996), a typical measure of predictive components of SPEM (Barnes, 2008; Becker & Fuchs, 1985).

For schizotypy, the question of the mechanisms underlying the SPEM deficit has not been properly investigated. The only study on neural correlates of SPEM in schizotypy (Meyhöfer et al., 2015) reported reduced activity in motion sensitive areas but no activity difference in the FEFs between schizotypes and controls. Although this finding points to the importance of motion perception rather than prediction, further investigations on the cognitive-perceptual mechanisms of SPEM in schizotypy are clearly needed. Therefore, the present study had two goals: *First*, to replicate the SPEM deficit in schizotypes and to examine whether schizotypal individuals performed worse than controls in tasks measuring motion perception and prediction. *Second*, to explore whether motion perception, prediction, or both would mediate the relationship between schizotypy and SPEM.

In this registered report, individuals with high vs. low overall O-LIFE scores (i.e., schizotypes and controls; $n = 86$ in each group) completed a sinusoidal SPEM task with a target frequency of 0.4 Hz, random dot kinematograms to measure motion perception, and a SPEM task with target blanking to measure prediction. The dependent variables were gain in the SPEM task and the coherence threshold in the random dot kinematograms (i.e., the percentage of coherently moving dots needed to correctly determine their direction). In the blanking task, we calculated the prediction score, that is, the difference between the residual gain in non-blanking and blanking trials. The higher the prediction score, the more the gain deteriorates during blanking, meaning that predictive processes are impaired.

The prediction score was higher in schizotypes compared to controls (Figure 9). However, the two groups did not differ in their gain or their coherence threshold, and neither motion perception nor prediction were found to mediate the (non-significant) relation between schizotypy and SPEM. Nevertheless, an additional, exploratory analysis yielded a significant association between motion perception and gain only in schizotypes but not in controls. This difference in correlation between groups was significant, indicating that only in schizotypes, better motion perception was correlated with a higher gain.

Overall, this study revealed impairments in predictive processes in schizotypy similar to (albeit less pronounced than) those found in schizophrenia patients (Hong et al., 2003, 2008; Hong, Avila, et al., 2005; Ivleva et al., 2014; Thaker et al., 1999, 1996). However, as these impairments were not associated with SPEM performance, it is likely that schizotypes compensate their faulty predictive processes with protective mechanisms maintaining the gain on a normal level. As motion perception was found to be associated with gain only in schizotypes, it is conceivable that they compensated their prediction deficits

by resorting to motion perception. Following this rationale, intact motion perception in schizotypes would explain why we were not able to find a SPEM deficit in this group. Thus, although motion perception did not mediate the association between schizotypy and SPEM (which was not surprising as there was no association between schizotypy and SPEM to be explained in the first place), these results suggest that motion perception is indeed an important factor for SPEM in schizotypy in terms of compensating for existing prediction deficits.

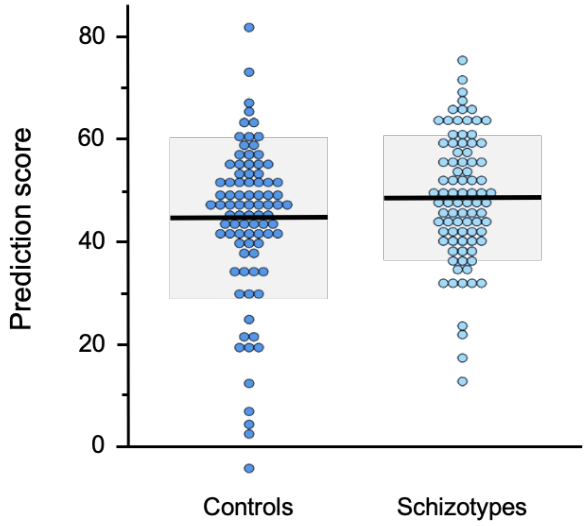

Figure 9. Key findings of Study 3. Distribution of prediction scores in schizotypes and controls. Schizotypes showed a significantly higher prediction score than controls (p = .034). The horizontal lines with surrounding grey areas reflect the group means ± 1 standard deviation. Adapted from "Mechanisms of smooth pursuit eye movements in schizotypy" by E. Faiola, I. Meyhöfer, and U. Ettinger, 2020, *Cortex, 125,* p. 197; copyright (2020), with permission from Elsevier.

3.4 Neural Correlates of SPEM in Schizotypy and Schizophrenia Spectrum Disorders

Despite various overlaps between schizotypes and patients with schizophrenia spectrum disorder (Ettinger et al., 2014; Nelson et al., 2013), only a small proportion of schizotypal individuals has been found to develop a psychotic disorder years later (Chapman et al., 1994). This suggests that certain protective mechanisms operate in schizotypal individuals, preventing them from developing a full-blown disorder (Barrantes-Vidal et al., 2015; Ettinger et al., 2014; Giakoumaki, 2012; Kwapil & Barrantes-Vidal, 2015). The search for such mechanisms requires direct comparisons between schizophrenia spectrum disorders and schizotypy regarding well-validated markers of psychosis (Hazlett et al., 2012). One of the best validated psychophysiological characteristics of psychosis is a deficit in SPEM (Levy et al., 2010; O'Driscoll & Callahan, 2008). While SPEM deficits similar to those in psychosis have been found in schizotypy (Gooding et al., 2000; Holahan & O'Driscoll, 2005; Koychev et

al., 2016; Meyhöfer et al., 2017; O'Driscoll et al., 1998; Smyrnis et al., 2007; van Kampen & Deijen, 2009), there are still indications of differences (and thus for potential protective mechanisms in schizotypes): *First*, SPEM deficits are less pronounced in schizotypy (Gooding et al., 2000; Lenzenweger & O'Driscoll, 2006) than in schizophrenia (O'Driscoll & Callahan, 2008). *Second*, neural correlates of SPEM in schizophrenia and schizotypy overlap only partially, with activity in frontal areas being reduced in schizophrenia (Hong, Tagamets, et al., 2005; Keedy et al., 2006; Tregellas et al., 2004) but intact in schizotypy (Meyhöfer et al., 2015). However, to draw clear conclusions regarding similarities and differences, direct comparisons of schizotypy and schizophrenia spectrum disorders regarding SPEM are necessary.

Therefore, the aim of this study was to compare schizotypal individuals to patients with recent onset psychosis with regard to both behavioral measures and neural correlates of SPEM. In order to increase the possibility of detecting subtle alterations in brain activity (Madsen et al., 2018; Modinos et al., 2012), a multivariate machine-learning approach was applied instead of classical fMRI analyses. We expected that patients and controls would be classified as two groups based on their SPEM performance and SPEM related brain activity. Considering earlier results (Hong, Tagamets, et al., 2005; Keedy et al., 2006; Lencer et al., 2005; Nagel et al., 2007; Tregellas et al., 2004), we assumed that this classification would be driven by a pattern of reduced activity in patients compared to controls in areas of the pursuit network, such as visual areas and the FEFs. In addition, we explored whether schizotypes would more likely be classified as controls or as patients based on their behavioral and neural SPEM data.

For this purpose, 61 control participants with low schizotypy scores, 41 positive schizotypes, 46 negative schizotypes, and 34 patients with recent onset psychosis (i.e., patients with various diagnoses from the schizophrenia spectrum who had been diagnosed no more than three years ago) underwent an fMRI measurement with concurrent assessment of SPEM. Eye movements were assessed with a sinusoidal SPEM task, alternating between blocks of SPEM (0.2 and 0.4 Hz) and blocks of fixation. For each participant, two contrast images were created, one image contrasting brain activity during SPEM against brain activity during fixation (SPEM contrast) and one image contrasting activity during high against activity during low target frequency (Frequency contrast). These contrast images were used for multivariate pattern classification. The classification of the behavioral data was based on gain, total frequency of saccades, and RMSE.

Based on the SPEM contrast images, controls and patients were classified with a balanced accuracy of 61.1%. Classification was based on reduced activity in participants classified as patients (compared to participants classified as controls) in areas of the pursuit network (amongst others, in visual areas and the FEFs and SEFs) as well as overactivity in participants classified as patients in several areas, including the hippocampus and the thalamus (Figure 10). The application of this classifier to the schizotypal samples assigned the majority of schizotypes (31 positive schizotypes and 36 negative schizotypes) to the control group. As only a small part of schizotypes (ten positive schizotypes and ten negative schizotypes) had been assigned to the patient group, we subsequently treated positive and negative schizotypes as one schizotypy group. A comparison of schizotypes classified as patients and schizotypes classified as controls revealed reduced activity in visual areas (primary visual cortex) but intact activity in frontal areas in schizotypes classified as patients. For the behavioral data and the Frequency contrast, classification of controls and patients was significant only at trend level. In order to further analyze potential group differences regarding behavioral data, classical univariate analyses were conducted, revealing performance impairments in patients compared to controls. However, the schizotypal samples did not differ significantly from controls or patients.

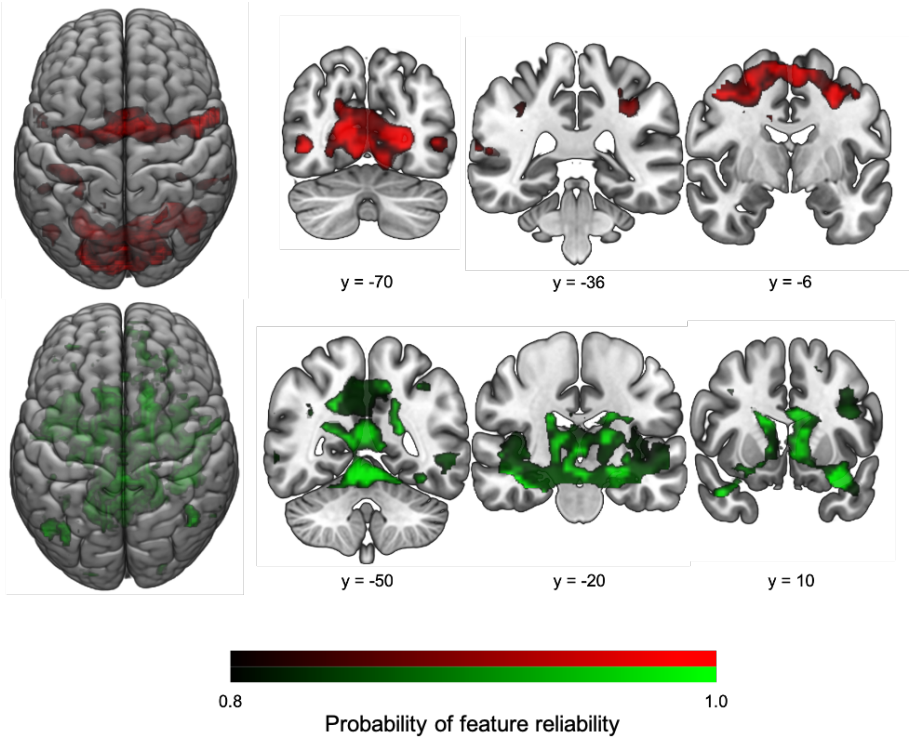

Figure 10. Key findings of Study 4. Brain areas contributing to the classification of controls and patients based on SPEM contrast images. Areas in red represent higher activity in participants classified as controls compared to participants classified as patients, areas in green represent higher activity in participants classified as patients compared to participants classified as controls. Images were thresholded to show a probability of feature reliability of at least 80%. Activities are shown for coronal slices. Coordinates are given in MNI space. Slices were created with MRIcroGL; $n = 61$ controls, $n = 33$ patients.

Taken together, these results replicate SPEM deficits in schizophrenia spectrum disorders (O'Driscoll & Callahan, 2008). In addition, they confirm earlier findings on SPEM related activity reductions in schizophrenia patients compared to healthy controls in visual motion processing areas and FEFs (Hong, Tagamets, et al., 2005; Keedy et al., 2006; Lencer et al., 2005; Nagel et al., 2007; Tregellas et al., 2004). These findings indicate that both motion processing and prediction seem to be central processes that drive SPEM deficits in patients with recent onset psychosis. In addition, findings on overactivity in the thalamus are in line with previous findings (Nagel et al., 2007) and might represent alternative SPEM strategies in participants classified as patients. Application of the classifier to schizotypes revealed potential indicators of protective mechanisms in schizotypy: *First*, schizotypes were classified rather as controls than as patients, meaning that SPEM related brain activity in schizotypes was largely intact (i.e., similar to brain activity in controls). *Second*, even schizotypes classified as patients (and thus displaying SPEM-related activity patterns similar to patients) did not show activity reductions in FEFs and SEFs typically present in schizophrenia patients. Matching previous results (Meyhöfer et al., 2015), this pattern suggests protective mechanisms in schizotypes in terms of healthy brain activity in frontal areas.

4 Discussion and Outlook

This chapter provides an integration of the results of the original studies. Links between the results of the different studies will be identified in order to draw final conclusions on the overall discoveries of the present thesis. In addition, general limitations as well as ideas for future studies will be covered in this chapter.

4.1 Integration

The results of the original studies presented in this thesis have implications regarding the theoretical foundations of schizotypy as well as dysfunctions in cognitive and oculomotor markers and protective mechanisms in schizotypy. In an additional attempt to integrate these implications, the significance of the results for schizotypy research as well as potential practical implications for the therapy of schizophrenia spectrum disorders will be emphasized.

4.1.1 Implications Regarding the Theoretical Foundations of Schizotypy

Schizotypy is usually defined as a three-dimensional construct, with the dimensions reflecting the three symptom categories postulated for schizophrenia, namely a positive, a negative, and a disorganized dimension (Nelson et al., 2013). As described earlier (see section 1.1.2), there is an ongoing debate on how to measure schizotypy, with questionnaires differing regarding the schizotypy facets they tap (see, e.g., Chapman et al., 1976, 1978; Eckblad & Chapman, 1983; Mason et al., 1995; Mason et al., 2005; Raine, 1991). Three of the four scales of the O-LIFE, one of the most widely used instruments for the assessment of schizotypy, correspond to the classic three dimensions suggested for schizotypy, with unusual experience measuring positive, introverted anhedonia measuring negative, and cognitive disorganization measuring disorganized schizotypy (Mason et al., 1995; Mason et al., 2005). However, the fourth scale, impulsive nonconformity, does not easily fit into the more common pattern of schizotypy as a three-dimensional construct. The question whether impulsive nonconformity is a valid aspect of schizotypy is subject to debate, and earlier factor analyses yielded inconsistent results in this context (Fonseca-Pedrero et al., 2015; Lin et al., 2013; Sierro et al., 2016). This is why an incomplete version of the O-LIFE, excluding impulsive nonconformity, is often used (Mason, 2015).

Study 1 of the present thesis was the first study to apply network analysis to the O-LIFE. Several interesting results have emerged from this analysis: In a large sample, four communities were revealed, reflecting almost perfectly the four scales of the O-LIFE. Importantly, only one single impulsive nonconformity item was assigned to a different community, implying that impulsive nonconformity is indeed

a distinct dimension that does not overlap with the others (i.e., it does not encompass the other domains, nor is it encompassed in them). Thus, the decision whether to include or exclude this scale does not affect the other scales and it seems, therefore, still legitimate to exclude impulsive nonconformity when measuring schizotypy.

However, additional results of the network analysis raise the question of whether impulsive nonconformity might be as important to schizotypy as the other domains (or, at least, as the positive and negative domains). First, edge weights connecting impulsive nonconformity and disorganization were larger than edge weights between disorganization and the positive domain. This result indicates that impulsive nonconformity is highly interrelated (more than the positive domain) with the community discovered as the most central within the schizotypy network. In addition, nodes of the impulsive nonconformity domain seemed to be as relevant within the network as the nodes of the positive and negative domains, indicated by the absence of differences in closeness and betweenness. Descriptively, closeness centrality of impulsive nonconformity was even higher compared to the positive and negative domains.

Therefore, when considering only the results of the network analysis, one might conclude that they challenge the assumption of schizotypy being a three-dimensional construct. However, it is important to take into account not only the mathematical approach (i.e., the network analysis) but also the theoretical foundations of schizotypy (Fonseca-Pedrero et al., 2015; Sierro et al., 2016). Impulsive nonconformity has been argued not to be a valid feature of schizophrenia, seeing that schizophrenia patients did not display elevated scores on this scale compared to control participants (Cochrane et al., 2010; Lin et al., 2013). It was argued that "if one defines schizotypy as a trait reflecting a disposition towards behaviours and cognitions that are found in more extreme form in schizophrenia, then [impulsive nonconformity] does not qualify as measuring a true index of schizotypy" (Cochrane et al., 2010, p. 152). The authors of the O-LIFE, in fact, did not claim impulsive nonconformity to be a facet of schizophrenia but rather a part of the broader psychosis spectrum, including, for example, bipolar disorder (Mason & Claridge, 2006). They justified their choice of a fourth scale by arguing that this would provide a broader indicator toward psychosis proneness (Mason & Claridge, 2006). Thus, whether to include impulsive nonconformity into the measurement of schizotypy remains a question of how schizotypy is defined: If one defines schizotypy as reflecting behaviors and experiences of *schizophrenia*, it should be measured without impulsive nonconformity. However, when defining schizotypy as reflecting characteristics of *psychotic disorders*, impulsive nonconformity may be as important as the other domains. In line with this, Grant et al. (2018) emphasized that "researchers should […] be clear about whether their measurement of schizotypy is to be understood as an index liability for schizophrenia *only*, liability for all psychotic disorders, or liability for 'psychosis in schizophrenia'" (p. S561).

However, instead of all researchers deciding for themselves how to define schizotypy, it seems desirable to establish an agreement upon a unitary theoretical foundation. The use of different questionnaires and the different ways to use a single questionnaire impede the comparability of studies and thus a meaningful integration of different scholars' work on schizotypy. Similarities and differences found between schizotypy and schizophrenia should not simply depend on the theoretical foundations the schizotypy measurements are based on. Therefore, a goal of future research on schizotypy should be to reconsider the current definitions and attempt to agree upon a universally valid concept.

4.1.2 Implications Regarding Cognitive Dysfunctions in Schizotypy

Cognitive dysfunctions represent a core feature of schizophrenia spectrum disorders; this had already been emphasized by Kraepelin when he coined the term *dementia praecox* (i.e., an early form of dementia). Since then, the importance of cognitive impairment for schizophrenia spectrum disorders has been well established (Freudenreich, 2020; Nuechterlein et al., 2014; Sheffield et al., 2019).

The results of Study 1 suggest that the importance of cognitive impairments in schizophrenia spectrum disorders can be transferred to schizotypy. The network analysis revealed a higher closeness centrality for the disorganization domain compared to all other domains. This finding implies that features of cognitive disorganization are highly related to features from the other schizotypy dimensions assessed by the O-LIFE. The level of cognitive disorganization in an individual may even predict the expression of the other domains. This matches previous factor-analytical results on various schizotypy questionnaires, revealing the highest correlations between disorganized schizotypy and the other schizotypy dimensions (Gross et al., 2014; Mason et al., 1995; Mason & Claridge, 2006). Moreover, the result is in line with a recent network analysis on schizophrenia spectrum patients, revealing that among positive, negative, and cognitive symptoms, the latter were the most central in the network (Hasson-Ohayon, Goldzweig, Lavi-Rotenberg, Luther, & Lysaker, 2018). Given that the items of the cognitive disorganization scale of the O-LIFE reflect aspects such as poor decision making, difficulties concentrating and maintaining attention as well as language abnormalities (Mason et al., 1995; Mason et al., 2005), it appears legitimate to conclude that self-reported cognitive impairments constitute a core feature of schizotypy as well.

In Study 2, we examined the effects of schizotypy, sleep deprivation, and their potential interaction effects on a broad range of high-level cognitive functions. Contrary to our expectations, schizotypes did not perform worse than controls in any of the cognitive tasks. In addition, there was no interaction effect between schizotypy and sleep deprivation, as performance in both inhibition and working memory was worse after sleep deprivation, but this effect was equally present in schizotypes and controls. At the first glance, these results may seem contradictory when compared with the high centrality of self-reported

cognitive impairments found in Study 1. They are, however, understandable when noting the differences between features expressed by the cognitive disorganization scale and functions assessed with the cognitive tasks in Study 2. These differences go beyond the simple fact that one measure captures subjective, self-reported impairments, while the other provides an objective assessment of cognitive dysfunctions. Although the items of the cognitive disorganization scale partly assess aspects similar to those measured in cognitive tasks (i.e., difficulties with concentration, attention, and decision-making), the items refer to a failure of focusing on one's thoughts and actions in everyday-life situations rather than to actual cognitive functions. For example, the items "Are you easily distracted from work by daydreams?" and "Are you easily distracted when you read or talk to someone?" from the cognitive disorganization scale of the O-LIFE refer to difficulties in sustaining attention in everyday life situations, which clearly differs from the capacity to sustain attention for a predefined, relatively short duration in the CPT-IP. Therefore, cognitive disorganization as a central aspect of schizotypy does not automatically imply that schizotypes are impaired in actual cognitive functions. It should be noted, however, that the two constructs are certainly related, seeing that cognitive disorganization has been found to be associated to impairments in cognitive tasks (e.g., Cappe et al., 2012). Nevertheless, this relation does not necessarily imply a full parallelism. Fittingly, Chan, Yan, et al. (2011) discovered that schizotypes did not differ from controls in tasks measuring executive functions but displayed a higher proportion of dysexecutive problems (i.e., problems in day-to-day cognitive functioning). In addition, a meta-analysis (Chun et al., 2013) revealed greater self-reported (i.e., subjective) cognitive complaints in schizotypes compared to controls but almost no differences in the actual cognitive abilities assessed by cognitive tests.

In proposing putative interaction effects of schizotypy and sleep deprivation on cognitive functions, I introduced additive-factors logic, stating that if the observable effects of two phenomena interacted, this would indicate that they rely on the same latent process (Sternberg, 1969; Sternberg, 2001). Therefore, an interaction effect would have indicated that a particular prerequisite (e.g., alterations in brain structure or function) was present in schizotypes, which would cause sleep deprivation to be particularly problematic for their cognitive functioning. As we did not find an interaction effect, it can be assumed that this is not the case, which is why schizotypes respond to sleep deprivation in the same way as control participants do. Sticking to the example of brain structure or function, this would imply that the impact of sleep deprivation on the brain differs from the neural characteristics associated with schizotypy. In addition, the missing interaction effect supports the assumption of intact cognitive functions in schizotypy: Apparently, schizotypy has so little effect on these functions that not even a psychosis-like state, such as sleep deprivation, can reduce cognitive performance in schizotypes more than in controls. Of note, these conclusions are quite speculative and are valid only presuming that the results of Study 2 are not simply a consequence of an improvable study design (e.g., considering the small sample size in both

groups). Additionally, it has to be noted that there is a large body of literature on cognitive deficits in schizotypal individuals (see section 1.2.1.2), which contradicts these assumptions. Although systematic meta-analyses revealed that overall, these effects are rather small (Chun et al., 2013; Steffens et al., 2018), they still seem to be present. Therefore, the question arises whether cognitive functions are only impaired in some schizotypal individuals but not in others. This possibility of schizotypy as a heterogeneous construct will be discussed later (see section 4.1.5).

Interestingly, an interaction effect of schizotypy and sleep deprivation has been found before, albeit not on cognitive functions but on SPEM (Meyhöfer et al., 2017). This again challenges the assumption that schizotypy and sleep deprivation rely on different latent processes. The crucial factor leading to these contradictory results might be the difference between complex functions in terms of high-level cognition measured in Study 2 and more specific functions, such as SPEM. It is conceivable that schizotypy is accompanied by deficits in basal, specific functions rather than in complex, high-level cognitive functions. This possibility will be elaborated in more detail in the following section.

4.1.3 Implications Regarding Oculomotor Dysfunctions in Schizotypy

Chun et al. (2013) assumed that the inconsistent findings on cognitive dysfunctions in schizotypy can be traced back to "not measuring the 'right stuff'" (p. 1). They argued that schizotypal individuals might display deficits especially in basal (e.g., motor or perceptual) functions, which are not tapped by complex cognitive tasks. It has been pointed out before that oculomotor measures benefit from being more specific compared to high-level cognitive measures (Hill et al., 2010; Reilly et al., 2008).

In fact, when examining SPEM performance and its underlying cognitive and perceptual mechanisms in Study 3, we found impairments in schizotypes in the predictive component of SPEM. These deficits were similar to (albeit less pronounced than) those displayed in schizophrenia patients (Hong et al., 2003, 2008; Hong, Avila, et al., 2005; Ivleva et al., 2014; Thaker et al., 1999, 1996). Therefore, the findings of Study 3 underline the suggestion that similarities between schizotypy and schizophrenia spectrum disorders become evident in basal rather than complex functions.

However, schizotypes displayed deficits only in the SPEM task with target blanking, which is specifically designed to assess abilities in prediction. In the regular SPEM task (with continuous target presentation), no schizotypy-related deficits were found (Studies 3 and 4). This finding is somewhat surprising, considering that schizotypy has been consistently associated with deficits in such tasks (see section 1.2.2.2). A possible explanation for this finding, however, is provided by the overall pattern of results in Study 3: It is well established that performance in the blanking task relies on prediction only, while SPEM in tasks with continuous target presentation is based on both prediction and motion perception

(for an overview, see Levy et al., 2010). Not only was motion perception unaffected in schizotypy, but in the schizotypal group (and not in the control group), performance in motion perception was associated with performance in the regular SPEM task. These findings suggest that schizotypes, when following a continuously presented target, compensate for faulty prediction by resorting to motion perception. This would explain why we did not find any deficits in the SPEM task with continuous target movement in schizotypy in Studies 3 and 4, *although* they apparently had difficulties with prediction. Schizophrenia spectrum patients, on the other hand, displayed deficits in this SPEM task (Study 4). In addition, alterations in brain function showed that apparently, impairments in both motion perception *and* prediction contributed to these deficits. These findings indicate that schizophrenia spectrum patients perform worse in regular SPEM tasks than controls and schizotypes, as they cannot resort to any compensatory mechanisms.

It could be argued that prediction as a mechanism of SPEM is a process even more basal than the SPEM response itself. The latter is composed of at least two sub-components, that is, prediction and motion perception (and probably additional processes, such as attention; Barnes, 2008). Therefore, the finding that schizotypes in the present studies were impaired in prediction but performed well on the regular SPEM task fits the assumption that schizophrenia-like deficits in schizotypy are more consistently found in very basal functions. However, the amount of studies reporting schizotypy-related deficits in regular SPEM tasks cannot be ignored. The contradictory findings of the present thesis compared to previous studies suggest that the SPEM deficit in schizotypy may not be as consistent as it has been suggested before. Additional studies on the predictive component of SPEM in schizotypy are necessary in order to draw clear conclusions on whether deficits in prediction are more consistently shown than deficits in the actual SPEM response.

When arguing that schizotypes show impairments in basal rather than complex functions, it first seems contradictory that motion perception as a very basal perceptual function was intact in the schizotypal group of Study 3. However, it seems implausible that *all* basic functions are impaired in schizotypy when complex functions appear to be intact: It would be difficult to explain how schizotypes maintain complex functions on a normal level without being able to recruit unimpaired basic functions in order to compensate for deficient ones. It is conceivable that when considering deficits in schizotypy, a distinction has to be made between basal perceptual (such as motion perception) and basal cognitive functions (such as prediction). However, this assumption is merely speculative, as the present data do not provide enough information to draw firm conclusions.

Taken together, it appears that schizotypes are impaired in the predictive component of SPEM, while they show intact abilities in motion perception. Therefore, in tasks that rely on both processes (i.e.,

SPEM tasks with continuous target presentation), they manage to maintain performance on a normal level due to compensatory mechanisms in terms of intact motion perception.

The classification of schizotypes in Study 4 partly reflects these considerations. The observation that schizotypes were classified rather as controls than as patients based on their SPEM related brain activity matches the assumption of schizotypes being able to maintain their SPEM performance on a normal level. Based on the results of Study 3 (i.e., impaired prediction in schizotypes), a consistent finding in Study 4 would have been that at least those schizotypes that had been classified as patients showed reduced brain activity in frontal areas, such as the FEFs and the SEF, as these areas are known to be important for predictive processes (e.g., Fukushima et al., 2002; Ilg & Thier, 2008; Lencer, Nagel, et al., 2004; Nagel et al., 2006; Schmid et al., 2001). However, schizotypes classified as controls and schizotypes classified as patients only differed regarding their activity in visual but not frontal areas. Several explanations come to mind for these seemingly contradictory findings: *First*, the inconsistence might simply be a problem of the different tasks we used in Studies 3 and 4. While in Study 3, dysfunctions in prediction had been found with a blanking task, which is specifically designed to assess predictive processes of SPEM, Study 4 contained only a regular SPEM task with continuous target presentation. Potential deficits in predictive processes could probably not be detected with this task or were at least not pronounced enough to be reflected in the neural underpinnings. Therefore, it would have been beneficial if we had included a blanking task in Study 4 to examine whether the deficits in prediction discovered on the behavioral level are also reflected in the neural correlates. *Second*, it has to be noted that the group of schizotypes that had been classified as patients was quite small, especially compared to the group of schizotypes classified as controls. This problem questions the reliability of the comparison analysis. *Third*, a different analysis approach was adopted in Study 4 compared to Study 3: In Study 3, we simply compared schizotypes to controls. In Study 4, however, we compared schizotypes that had been classified as patients (and thus showed brain activity patterns similar to those of patients) to schizotypes classified as controls. For a better comparison of the studies, it would have been beneficial to additionally compare the schizotypal groups to the control group in Study 4.

Altogether, these partially inconclusive findings suggest that the question of the mechanisms of SPEM in schizotypy is not finally clarified and needs further investigation. This is important especially against the backdrop of a previous study on neural correlates of SPEM in schizotypy (Meyhöfer et al., 2015). Meyhöfer et al. (2015) found that activity in motion-sensitive areas was reduced in schizotypes compared to controls, while activity in frontal areas associated with the predictive component of SPEM (FEFs, SEF) did not differ between the two groups. This does not match the assumption that SPEM in schizotypy is driven by intact motion perception compensating for deficient prediction. However, what we can conclude from Studies 3 and 4 is that the SPEM deficit in schizotypy does not seem to be as

consistent as it was presented in previous publications. It is likely that this is due to compensatory mechanisms in schizotypes, and the exact properties of these mechanisms have to be investigated in more detail in the future. Besides motion perception and prediction, additional potential mechanisms driving SPEM in schizotypy (e.g., attention) should be taken into account.

4.1.4 Implications Regarding Protective Mechanisms in Schizotypy

The absence of deficits in schizotypal individuals in the regular SPEM task and in high-level cognitive functions leads back to the suggestion that schizotypes can resort to certain protective mechanisms that help avoid a full-blown disorder. Although protective or compensatory mechanisms have already been discussed in the previous section, I would like to put more emphasis on this subject and especially point out how the results of Study 2 fit the assumption of protective mechanisms in schizotypy.

The strongest support for protective mechanisms in schizotypy is provided by the results of Study 3 (and 4), as already indicated in the previous section. In both studies, schizotypes performed equally well in a regular SPEM task compared to controls, although predictive processes, which are known to be a key component of SPEM (Barnes, 2008), were impaired in schizotypy (Study 3). This suggests that schizotypes compensated their faulty prediction by relying on a different mechanism in order to maintain their SPEM performance on a high level (i.e., the same level as controls). Obviously, a compensatory mechanism that helps maintain performance on a normal level has to be associated with the corresponding performance variable. In Study 3, this was indeed the case for motion perception: Motion perception correlated with SPEM only in the schizotypy but not in the control group, indicating that in schizotypes, better motion perception was accompanied by better SPEM performance. This combination of results suggests that schizotypes compensated impairments in predictive processes by resorting to motion perception. That is, they might have shifted the balance of the two contributing mechanisms by relying more heavily on the perceptual aspect of SPEM than on the predictive component of the overall process. As motion perception was intact in schizotypy, this would explain the missing SPEM impairments in this group.

Additionally, in Study 4, schizotypes did *not* display activity reductions in frontal areas (FEFs and SEF) that have been found in schizophrenia patients in some studies (Hong, Tagamets, et al., 2005; Keedy et al., 2006; Tregellas et al., 2004). Therefore, it may be argued that protective mechanisms were present in terms of intact activity in frontal areas, which are key structures for predictive processes. This contradicts, however, the findings of Study 3 indicating protective mechanisms that compensate for a *deficit* in predictive processes. As mentioned previously, several factors impeded the studies from being per-

fectly comparable, which might explain the contradictory results. While it seems a reasonable conclusion that certain protective mechanisms operate in schizotypes during SPEM, the question whether it is motion perception, prediction, or an entirely different process, remains to be investigated in more detail in future studies. As Study 3 was a registered report with a precise a-priori power analysis, the results of this study may, however, be considered to be more reliable then the additional comparison analysis with unequal sample sizes in Study 4.

The results of Study 2 provide the basis for a similar, albeit merely speculative suggestion. The cognitive tasks used in Study 2 usually tap not only the cognitive function of interest (e.g., working memory) but also other sub-components, which contribute to task performance (e.g., attention), a problem widely known as the task-impurity problem (Miyake & Friedman, 2012). The finding that schizotypes did not display any deficits in complex, high-level cognitive functions might be traced back to compensatory mechanisms in that schizotypes compensate for deficits in one sub-component of a certain cognitive task (e.g., working memory) by resorting to another, intact sub-component (e.g., attention). However, as Study 2 does not provide any information on the performance in the different sub-processes of the cognitive tasks, there could be different explanations for the lack of cognitive deficits in schizotypy than protective mechanisms.

Another indication for protective mechanisms in schizotypes is that they did not seem to be affected by sleep deprivation more than controls (Study 2). This contradicts findings on schizophrenia spectrum disorders, underlining poor sleep quality or sleep disorders as a central problem of the disorder and even a target for intervention (Klingaman et al., 2015). A possible explanation might be that sleep deprivation affects brain areas that are somehow "protected" in schizotypy. Another putative explanation is that the impact sleep deprivation has on certain brain areas is compensated by a higher engagement of other brain areas (see Chuah & Chee, 2008). To explore these assumptions in more details, it would be interesting to examine the neural correlates of sleep deprivation in schizotypy. It has to be noted, however, that sleep deprivation *did* worsen performance in schizotypes more than in controls regarding SPEM (Meyhöfer et al., 2017). As interaction effects were found, however, only regarding one out of numerous measures, this does not entirely contradict these suggestions. Moreover, these conclusions are corroborated by an additional study that did not find any interaction effect of schizotypy and sleep deprivation on prepulse inhibition (Meyhöfer et al., 2019).

To sum up, the studies of the present thesis provide valuable data underlining the assumption that schizotypy is accompanied by certain protective mechanisms that keep a schizotypal individual from developing the whole spectrum of deficits found in schizophrenia and other psychotic disorders. Seeing as such mechanisms seem to operate in schizotypes but not in schizophrenia spectrum patients, the question

arises at which point on the continuum between schizotypy and a full-blown disorder these compensatory mechanisms become ineffective or disappear. Although the results of the present thesis do not provide a definite answer to this question, some suggestions can be derived based on the original studies. Among other points, this will be further discussed in the following section.

4.1.5 General Implications for Schizotypy

The last sections gave rise to the idea that especially basic, specific functions rather than complex, high-level functions are impaired in schizotypy. However, not *all* basic functions seem to be impaired, as evident through intact motion perception in Study 3. As a consequence, it is conceivable that these *intact* basic functions work as protective mechanisms in order to compensate for other, *impaired* basic functions. Thus, schizotypes might be able to maintain performance in more complex functions on a normal level due to well-working sub-components that feed into these complex functions and thus work as protective mechanisms. Schizophrenia spectrum patients, however, do not seem to have such protective mechanisms at their disposal, which is why they show a much broader range of functional impairments. When returning to the initially proposed idea of a psychosis continuum that ranges from normal mental health to psychopathology (Allardyce et al., 2007), this implies that certain deficits develop along this continuum, or, in other words, certain protective mechanisms lose their protective nature along the continuum.

Although no schizotypy-related deficits in high-level functions were found in the present thesis, it would be premature to conclude that schizotypy is completely free of impairments in those functions. It has to be taken into account that several earlier studies reported deficits in high-level cognitive functions as well as impairments in regular SPEM tasks in schizotypy after all (see sections 1.2.1.2 and 1.2.2.2). Therefore, rather than suggesting that these functions are generally intact in schizotypy, a more plausible conclusion would be that certain schizophrenia-like features are present only in *some* schizotypes, presumably in those with extreme expressions of schizotypy, while others become manifest already in individuals with a moderate level of schizotypy.

In other words, the onset of a deficit on the schizotypy continuum varies between different functions. Cognitive disorganization, including everyday-life cognitive impairments, such as difficulty sustaining attention in social situations, is a highly central aspect of schizotypy and strongly associated with other schizotypy features. Therefore, it seems likely that on a continuum from low to high schizotypy, these functions are already affected at the lower end. Furthermore, mechanisms of SPEM (in this case, prediction) seem to be impaired earlier than the actual SPEM response. Individuals at the lower end of the

continuum might be able to compensate for deficits in important mechanisms of SPEM in order to maintain their SPEM performance on a normal level. In addition, high-level functions, such as complex cognitive abilities, seem to be intact at the beginning of the continuum, conceivably due to compensatory mechanisms that help maintain these functions on a normal level. As these compensatory mechanisms probably do not operate (or decrease in effectiveness) already at extreme levels of schizotypy, this is when impairments in those complex cognitive abilities may develop. In addition, it is likely that from the onset of a deficit until the end of the continuum, the deficit increases in severity. Effect sizes of SPEM deficits, cognitive impairments, and other markers of psychosis are usually smaller in schizotypes compared to schizophrenia spectrum patients (see, e.g., Gooding et al., 2000; Lenzenweger & O'Driscoll, 2006; O'Driscoll & Callahan, 2008; Schaefer et al., 2013; Steffens et al., 2018).

It can be concluded that the results of the original studies presented here reflect the complex and heterogeneous nature of schizotypy. The schizotypy continuum does not seem to simply reflect an increase in intensity of a given set of schizophrenia-like deficits. Rather, it appears to comprise an increase in the *quantity* of schizophrenia-like deficits (i.e., additional deficits develop along the continuum).

The suggestion that features similar to those in schizophrenia spectrum disorders develop along the schizotypy continuum implies that a clearer differentiation of this continuum needs to be adopted in experimental studies on schizotypy. What appears to be problematic in the present thesis as well as in several previous schizotypy studies is that the adopted measurements of schizotypy probably do not allow to (i) capture very high expressions of schizotypy and (ii) differentiate between different expressions on the schizotypy continuum. Schizotypal participants are usually identified by predefining a certain cut-off for the schizotypy questionnaire and assigning all participants above this cut-off to the schizotypal group. In the original studies of the present thesis, the cut-off was defined as the score that lies 1.25 standard deviations above the mean score. Several other studies that found oculomotor or cognitive deficits in schizotypy (Gooding et al., 2000; Gooding et al., 2006; Holahan & O'Driscoll, 2005; Kerns & Becker, 2008; Meyhöfer et al., 2015) used higher thresholds (e.g., two standard deviations), suggesting that the level of schizotypy was higher in these studies. With a higher cut-off, the probability of finding deficits that are not impaired in lower expressions of schizotypy might be higher. With the methods applied in the present original studies, we might not have been able to capture the upper end of the continuum (or, at least, not this part alone). In addition, different expressions of schizotypy and thus the schizotypy continuum are rarely considered in experimental studies. To the best of my knowledge, among all studies on oculomotor or cognitive dysfunctions in schizotypy, only one included a comparison of medium and high expressions of schizotypy (Koychev et al., 2016). Altogether, a large number of schizotypy studies indicate that schizotypy is not being sufficiently differentiated. However, if we want to use schizotypy in order to further our understanding of schizophrenia spectrum disorders, it is essential we deal with schizotypy in a more differentiated way.

To do so, it is important to adopt a more unified psychometric approach toward schizotypy. The initial question could be how to measure high levels of schizotypy. Universal cut-offs should be defined in order to (i) be able to actually capture high expressions of schizotypy and therefore increase the probability of finding similarities with schizophrenia spectrum disorders and (ii) increase comparability across studies and be able to draw reliable conclusions on areas that are dysfunctional and areas that are not affected in schizotypy. In addition, the schizotypy continuum should be taken into account more strongly: Using not only one but multiple cut-offs would help consider the continuum of schizotypy in experimental designs. An additional important aspect that should be considered is to start adopting the continuum concept already at the item level of schizotypy questionnaires. The response format of self-report instruments to measure schizotypy is usually a forced choice yes-no dichotomy, although the usage of Likert scales would better reflect the idea of schizotypy as a continuum from low to high expressions.

An additional issue in schizotypy research has already been mentioned before: In Study 1, it became evident that the theoretical foundations of schizotypy need further examination, or that at least a unified understanding of the personality construct needs to be adopted across experimental studies. Various theoretical foundations of schizotypy and the different questionnaires that are associated with these foundations complicate the unification of schizotypy research. It is, therefore, not only important to take the continuum of schizotypy seriously but also to agree upon an answer to the question what schizotypy actually is (i.e., which dimensions it includes) and, correspondingly, with which questionnaires or subscales it should be measured. Obviously, the heterogeneity of questionnaires is not only an issue in schizotypy but in other personality constructs as well. However, the wide range of schizotypy questionnaires seems to be particularly heterogeneous, with inconsistencies not only regarding their subscales but also regarding the wording of the items (e.g., the clinical focus of the SPQ versus the personality focus of the O-LIFE).

Apart from the previous topic, I would like to discuss the meaning of the present results for the application of schizotypy as a model system of psychosis. As mentioned earlier (see section 1.1.2), schizotypy can be an important tool when it comes to identifying model systems of psychosis, which can be helpful for the evaluation of newly developed drugs (Ettinger & Kumari, 2015; Koychev et al., 2011). After an extensive investigation of schizotypy across four different studies, it can be concluded that, although schizotypy might indeed serve as a model system of psychosis, the similarities between schizotypy and schizophrenia spectrum disorders are quite selective. However, as schizophrenia spectrum disorders constitute a highly complex condition, it is normal that model systems are not able to mimic all aspects (Steeds, Carhart-Harris, & Stone, 2015). It is, however, essential to choose appropriate markers when applying schizotypy as a model system of psychosis. The present studies as well as previous results

(Chun et al., 2013) emphasize the importance of basal, specific rather than complex, high-level markers to detect similarities between schizotypy and schizophrenia spectrum disorders. This should be taken into account when considering schizotypy as a psychosis model. It should be noted that there might be other psychosis models that are actually more useful, in that their similarity to psychosis is higher or the similarities are more stable than in schizotypy. However, it should be kept in mind that other types of model systems that include drug administration, sensory or sleep deprivation are far more ethically contestable compared to the schizotypy model system. Apart from that, our results suggest that the combination of schizotypy with the sleep deprivation model system does not seem to have additional beneficial effects when it comes to evoking psychosis-like features.

Finally, as pointed out in the beginning, research on schizotypy is not only interesting in the context of schizophrenia spectrum disorders. An additional important aspect of schizotypy research is schizotypy itself, as it is associated with several adverse behaviors and experiences (A. S. Cohen et al., 2015). In this context, the results of the present thesis can be summarized quite accurately with the title of the work by Mohr and Claridge (2015): “Schizotypy – Do not worry, it is not all worrisome”. In this paper, the authors refer to findings on advantageous functioning in schizotypy, such as enhanced creativity, indicating the presence of protective or compensatory mechanisms in schizotypy. Similarly, the present results suggest that normally, schizotypes seem to be able to compensate quite well for existent deficits. They therefore manage to maintain important high-level functions on a normal level. Nevertheless, the impairments that we found, albeit small, are not to be disregarded. The best compensatory mechanisms might fail eventually, especially considering that they probably require more energy than the mechanisms that individuals with low schizotypy levels rely on. Therefore, it is important to take schizotypy seriously and to continue research on this personality construct not only to draw conclusions for clinical disorders but also to get a better understanding of schizotypy itself.

4.1.6 Practical Implications for Schizophrenia Spectrum Disorders

The assumption that at the lower range of the psychosis continuum, high-level functions are still intact due to compensatory mechanisms might have important implications for therapeutic or training approaches in schizophrenia spectrum disorders. Over the last years, the popularity of trainings to improve cognitive dysfunctions in schizophrenia spectrum disorders has increased. Two competing approaches are predominant within this field (Minzenberg & Carter, 2012): Some approaches follow the assumption that cognitive functions are restored top-down, that is, via directly improving high-level processes. Other approaches are based on a bottom-up perspective, proposing that the improvement of cognition is driven primarily by optimizing simple perceptual components. Considering the present results, I would suggest that the bottom-up perspective might be the more efficient one when it comes to cognitive remediation

strategies in schizophrenia. Targeting basic (perceptual) functions in the cognitive training of schizophrenia spectrum patients might help them to develop mechanisms that can compensate for deficiencies in other functions, similar to the way it seems to work for schizotypal individuals. Thus, bottom-up approaches might be more efficient in that they specifically target those processes that might be essential for performance improvements. Transferring these thoughts to SPEM (on the premise that SPEM can be interpreted as a complex function), this means that instead of training SPEM performance directly via repeated SPEM tasks, it might be more efficient to train separate components of SPEM. As schizophrenia patients seem to be impaired in both motion perception and prediction (see Study 4), a training of motion perception might help compensate for the deficiencies in prediction.

Moreover, the high centrality of cognitive disorganization in the schizotypy network might have implications for approaches of early recognition and prevention of schizophrenia spectrum disorders. The network analysis suggests that cognitive disorganization is likely to co-occur with and even predict the other dimensions of schizotypy, meaning that individuals with elevated cognitive disorganization are likely to display a wide range of psychosis-like characteristics. Fittingly, cognitive disorganization has been shown to predict subsequent transitioning to psychosis in the at-risk mental state (i.e., in individuals with prodromal symptoms of psychosis; Demjaha, Valmaggia, Stahl, Byrne, & McGuire, 2012). Therefore, instead of focusing too much on positive symptoms, early detection methods should concentrate on aspects of cognitive disorganization. Also, prevention strategies should be directed at reducing cognitive disorganization, as this might also help diminish other aspects of schizophrenia spectrum disorders.

4.2 Limitations

The conclusions I have drawn in the previous sections have to be considered against the backdrop of certain limitations that should be addressed in future studies. One limitation concerns the use of different approaches to measure schizotypy across the studies. In Study 2, only positive schizotypy was examined, while Study 4 contained a positive and a negative schizotypal group, and in Study 3, schizotypy was assessed with the overall O-LIFE score. For a better comparability of the studies, it would have been beneficial to use a consistent concept of schizotypy, for example, to uniformly examine both positive and negative dimensions of schizotypy separately. However, the more important parameter for comparability is that all studies used the O-LIFE as an instrument to measure schizotypy. This is essential because, as stated above, different schizotypy questionnaires follow different theoretical approaches to schizotypy (e.g., personality focus of the O-LIFE vs. clinical focus of the SPQ; see Mason et al., 1995; Mason et al., 2005; Raine, 1991).

As discussed earlier (see section 4.1.5), it is also conceivable that the threshold we used in all three studies to assign participants to the schizotypal groups might have been too low. Many of the previous studies that found differences between schizotypal individuals and control participants in cognitive and oculomotor measures used higher thresholds (e.g., Gooding et al., 2000; Gooding et al., 2006; Holahan & O'Driscoll, 2005; Kerns & Becker, 2008; Meyhöfer et al., 2015). Moreover, the designs of the original studies of the present thesis were not appropriate to systematically capture schizotypy as a continuum. As we only used one threshold to identify schizotypal individuals, the resulting groups most certainly included participants with varying levels of schizotypy.

Altogether, the original studies of the present thesis as well as numerous earlier studies indicate that effects of schizotypy on various performance variables are rather small. Accordingly, it is vital that sample sizes be large enough to detect these small effects. In Study 2, a larger sample size may have been necessary in order to uncover effects of schizotypy on cognitive functions. In general, studies examining effects of schizotypy always benefit from a detailed a-priori power analysis, as applied in Study 3. Only in this case it is possible to draw firm conclusions about similarities and differences between schizotypy and schizophrenia spectrum disorders afterwards.

Finally, the conclusions on similarities and differences between schizotypy and schizophrenia spectrum disorders derived from Studies 2 and 3 are based entirely on post-hoc comparisons of studies that examined schizotypy and schizophrenia separately. It would have been more conclusive if these studies had included direct comparisons of the two groups. We did, however, take a first step toward closing this gap in the schizotypy literature and performed such a direct comparison in Study 4.

4.3 Future Avenues

When it comes to similarities and differences between schizotypy and schizophrenia spectrum disorders as well as protective mechanisms in schizotypy, the results of the present thesis leave several questions unanswered. This is why it is important to advance the examination of schizotypy as a tool to search for etiological factors of schizophrenia spectrum disorders. Some suggestions how schizotypy research might be improved have already been mentioned earlier (see section 4.1.5). At this point, I would like to propose some additional approaches that future studies on this topic might benefit from.

The findings of the present thesis suggest that schizotypes benefit from certain protective mechanisms that often support them in maintaining their performance close to what is considered normal. However, it is not finally clarified what the presence of protective mechanisms actually means. For example, does intact motion perception in schizotypy really contribute to preventing schizotypes from developing a psychotic disorder? Or is it simply a mechanism to compensate for isolated function impairments? The

only way to obtain reliable answers to the question which mechanisms prevent schizotypes from developing a schizophrenia spectrum disorder are longitudinal approaches similar to the study by Chapman et al. (1994). However, instead of examining how many schizotypal individuals develop a psychotic disorder, it would be interesting to explicitly explore the specific characteristics in which schizotypes that do and those that do not develop a disorder differ from each other. With such an experimental design, it would be possible to draw firm conclusions on how certain characteristics in schizotypy protect from or lead to the development of a psychotic disorder.

As direct comparisons of schizophrenia spectrum disorders and schizotypy remain scarce, this approach should be carried forward. With a direct comparison in Study 4, we were able to draw interesting conclusions on putative protective mechanisms in schizotypy. Such comparison studies should be extended to different markers of psychosis, such as other oculomotor functions (e.g., antisaccades) or the cognitive functions we examined in Study 2. In addition, comparison studies would benefit from classification analyses. However, rather than only examining whether schizotypal individuals are classified as controls or as schizophrenia spectrum patients, future studies should focus more on the mechanisms that are associated with this classification. One possible research question could be to explore whether schizotypes classified as patients and schizotypes classified as controls differ regarding characteristics that are considered to be risk factors of schizophrenia spectrum disorders (e.g., urbanicity or adverse life events in childhood).

Moreover, it would be interesting to conduct a study similar to Study 3 but with high-level cognitive functions instead of SPEM. That is, high-level cognitive functions should be segmented into sub-processes that are central contributors of these functions in order to examine the performance of schizotypal individuals in these sub-processes. This might confirm the suggestion that high-level cognitive functions are intact in (some) schizotypes because of intact sub-processes that protect against deficits in other sub-processes, similar to the protective mechanisms that were found in Study 3.

4.4 Conclusion

Overall, the results of the present thesis suggest that deficits similar to those found in schizophrenia spectrum disorders seem to develop along a continuum from low to high schizotypy. Individuals at the lower end of this continuum seem to be impaired in rather basic, specific functions, while compensatory or protective mechanisms help them to maintain performance in high-level functions on a normal level. Deficits in more complex cognitive functions might be present at the upper end of the continuum, where protective factors are not as effective anymore. This is a strong argument for reconsidering the current state of schizotypy research in order to (i) better differentiate the concept of schizotypy in experimental

studies and (ii) adopt a unitary understanding of schizotypy across different studies to simplify comparability.

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List of Abbreviations

BOLD	Blood Oxygenation Level-Dependent
CPT-IP	Continuous Performance Test – Identical Pairs
CV	Cross-Validation
DSM	Diagnostic and Statistical Manual of Mental Disorders
FEF	Frontal Eye Field
fMRI	Functional Magnetic Resonance Imaging
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
O-LIFE	Oxford-Liverpool Inventory of Feelings and Experiences
RMSE	Root Mean Square Error
SEF	Supplementary Eye Field
SPEM	Smooth Pursuit Eye Movements
SPQ	Schizotypal Personality Questionnaire
SVM	Support Vector Machine
VCPCR	Video-Based Combined Pupil and Corneal Reflection

List of Additional Publications

Additional publications mentioned in the present thesis.

Meyhöfer, I., Ettinger, U., **Faiola, E.**, Petrovsky, N. & Kumari, V. (2019). The effects of positive schizotypy and sleep deprivation on prepulse inhibition. *Schizophrenia Research, 209,* 284-285.

Meyhöfer, I., Steffens, M., **Faiola, E.**, Kasparbauer, A., Kumari, V. & Ettinger, U. (2017). Combining two model systems of psychosis: The effects of schizotypy and sleep deprivation on oculomotor control and psychotomimetic states. *Psychophysiology, 54*(11), 1755-1769.

Additional publications thematically related to the present thesis.

Magnusdottir, B. B., **Faiola, E.**, Harms, C., Sigurdsson, E., Ettinger, U. & Haraldsson, H. M. (2019). Cognitive measures and performance on the antisaccade eye movement task. *Journal of Cognition, 2*(1), 3.

Ettinger, U., **Faiola, E.**, Kasparbauer, A., Petrovsky, N., Chan, R., Liepelt, R. & Kumari, V. (2017). Effects of nicotine on response inhibition and interference control. *Psychopharmacology, 234*(7), 1093-1111.

The present thesis is based upon four original studies (see Table 2). To avoid violations of copyright, the original articles have not been included in this thesis. They can be found online via the respective reference.