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The association of psychotic disorders, dopaminergic agents and resting-state EEG/MEG functional connectivity

Inaugural Dissertation submitted to the Department of Psychology of the University of Basel by

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Declaration of Authorship

I, Amatya Johanna Mackintosh (born October 1st, 1986), hereby declare that I have contributed independently and substantially to this dissertation without any assistance from third parties who are not indicated. I have used only the resources indicated and have cited all references. Published manuscripts were prepared in cooperation with co-authors and have not been submitted elsewhere for review or consideration, nor have they been published elsewhere. This dissertation includes the following three manuscripts:

- Mackintosh, A. J., de Bock, R., Lim, Z., Trulley, V. N., Schmidt, A., Borgwardt, S., & Andreou, C. (2021). Psychotic disorders, dopaminergic agents and EEG/MEG resting-state functional connectivity: a systematic review. Neuroscience & Biobehavioral Reviews, 120, 354-371. https://doi.org/10.1016/j.neubiorev.2020.10.021
- Mackintosh, A. J., Borgwardt, S., Studerus, E., Riecher-Rössler, A., de Bock, R., & Andreou, C. (2020). EEG Microstate Differences in Medicated vs. Medication-Naïve First-Episode Psychosis Patients. Frontiers in Psychiatry, 11, 1320. https://doi.org/10.3389/fpsyt.2020.600606
- De Bock, R., Mackintosh, A. J., Maier, F., Borgwardt, S., Riecher-Rössler, A., & Andreou, C. (2020). EEG microstates as biomarker for psychosis in ultra-high-risk patients. Translational Psychiatry, 10(1), 1-9. https://doi.org/10.1038/s41398-020-00963-7

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Abbreviations

APS	Attenuated psychotic symptoms
BLIPS	Brief limited intermitted psychotic symptoms
BOLD	Blood-oxygen-level-dependent
BS	Basic symptoms
BSIP	Basler Screening Instrument for Psychosis
BPRS	Brief Psychiatric Rating Scale
COMT	Catechol-*O*-methyltransferase
DSM -5®	Diagnostic and Statistical Manual of Mental Disorders, Version 5
EEG	Electroencephalography
FEP	First-episode psychotic disorders
mFEP	Medicated patients with first-episode psychotic disorders
uFEP	Unmedicated, medication-naïve patients with first-episode psychotic disorders
FePsy	Basel Projekt zur Früherkennung von Psychosen
fMRI	Functional Magnetic Resonance Imaging
GRD	Genetic risk and deterioration syndrome
HC	Healthy controls
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Version 10
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
sMRI	Structural Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
NMDA	*N*-methyl-D-aspartate
UHR	Ultra-high-risk state for psychotic disorders
UHR-T	Ultra-high-risk patients with transition to psychotic disorders at follow-up
UHR-NT	Ultra-high-risk patients without transition to psychotic disorders at follow-up
UPK	University of Basel Psychiatric Clinics

Abstract

Psychotic disorders are complex and heterogeneous mental disorders with low recovery rates despite a great amount of research on the topic. Various hypotheses exist as to the etiology of psychotic disorders. Amongst these, the dopamine hypothesis and the dysconnectivity hypothesis have been the most enduring in the last six decades. Little is known on how the dopamine and the dysconnectivity hypothesis are associated. The overarching research question of this thesis is to investigate this knowledge gap.

Resting-state magneto- and electroencephalography (MEG, EEG) were chosen as non-invasive measurement modalities of dysconnectivity at the source and sensor level of the brain in publication 1. Parameters of resting-state EEG microstate classes A-D were used as a global analysis method of functional connectivity at the sensor level of the brain in publications 2 and 3.

The first research question focused on finding systematic evidence on the association of the two hypotheses and was addressed by means of a systematic review (publication 1) of 20 studies published since 2000. Based on the review, no definite conclusion on the association of antipsychotic medication (that mainly acts on the dopamine system) and source- and sensor-level EEG/MEG functional connectivity could be drawn.

The second research question focused on whether differences in parameters of resting-state EEG microstate classes A-D are associated to antipsychotic medication. It was addressed by a study (publication 2) that compared 19-channel clinical EEG recordings of medicated (mFEP, n = 17) and medication-naïve (untreated; uFEP, n = 30) patients with first-episode psychotic disorders (FEP). The study results revealed significant decrease of microstate class A and significant increase of microstate class B to differentiate mFEP from uFEP.

The third research question focused on whether differences in parameters of resting-state EEG microstate classes A-D are associated with psychosis illness progression and transition to psychosis in FEP and ultra-high-risk (UHR) patients. It was addressed by a study (publication 3) that found significantly increased microstate class A to differentiate a combined group of medication-naïve FEP (n = 29) and UHR patients (n = 54) together from healthy controls (HC, n = 25); significantly decreased microstate class B to differentiate FEP from all UHR patients combined; and significantly decreased microstate class D to differentiate UHR-T patients with (n = 20) from UHR-NT patients without (n = 34) later transition to psychotic disorders using 19-channel EEG recordings.

In conclusion across all three publications, an association between the dopamine and the dysconnectivity hypothesis could be demonstrated by means of resting-state EEG microstates assessed in publication 2 and 3. No definite conclusion could be drawn by the systematic review (publication 1). More studies with longitudinal designs are needed to rule-out between-subject differences, track response trajectories, pre-post effects of antipsychotic medication and their association with dysconnectivity. With increased effort, resting-state EEG microstates could contribute to establishing a robust biomarker in a multi-domain approach in order to inform clinicians for the diagnosis, treatment and outcome prediction of psychotic disorders.

1. Introduction

In the following chapter, the theoretical background of this thesis will be outlined. It includes a background on psychotic disorders and the ultra-high-risk (UHR) state of psychotic disorders, as well as the dopamine and the dysconnectivity hypotheses which form the backbone of this dissertation. The measurement modalities and analysis methods of resting-state electroencephalography (EEG) functional connectivity that were chosen for the three publications will follow. The main research questions and how the three publications were designed to answer them will be presented in the last sub-chapters of this introduction.

1.1 Psychotic disorders and the ultra-high-risk state (UHR)

Psychotic disorders are typically diagnosed with a combination of delusions, hallucinations, disorganized speech, catatonic behavior, and negative symptoms (DSM-5®; American Psychiatric Association, 2013). The lifetime prevalence of psychotic disorders is estimated at 0.75% (Moreno-Kustner et al., 2018), with a lifetime comorbidity rate with other disorders of 47.7% (Siu et al., 2018) and a worldwide prevalence of 20.9 million cases in 2016 (Charlson et al., 2018). Patients' life expectancy is estimated to be shortened by 15 to 20 years due to increased physical morbidity compared to the general population (Laursen et al., 2014). A wide range of functional domains have been found to determine patient's disability, including impairments in cognition, social cognition, everyday functional skills, social skills, negative symptoms and difficulties in self-assessment of abilities (Harvey et al., 2019). Importantly, good functional outcomes were found to be related to shorter duration of untreated psychotic disorders (Santesteban-Echarri et al., 2017) which gave rise to early detection and intervention programs for psychotic disorders.

A premorbid/prodromal stage was observed to proceed a first psychotic episode (FEP) by several years (Häfner et al., 1998) during which patients might present gradual and subtle changes in thoughts, perception, behaviors, cognition and functioning (Yung et al., 1996). The state preceding a psychotic disorder was termed 'at-risk-mental-state' (ARMS), 'clinical-high-risk' (CHR) or 'ultra-high-risk' (UHR) of developing a psychotic disorder (Yung et al., 2005, 1998, 1996), with the terms used interchangeably. The UHR criteria used in the publications of this thesis consist of the presence of either (a) attenuated positive symptoms; (b) brief limited psychotic symptoms; or (c) genetic vulnerability accompanied by a functional decline (for reviews see Fusar-Poli et al., 2014; Yung et al., 2012). A comprehensive meta-analysis found that 18% of UHR patients transition to psychotic disorders after 6 months of follow-up, 22% after 1 year, 29% after 2 years and 36% after 3 years (Fusar-poli et al., 2012). In order to improve prediction of the UHR state, a large body of research explored biomarkers for psychotic disorders (Perkovic et al., 2017; Riecher-Rössler and Studerus, 2017; Rodrigues-Amorim et al., 2017; Schmidt et al., 2017). In line with the diathesis-stress model (Walker and Diforio, 1997), stress exposure was proposed as risk factor of developing psychotic disorders such as childhood adversity (Varese et al., 2012), migration (Cantor-Graae and Selten, 2005; McGrath et al., 2004), urbanicity (McGrath et al., 2004) as well as pre-existing vulnerability such as genetic factors and neurodevelopmental hazards (Varese et al., 2012).

1.2 Two pathophysiological models of psychotic disorders

The two pathophysiological models of psychotic disorders, namely the dopamine and the dysconnectivity hypotheses, that form the theoretical background of all three publications will be elucidated as follows.

1.2.1 Dopamine hypothesis

The dopamine hypothesis was first suggested in 1963 (Carlsson and Lindqvist, 1963) and has since been revised and extended (Davis et al., 1991; Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999; Snyder et al., 1974). It stems from the serendipitous clinical findings that chlorpromazine effectively treated positive symptoms back in the 1950s (Delay et al., 1952; Stahl, 2013). Psychoactive stimulants acting on the dopamine system were later shown to induce psychotic symptoms (Lieberman et al., 1990) which further supported the hypothesis. To that end, first-generation antipsychotics were shown to block D2-receptors and reduce the dopamine hyperactivity in the brain in general (Creese et al., 1976; Seeman and Lee, 1975). Later, it was suggested that prefrontal hypo-dopaminergia and subcortical hyper-dopaminergia both characterize psychotic disorders (Davis et al., 1991). Negative symptoms were associated to reduced phasic dopamine responses to stimuli, whereas positive symptoms were associated to increased spontaneous dopamine release (Maia and Frank, 2017). In patients at high risk for a psychotic disorder, elevated peripheral dopamine was found as well (Sumiyoshi et al., 2000) which was specific to prodromal individuals who later progressed to a psychotic disorder with further dopamine increase in the psychotic disorder (Howes et al., 2011). Most currently licensed antipsychotic drugs mainly act as dopamine antagonists besides targeting other neurotransmitter systems such as serotonin and *N*-methyl-D-aspartate (NMDA) receptors (Stahl, 2016, 2013).

In further developing the dopamine hypothesis, susceptibility genes were suggested to interact with environmental risk factors (such as stress, pregnancy, obstetric complications, drug abuse) leading to dopamine dysfunction at the presynaptic control level (for reviews see Howes and Kapur, 2009; Howes and Murray, 2014). The genes that have been suggested to mediate dopaminergic functioning include the gene for a major dopamine catabolic enzyme catechol-*O*-methyltransferase (COMT; Williams et al., 2007) and for the brain-derived neurotrophic factor (BDNF; Peciña et al., 2014).

1.2.2 Dysconnectivity hypothesis

The dysconnectivity hypothesis was chosen as the second main hypothesis on which this dissertation is based on. Besides the dopamine hypothesis, it forms another early and enduring pathogenetic model of psychotic disorders. It conceptualizes psychotic disorders as dysconnection between the brain's neural networks (Andreasen, 1999; Beaumont and Dimond, 1973; Friston, 1998, 1996; Stephan et al., 2009). Dysconnectivity is described as a failure of effective integration within and between brain areas, with increased or decreased functional interactions. It is based on neuroimaging evidence on structural and functional connectivity (Ribolsi et al., 2009; Schmitt et al., 2011; Stephan et al., 2009). Structural connectivity

refers to the anatomical fiber pathways connecting different brain areas typically assessed by structural Magnetic Resonance Imaging (sMRI) methods. Functional connectivity on the other hand is the statistical temporal correlation (coherence) between neurophysiological time series of spatially distributed neural populations which may or may not be directly anatomically linked (Fingelkurts et al., 2005; Lomas et al., 2015).

The brain's functional connectivity can be assessed by means of functional MRI (fMRI) with high spatial but low temporal resolution measuring fluctuations at < 0.1 Hz, or by means of electro-encephalography (EEG) and magnetoencephalographic (MEG) recordings. Whilst fMRI fluctuations are largely dependent on anatomical connectivity (Wang et al., 2013), EEG and MEG coherence measures are more affected by state factors such as cognitive setting, stimulus context and sleep (Supp et al., 2011). EEG and MEG both permit non-invasive assessments of electrical currents in neuronal populations at relatively low costs. With a high temporal resolution of milliseconds (Koenig et al., 2002) they thus capture the fast rhythmic fluctuations of neural populations in frequency bands ranging from 1 Hz up to 200 Hz (Lehmann et al., 2014). This allows the study of coupling patterns that might not be captured by fMRI (Engel et al., 2013).

An extensive amount of research has demonstrated EEG/MEG functional connectivity alterations in resting-state as well as task-related networks in patients at high-risk for psychotic disorders (Fusar-poli et al., 2012) and patients with psychotic disorders (for reviews see Alamian et al., 2017; Maran et al., 2016; Radua et al., 2012; Uhlhaas, 2013). Resting-state functional connectivity refers to spatially organized networks in an awake state in which subjects are not performing an explicit mental or physical task (van Diessen et al., 2015) and reflects intrinsic activity of the brain during spontaneous, task-independent states (Greicius et al., 2003). Stimulus processing as well as behavioral phenomena are suggested to mimic the underlying intrinsic organization of the brain which makes resting state networks meaningful in understanding brain function (Fox et al., 2005).

In patients with psychotic disorders, global and local alterations of resting-state information processing with diffuse discoordination/disorganization of neural networks across the whole brain has been found. These have been reported within the Default-Mode-Network (DMN), enhanced long-range functional connectivity between the thalamus and sensorimotor areas, reduced functional connectivity between the thalamus and prefrontal cortex, as well as within the frontal cortex (Alamian et al., 2017). However, findings remain conflicting with increased, decreased and no differences across frequency bands reported in widespread brain areas for patients with psychotic disorders compared to healthy controls (Maran et al., 2016).

1.3 Analysis methods

Different analysis methods of resting-state EEG/MEG functional connectivity were chosen for publication 1 and publications 2 & 3. These will be presented in the following, including the different particularities of EEG and MEG functional connectivity measures.

1.3.1 Resting-state EEG/MEG functional connectivity

First of all, EEG and MEG each own some advantages over the other in assessing resting-state functional connectivity. EEG is better suited to measure long-range connectivity and localizes brain sources more precisely when dipoles are radially orientated (Nunez and Williamson, 1996). However, EEG it is more prone to volume conduction effects than MEG (Winter et al., 2007). Brain sources of tangentially oriented dipoles on the other hand are better recorded by MEG that captures short-range connectivity better (Srinivasan et al., 2007).

In both recording systems, resting-state functional connectivity can be assessed at the 2D surface of the scalp with so-called sensor-level analysis methods. These are expected to be ambiguous and do not reveal true functional connectivity (Nolte et al., 2004), as electrical neural sources do not radially project to the scalp, are dependent on the chosen reference and are sensitive to effects of volume conductance (Lehmann et al., 2014). Spurious correlations between EEG/MEG-sensor estimates for resting-state measurements are the consequence (Winter et al., 2007). A possible solution to this problem is the transformation of EEG/MEG-data into intracranial-based source-level analysis models that omit zero-phase angle through orthogonalization (so called lagged coherence; Hipp et al., 2012; Nolte et al., 2004). These allow for reconstructions of the underlying generators of neuronal network activities and are suggested as a more valid method for assessing functional connectivity (Sakkalis, 2011; Schoffelen and Gross, 2009; Thatcher et al., 2007). In the systematic review (publication 1), studies with both analysis methods assessing EEG/MEG functional connectivity at the sensor as well as the source level of the brain were included.

Besides these source- and sensor-level estimates which can lead to different results in EEG/MEG-research, EEG/MEG analysis methods can further be divided into phase- and amplitude-based functional connectivity measures which in turn are suggested to serve distinct processes (He et al., 2019). Coherence measures based on the phase alignment of oscillatory waves can reflect global state changes of the brain such as sleep, are affected by stimulus context or cognitive setting and can be used to capture the communication between separate neural populations within a network (Supp et al., 2011). On the other hand, correlation measures that are mainly based on the covariance of the amplitude of the underlying oscillatory waves are well suited to capture slow fluctuations of up to 0.1 Hz such as in fMRI (Engel et al., 2013). These are largely dependent on anatomical connectivity and can be used to determine the availability of neural network populations (Wang et al., 2013). Again, studies using both phase- and amplitude-based measures were included in the systematic review.

1.3.2 Resting-state EEG microstates

Resting-state EEG microstates are a global measure of functional connectivity. They are spatial configurations of scalp global field power that were originally divided into four topographies (A, B, C, D; Koenig et al., 1999) and later into seven so called microstate classes (A, B, C, D, E, F, G; Custo et al., 2017), each with a different orientation of scalp-electric field. These non-overlapping configurations of brain electric states remain stable for 40-100 milliseconds and thus occur several times per second (Koenig et al., 2002; Lehmann et al., 1987). They were hypothesized to be the fundamental building blocks of human information processing (Lehmann et al., 1987). The original four microstate classes were found to explain 65-84% (Michel and Koenig, 2018), all seven classes 84.8% of EEG data variance (Custo et al., 2017). Microstate classes are measured by three statistical parameters; the duration of each class in milliseconds, the mean number of occurrence per second and the percentage of time covered by each class (Koenig et al., 2002). The original four microstate classes were shown to have high test-retest reliability and cross-method consistency (Khanna et al., 2014).

All resting-state EEG microstate classes have been shown to differentiate between medicated (Andreou et al., 2014; Baradits et al., 2020; Giordano et al., 2018; Murphy et al., 2019; Soni et al., 2018), and medication-naïve patients with psychotic disorders compared to healthy controls (de Bock et al., 2020; Kikuchi et al., 2007; Lehmann et al., 2005; Nishida et al., 2013). They were also found to differentiate patients in the high-risk state of psychotic disorders (Andreou et al., 2014; de Bock et al., 2020; Tomescu et al., 2014), as well as patients with mood (Al Zoubi et al., 2019; Damborská et al., 2019) and anxiety disorders compared to healthy controls (Al Zoubi et al., 2019; Kikuchi et al., 2011). Two meta-analyses found increased occurrence of microstate C and decreased duration of microstate D to be consistently reported across studies in medicated (da Cruz et al., 2020) as well as medication-naïve (Rieger et al., 2016) patients with psychotic disorders. Research with simultaneous EEG-fMRI methods was able to correlate microstate classes to different resting-state networks (Britz et al., 2010; Custo et al., 2017). In task-based EEG recordings, microstate classes were found to correlate to visual processing and verbalization compared to no-task resting (Milz et al., 2016).

1.4 Research questions and aim of the thesis

The overarching research question of this thesis centers on whether the dopamine and the dysconnectivity hypotheses are associated. Both hypotheses are amongst the most enduring pathophysiological models for psychotic disorders, however little is known about how they are linked. The three research questions that translate from the overarching research question and form the backbone of this thesis (see Figure 1) will be elaborated in three sub-chapters as follows. Their operationalizations and hypotheses will be outlined. A discussion on the results will follow in the discussion chapter.

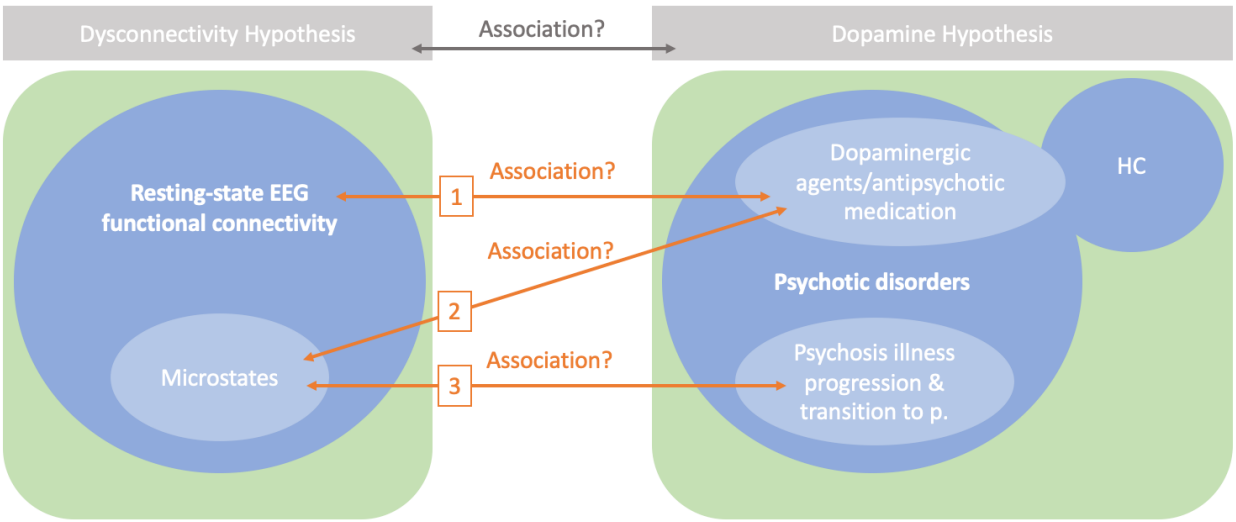

Figure 1: Overarching research question (grey arrow) and three main research questions 1-3 (orange arrows) of the respective publications 1-3.

1.4.1 *First research question: Does systematic evidence exist on the association of dopaminergic agents with resting-state electro- and magnetoencephalographic (EEG/MEG) brain functional connectivity assessed by sensor- as well as source-level measures?*

To answer this first research question a systematic review was conducted. The existing literature published since 2000 that used resting-state EEG/MEG functional connectivity measures reported by frequency band according to pre-defined inclusion and exclusion criteria was reviewed. The inclusion criteria were set according to the PICOS framework (Participants, Interventions, Comparisons, Outcome and Study Design; Methley et al., 2014). As most licensed antipsychotic medications target (amongst others) the dopamine neurotransmitter system (Stahl, 2013), the first research question was operationalized as such that participant groups with or without antipsychotic medication intake or genes acting on the dopamine system were compared.

Specifically, the following comparisons were targeted for resting-state EEG/MEG functional connectivity differences between:

1) Medication-naïve patients with psychotic disorders and healthy controls;
2) Medicated patients with psychotic disorders and healthy controls;
3) Medication-naïve and medicated patients with psychotic disorders;
4) Patients with psychotic disorders before and after treatment with antipsychotic medication;
5) Healthy controls before and after administration of a dopamine agent;
6) Populations with a gene expression that involves dopaminergic neurotransmission.

1.4.2 *Second research question: Are differences in parameters of resting-state EEG microstate classes A-D associated to antipsychotic medication in FEP patients?*

Antipsychotic medication is still considered first-line treatment for psychotic disorders but comes with high discontinuation rates (for reviews see Bowtell et al., 2018; Gentile, 2019), intolerable side-effects (for a review see Kaar et al., 2019), and only a minority resulting in good responses (Leucht et al., 2017). To date, little is known on how antipsychotic medication is associated to resting-state EEG microstates in patients with psychotic disorders.

The relation between resting-state EEG microstates and antipsychotic medication intake was investigated using 19-channel EEG recordings in a sample of FEP patients (n = 47) recruited through the FePsy project (Riecher-Rössler et al., 2013, 2007) at the University of Basel Psychiatric Clinics (UPK). The study was designed to find differences in parameters of microstate classes A-D that might be attributed to the medication status of the two patient groups beyond the effect of the disorder. Specifically, medicated FEP patients (mFEP, n = 17) were compared to a control group of FEP patients who were medication-naïve (untreated; uFEP, n = 30). Based on previous research, it was hypothesized that microstate classes A and B would differentiate the two patient groups.

1.4.3 *Third research question: Are differences in parameters of resting-state EEG microstate classes A-D associated with psychosis illness progression and transition to psychosis in FEP and UHR patients?*

This third research question takes resting-state EEG microstates a step further and investigates how they associate to the entire spectrum of psychotic disorders, independent of antipsychotic medication. The four participant groups included in the study were therefore medication-naïve in terms of antipsychotic medication. The sample included FEP patients (n = 29), UHR patients with (UHR-T, n = 20) and without (UHR-NT; n = 34) later transitions to a psychotic disorder at follow-up, and healthy controls (HC; n = 25) from the FePsy project (Riecher-Rössler et al., 2013, 2007) at UPK. Using 19-channel EEG recordings, the comparisons were set up to examine whether resting-state EEG microstates could serve as:

1) State marker for general psychopathology (by comparing FEP & UHR-T & UHR-NT to HC)
2) State marker selective for psychosis illness progression (by comparing FEP to UHR-T & UHR-NT)
3) Trait marker for later transition to a psychotic disorder (UHR-T vs. UHR-NT)

Parameters of microstate classes A-D were expected to reveal both state and trait differences. However, the comparisons were set up in an explorative way as they were not investigated so far. Thus, no changes in specific parameters of microstate classes A-D were hypothesized.

2. Publications

The three publications of this thesis will now follow in full-length as published by the respective journals. The first two publications are first-authorships, the third publication is a shared first-authorship with my fellow PhD colleague Renate de Bock. The main findings of the three publications and how they answer the research questions which they aimed to investigate will be discussed in the succeeding discussion chapter.

1) Mackintosh, A. J., de Bock, R., Lim, Z., Trulley, V. N., Schmidt, A., Borgwardt, S., & Andreou, C. (2021). Psychotic disorders, dopaminergic agents and EEG/MEG resting-state functional connectivity: a systematic review. Neuroscience & Biobehavioral Reviews, 120 (1), 354-371. https://doi.org/10.1016/j.neubiorev.2020.10.021

2) Mackintosh, A. J., Borgwardt, S., Studerus, E., Riecher-Rössler, A., de Bock, R., & Andreou, C. (2020). EEG Microstate Differences in Medicated vs. Medication-Naïve First-Episode Psychosis Patients. Frontiers in Psychiatry, 11, 1320. https://doi.org/10.3389/fpsyt.2020.600606

3) De Bock, R., Mackintosh, A. J., Maier, F., Borgwardt, S., Riecher-Rössler, A., & Andreou, C. (2020). EEG microstates as biomarker for psychosis in ultra-high-risk patients. Translational Psychiatry, 10(1), 1-9. https://doi.org/10.1038/s41398-020-00963-7

2.1 Publication 1: Psychotic disorders, dopaminergic agents and EEG/MEG resting-state functional connectivity: a systematic review

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Psychotic disorders, dopaminergic agents and EEG/MEG resting-state functional connectivity: A systematic review

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ABSTRACT

Both dysconnectivity and dopamine hypotheses are two well researched pathophysiological models of psychosis. However, little is known about the association of dopamine dysregulation with brain functional connectivity in psychotic disorders, specifically through the administration of antipsychotic medication. In this systematic review, we summarize the existing evidence on the association of dopaminergic effects with electro- and magnetoencephalographic (EEG/MEG) resting-state brain functional connectivity assessed by sensor- as well as source-level measures. A wide heterogeneity of results was found amongst the 20 included studies with increased and decreased functional connectivity in medicated psychosis patients vs. healthy controls in widespread brain areas across all frequency bands. No systematic difference in results was seen between studies with medicated and those with unmedicated psychosis patients and very few studies directly investigated the effect of dopamine agents with a pre-post design. The reported evidence clearly calls for longitudinal EEG and MEG studies with large participant samples to directly explore the association of antipsychotic medication effects with neural network changes over time during illness progression and to ultimately support the development of new treatment strategies.

1. Introduction

An extensive body of research of the past decades has aimed to better understand the pathophysiology of psychotic disorders. The core symptoms of these disorders encompass delusions and hallucinations, disorganized speech, catatonic behavior and negative symptoms (DSM-5®, American Psychiatric Association, 2013). Their worldwide lifetime prevalence has been estimated at 0.749 % (Moreno-Kustner et al., 2018). Psychosis patient's life years were suggested to be adjusted by 7.4 % due to the disability (Whiteford et al., 2013) and patients' life expectancy is 15–20 years shorter compared to the general population due to increased physical morbidity (Laursen et al., 2014).

One of the most enduring pathogenetic models of psychotic disorders is the dopamine hypothesis, which has undergone multiple iterations (Davis et al., 1991; Howes and Kapur, 2009; Laruelle and Abi-Dargham, 1999; Snyder et al., 1974) since its first inception in 1963 (Carlsson and Lindqvist, 1963). It evolved from serendipitous clinical findings in the 1950s that chlorpromazine was effective in treating positive symptoms (Delay et al., 1952; Stahl and Stahl, 2013) and later evidence that psychoactive stimulants could induce psychosis (Lieberman et al., 1990). Further studies showed that key pharmacological properties of first-generation antipsychotics blocked D2-receptors and reduced the dopamine hyperactivity in the brain in general (Creese et al., 1976; Seeman and Lee, 1975). The simple excess of dopamine was later questioned and it was suggested that prefrontal hypo-dopaminergia and subcortical hyper-dopaminergia both characterize psychotic disorders (Davis et al., 1991). A more recent elaboration of the hypothesis postulates that an interaction of susceptibility genes with environmental risk factors (such as stress, pregnancy, obstetric complications, drug abuse) leads to dopamine dysfunction at the presynaptic control level

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(Howes and Kapur, 2009; Howes and Murray, 2014). Reduced phasic dopamine responses to stimuli have been associated to negative symptoms, increased spontaneous dopamine release to positive symptoms (Maia and Frank, 2017). In accordance with this most enduring neurobiological model of psychosis, all currently licensed antipsychotic drugs act as dopaminergic antagonists, although they also target a variety of other neurotransmitter systems (Stahl and Stahl, 2013). However, recovery rates of patients with psychotic disorders have been estimated at 13.5 % (Jääskeläinen et al., 2013), with relatively high treatment discontinuation rates (64−82%) within 18 months of antipsychotic medication due to inefficiency or intolerable side effects (Lieberman et al., 2005). This clearly calls for further insight into the mechanisms of action on how antipsychotic treatment excerts its neuronal effects.

On a different level, psychotic disorders have been conceptualized as dysconnection between the brain's neural networks; which forms another enduring pathogenetic model of these disorders (Andreasen, 1999; Beaumont and Dimond, 1973; Friston, 1998, 1996; Stephan et al., 2009). Dysconnectivity is described as a failure of effective integration within and between brain areas (with increased or decreased functional interaction of brain areas) and is based on neuroimaging evidence on structural and functional connectivity (Ribolsi et al., 2009; Schmitt et al., 2011; Stephan et al., 2009). Whilst structural connectivity refers to the anatomical fiber pathways connecting different brain areas typically assessed by structural Magnetic Resonance Imaging (MRI) methods, functional connectivity is the statistical temporal correlation (coherence) between neurophysiological time series of spatially distributed neural populations (Fingelkurts et al., 2005; Lomas et al., 2015) which may or may not be directly anatomically linked. Resting-state functional connectivity, which this review focusses on, refers to spatially organized networks in an awake state in which subjects are not performing an explicit mental or physical task (van Diessen et al., 2015) and reflects intrinsic activity of the brain during spontaneous, task-independent states (Greicius et al., 2003). Stimulus processing as well as behavioral phenomena are suggested to mimic the underlying intrinsic organization of the brain which makes resting-state networks meaningful in understanding brain function (Fox et al., 2005).

The brain's functional connectivity can be assessed by means of functional MRI (fMRI) with high spatial but low temporal resolution measuring fluctuations at <0.1 Hz, or by means of electroencephalography (EEG) and magnetoencephalographic (MEG) recordings. The latter two both permit non-invasive assessments of electrical currents in neuronal populations with a high temporal resolution of milliseconds (Koenig et al., 2002), and thus capture the fast rhythmic fluctuations of neural populations in frequency bands ranging from 1 Hz to up to 200 Hz (Lehmann et al., 2014; Swann et al., 2015), allowing the study of coupling patterns that might not be captured by fMRI (Engel et al., 2013). Furthermore, EEG coherence measures are more affected by state factors such as cognitive setting, stimulus context and sleep (Supp et al., 2011), whereas fMRI BOLD fluctuations are largely dependent on anatomical connectivity (Wang et al., 2013).

An extensive amount of research has demonstrated EEG/MEG functional connectivity alterations in resting-state networks in patients with psychotic disorders and there are extensive reviews covering the topic (for example see Alamian et al., 2017; Maran et al., 2016; Radua et al., 2012; Uhlhaas, 2013). However, there are several methodological particularities in EEG and MEG that need to be taken into consideration when assessing these findings: Electrical neural sources do not radially project to the scalp, are dependent on the chosen reference and are sensitive to effects of volume conductance (Lehmann et al., 2014). Therefore, EEG and MEG sensor-level signals, recorded from electrodes on the 2D surface of the scalp, are ambiguous and do not reveal true functional connectivity between brain regions (Nolte et al., 2004). Intracranial-based source-level models that omit zero-phase angle (so-called lagged coherence; Nolte et al., 2004) better solve these problems and are suggested as a more valid method for assessing functional connectivity (Sakkalis, 2011; Schoffelen and Gross, 2009; Thatcher Biver and North, 2007), albeit it has been suggested that genuine zero-lag interactions may occur in sub-networks of cortical systems (Gollo et al., 2014).

Furthermore, little is known about how EEG/MEG dysconnectivity is associated with the dopamine dysregulation in psychotic disorders and specifically how dysconnectivity is influenced by the administration of antipsychotic medication in psychosis patients. Reports of resting-state fMRI investigations have shown that antipsychotic medication intake may normalize short- and long-range functional connectivity between brain regions (Guo et al., 2017), improve cortico-striatal functional connectivity (Sarpal et al., 2015), as well as modulate connectivity of the default mode network (DMN) (Sambataro et al., 2010) and the resting-state networks to a certain extent (Kraguljac et al., 2016). However, to the best of our knowledge, there has not yet been a review that specifically targets the question of how factors affecting dopaminergic neurotransmission are associated with EEG and MEG resting-state (dys-) connectivity in patients with psychotic disorders.

The aim of this systematic review is therefore to explore the association between the two pathogenetic models of psychotic disorders (i.e., dopamine dysregulation and dysconnectivity) by reviewing the existing evidence on dopamine effects on EEG and MEG resting-state functional connectivity. We explore both pharmacological agents acting on, and genes associated with, the dopamine system.

2. Methods

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) and its protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database on 26th July 2018 (registration number CRD42018099667, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=99667)

2.1. Search

Pubmed, Embase, Webofknowledge and PsychInfo databases were used for the systematic literature search. The search key was '(psychos* OR psychot* OR schizophren* OR dopa* OR antipsychot*) AND (EEG OR MEG) AND (connectivity OR coher* OR synchron*) AND (resting)' in all fields for the search periods of 2000 through to 2020. The last search was conducted on June 18th, 2020. Additionally, a manual search of the references of the included studies was performed.

2.2. Eligibility criteria

Study inclusion criteria according to the PICOS framework (*Participants, Interventions, Comparisons, Outcome and Study Design*; Methley et al., 2014) were as follows:

1 *Outcome*: spatial measures of resting-state EEG/MEG brain functional connectivity at the sensor or source level, calculated for at least one of the following frequency bands: delta, theta, alpha, beta, gamma;
2 *Participants, Interventions, Comparisons, Study Design*: Either (a) drug-naïve patients with psychotic disorders vs. healthy controls (cross-sectional design); or (b) medicated patients with psychotic disorders vs. healthy controls (cross-sectional design); or (c) drug-naïve vs. medicated patients with psychotic disorders (cross-sectional design); or (d) patients with psychotic disorders before vs. after administration of antipsychotic drugs (longitudinal design); or (e) healthy individuals before and after drug administration (longitudinal design); or (f) populations with vs. without expression of a gene affecting dopaminergic neurotransmission (cross-sectional design).

Studies that met one or more of the following criteria were excluded: 1) animal models; 2) languages other than English; 3) papers not reporting results in a study population such as reviews, conference

papers, case reports, commentaries or other theoretical articles including computational models; 4) global measures of connectivity (i.e. omega complexity, microstate analysis); 5) connectivity analyses that did not assess spatial connections; 6) studies that did not report frequency-specific results; 7) participants with any health conditions (i.e. minor physical abnormalities, neurological disorders, IQ < 70); 8) patients with dopamine dysregulation or psychotic symptoms in the context of other neurological or psychiatric disorders (e.g. Parkinson's disease, ADHD, epilepsy); 9) studies with mixed samples including both medicated and medication-naïve patients. In the latter case, the corresponding authors of the study were contacted with the request to provide results on homogeneous samples. No exclusion criteria were applied with respect to specific psychotic disorders or illness duration, the full psychosis spectrum was included.

2.3. Study selection

After articles were identified through the above-outlined search strategy and records of duplicates were removed, titles and abstracts were screened independently by the first (AJM) and third authors (ZL). Records were excluded if they fulfilled at least one exclusion criterion. All excluded and included articles were reviewed and potential discrepancies resolved by one of the senior authors. Of all included abstracts, full-text articles were assessed for eligibility independently and decisions and reasons for exclusion were once more reviewed by one of the senior authors (see Fig. 1 for an overview of reasons for exclusion).

2.4. Data extraction

The following variables were extracted from each paper if available: 1) name of the study; authors and publication year; 2) study design; 3) study population (participant groups, diagnosis type, female/male distribution, age, sample size); 4) intervention type (medication, dose, administration type & frequency); 5) comparator/control; 6) EEG/MEG method and recording information; 7) type of connectivity analysis (sensor- or source-level analysis); 8) the exact frequency bands applied from delta, over to theta, alpha, beta, through to gamma; 9) functional connectivity results per frequency band. The data were extracted by one of the authors, reviewed by the first author with guidance by one of the senior authors.

2.5. Quality assessment

In order to assess the quality of the included studies, an item-checklist was applied based on a previously published quality assessment by Fusar-Poli et al. (2013). The categories of the check-list were adapted for the purpose of this review and include: (1) study design (incl. sample size); (2) demographic and sample characteristics (incl. inclusion criteria, exclusion criteria, gender, IQ/education level, diagnostic instrument, duration of illness, and comorbid diagnosis); (3) results (incl. other medication, and EEG/MEG segments used for analysis). All categories are listed in Table 6 and were scored with a range of a minimum of 0 to a maximum of 2 points. Each study was then rated according to the sum of the total points across all categories with high quality (above 80 % of the maximal sum of points), moderate-high (60–79 %), moderate (40–59 %), moderate-low (20–39 %), and low quality (below 19 %). The full quality assessment of each study can be found in Table 7.

3. Results

3.1. Search results

After removal of search duplicates, a total of 804 articles were screened for potential inclusion. 20 articles qualified for inclusion (see Flow Diagram, Fig. 1). Of these, 13 papers used EEG/MEG resting-state brain functional connectivity methods that computed results at the source level and seven papers at the sensor level. These two analysis approaches are reported separately per frequency band. In each analysis group, one paper used a longitudinal design, while all other papers used a cross-sectional design. These are reported in sub-chapters. Two papers with source-level and one paper with sensor-level analysis compared *medication-naïve* first-episode psychosis patients to healthy controls and are reported separately from the papers on *medicated* psychosis patients to enable indirect comparisons of findings in *medicated* vs. *medication-naïve* patients. Finally, there were two papers that examined genes acting on the dopamine system and their effects on sensor-level EEG/MEG functional connectivity. These are reported in a third chapter. Surprisingly, no studies were found that directly compared medicated to non-medicated psychosis patient groups.

In the following, studies that assessed more than 30 participants per group are indicated as *large-sample studies* to help orient the reader.

3.2. Association of dopaminergic medication with EEG/MEG source-level functional connectivity

(a) Cross-sectional comparisons: Patients with psychotic disorders versus healthy controls (Table 1)

3.2.1. Delta frequency band

From the 10 papers that used source-level EEG/MEG functional connectivity analysis to compare *medicated* psychosis patients to healthy controls, six examined the delta band. Most of these reported no significant differences between *medicated* psychosis patients and healthy controls (n = 4) using EEG (Andreou et al., 2015a; Kirino et al., 2018), MEG (Gjini et al., 2020), and simultaneous EEG-fMRI (Razavi et al., 2013). Two large-sample studies reported differences between *medicated* psychosis patients and healthy controls, although they were in opposite directions: A simultaneous EEG-fMRI study by Baenninger et al. (2017) reported decreased connectivity in psychosis patients in the default mode network, temporal and parietal regions, thalamus, cerebellum and limbic areas. In contrast, Di Lorenzo et al. (2015) observed increased EEG connectivity in psychosis patients using lagged-phase synchronization mainly between the left prefrontal cortex and the cingulate cortex, occipital and right parieto-temporal regions.

From the two papers that compared *medication-naïve* first-episode psychosis patients to healthy controls, one reported increased EEG connectivity in the delta band concerning right fronto-parietal and fronto-temporal regions using intracortical lagged coherence (Lehmann et al., 2014), while the other reported no differences in delta-band EEG connectivity using lagged phase synchronization (Ramyead et al., 2016).

3.2.2. Theta frequency band

The theta frequency band was examined by eight source-level papers. Half of these reported no significant differences between *medicated* psychosis patients and healthy controls (n = 4) using simultaneous EEG-fMRI (Baenninger et al., 2017; a large-sample study), EEG (Kirino et al., 2018) and MEG (Gjini et al., 2020; Rutter et al., 2013). On the other hand, four studies reported connectivity changes in *medicated* psychosis patients compared to healthy controls (Andreou et al., 2015a; Di Lorenzo et al., 2015; Razavi et al., 2013; Umesh et al., 2016). Of these, three studies reported EEG connectivity increases in *medicated* psychosis patients compared to healthy controls in widespread areas between most ROI pairs across the entire brain using lagged-phase synchronization in a large-sample study (Di Lorenzo et al., 2015), in frontal, temporal, parietal and midline areas using a multivariate interaction measure (Andreou et al., 2015a) and between the left and right inferior parietal lobe and right middle frontal gyrus using a lagged-linear connectivity measure (Umesh et al., 2016). One study found decreases in connectivity in *medicated* psychosis patients compared to healthy controls which was associated with the left working memory network using simultaneous EEG-fMRI (Razavi et al., 2013).

The two papers investigating *medication-naïve* first-episode psychosis patients compared to healthy controls found no significant connectivity results in the theta band using EEG intracortical-lagged coherence (Lehmann et al., 2014) and EEG lagged-phase synchronization (Ramyead et al., 2016).

3.2.3. Alpha frequency band

The alpha frequency band was examined in eight source-level papers, the majority of which reported no significant connectivity differences between *medicated* psychosis patients and healthy controls (n = 5) using EEG (Andreou et al., 2015a; Kirino et al., 2018), MEG (Gjini et al., 2020; Rutter et al., 2013) and simultaneous EEG-fMRI (Razavi et al., 2013). Three papers on the other hand found connectivity changes in *medicated* psychosis patients compared to healthy controls (Baenninger et al., 2017; Di Lorenzo et al., 2015; Hinkley et al., 2011). Of these, one large-sample study found connectivity increases in *medicated* psychosis patients compared to healthy controls in the lower alpha band between the left occipital, temporal and parietal areas using simultaneous EEG-fMRI (Baenninger et al., 2017). Another large-sample study found connectivity decreases in *medicated* psychosis patients compared to

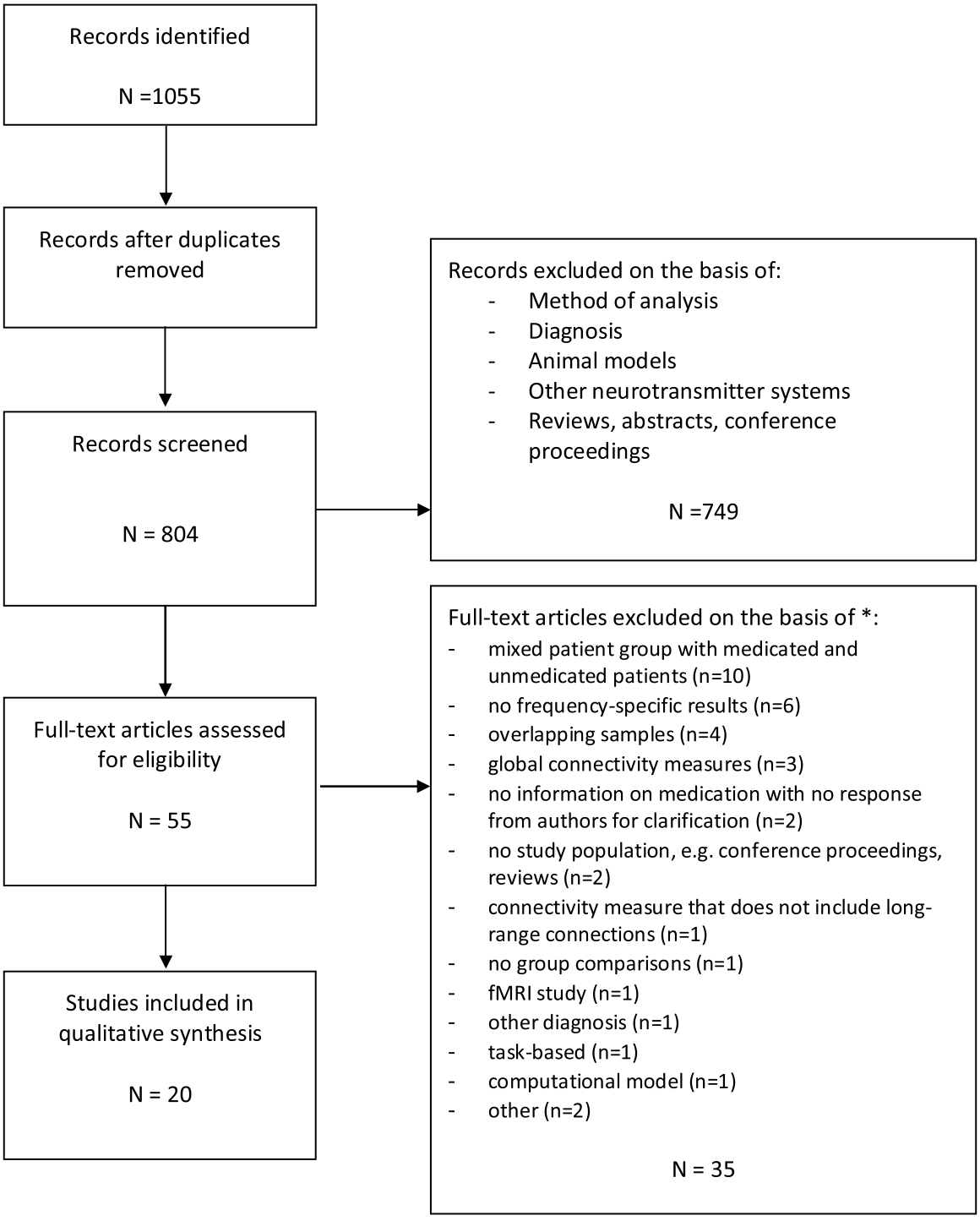

Fig. 1. Diagram of studies included in the present systematic review (based on Moher et al., 2009);* Full-text studies were excluded as soon as one exclusion criterion was fulfilled.

Table 1
Association of dopaminergic *medication* with EEG/MEG *source-level* functional connectivity in cross-sectional comparisons; patients with psychotic disorders versus healthy controls.

Reference	Frequency range (Hz)	Design	Resting-state EEG	Source localization method	Connectivity measure (Ph/A)	Topographic analysis	N Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
(Andreou et al., 2015a)	δ (3) θ (6) α (10) β1 (16) β2 (25) γ (40)	Cross-sectional	64-channel EEG EC 5-10 min	eLORETA	Multivariate interaction measure (MIM) (Ph)	Between region	19 FEP (2/17); 23.53 ± 4.3 23 HC (5/18); 24.95 ± 5.4	CPZE 239.59 (182.4) (n = 16)	AD n = 6	θ: FEP > HC, mainly le F/T/P/ML *Other findings*: - No significant effects of medication as covariate - Negative correlation between θ MIM and verbal memory - Trendwise ↑ θ power in FEP compared to HC
(Andreou et al., 2015b)	γ (40)	Cross-sectional	64-channel EEG EC 5-10 min	eLORETA	Orthogonalized power envelope correlation (PEC) (A)	Between-region	22 FEP (3/19); 24.09 ± 5.1 22 HC (5/17); 24.35 ± 5.1	CPZE 188.64 (181.0) (n = 18)**	AD n = 6	γ FEP > HC, mainly bilateral F/Ins & le T/ML *Other findings:* - Higher PEC in patients with low positive symptoms - No significant differences in γ power
(Baenninger et al., 2017)	δ (1-3.5) θ (4-7.5) α1 (8.5-10.5) α2 (10.5-12.5) β (13-30)	Cross-sectional	31-channel EEG EO/EC 6-8min*	EEG-informed MRI (parametric modulator of BOLD response: global field synchronization; GFS) (Ph)		Between-region	42 PP (5/37); 39.1 ± 12.0 37 HC (8/29); 34.6 ± 11.7	CPZE 346.8 (234.6)	Not reported	δ: PP < HC DMN/T/P/Th/Cer/Lim α1: PP > HC le O/T/P (i.e. Prc/Cu) β: PP > HC ri Prc/Cu *Other findings:* - No significant correlation with CPZE - No correlations with symptoms
(Di Lorenzo et al., 2015)	δ (1.5-4) θ (4-8) α (8-12) β1 (12-20) β2 (20-30 γ (30-80)	Cross-sectional	40-channel EEG EC 3 min	eLORETA	Lagged phase synchronization (LPS) (Ph)	Between-region	77 SZ (26/51); 35.44 ± 11.05 of which - 25 (11/14) with short (ShD) illness duration (<5y); 25.72 ± 4.32 - 52 (15/37) with long (LD) illness duration (>5y); 40.12 ± 10.23 78 HC (36/42); 32.78 ± 10.94	CPZE 306.10 (167.27)	BZP n = 18 AD n = 18 ACV n = 10 ACH n = 7	δ: SZ > HC mainly between le PFC and CC/O/ri P-T θ: SZ > HC with widespread distribution between most ROI pairs of all brain areas α: SZ < HC, PFC/P-T/CC β1: SZ > HC, mainly PFC/O/P β2: SZ < HC in lLFC-lPCC, rOFC-rSMA γ: SZ > HC, mainly between ri O and ri PFC/P-T/CC *Other findings:* LD vs. ShD: ↓ δ,↑ θ PFC/CC/P/T, ↑↓ β2, ↓ γ with widespread distribution
(Gjini et al., 2020)	δ (1-4 Hz) θ (4-8 Hz) α (8-12 Hz) β1 (12-20 Hz) β2 (20-30 Hz) γ (30-50 Hz)	Cross-sectional	148 channel MEG EO 10 min	MRFOCUSS	MEG Coherence source imaging (CSI) (Ph)	Global connectivity***	10 NDS (3/7) 40.3 ± 11.25 10 DS (3/7) 41.9 ± 11.1 10 HC (3/7) 42.7 ± 9.7	All patients on stable medication for 4 weeks, dose not reported.	Not reported	β: DS > HC (P) *Other findings:* - discriminative analysis: 554 of 4000 pixels activated in patients and not in controls - δ: DS > NDS MEG relative power in sensor space, EEG absolute power - β2: NDS > DS resting-state MEG relative power in sensor space, NDS = DS > HC EEG absolute power

(*continued on next page*)

Table 1 (*continued*)

Reference	Frequency range (Hz)	Design	Resting-state EEG	Source localization method	Connectivity measure (Ph/A)	Topographic analysis	N Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
(Hinkley et al., 2011)	α (6-14)	Cross-sectional	275-channel MEG EC 4 min	Minimum-variance beamformer	Imaginary coherence (IC) (Ph)	Global connectivity***	30 SZ (7/23); 38.4 ± 11.1 15 HC (4/11); 43 ± 12.2	All patients medicated; dose not reported	Not reported	- α: DS < HC EEG & MEG absolute and relative power α: SZ < HC in le MFG, le PG and ri STG α: SZ > HC in O, ri PFC & ri IFG, and MOG *Other findings:* - Negative correlation of α IC - in le IPL and ri AI with positive symptoms - in le PFC with negative symptoms - in medial PFC (ACC) with depressive symptoms - in ri MFG with cognitive symptoms - No significant differences in α power - No correlations with medication
(Kirino et al., 2018))	δ (1.5-6) θ (6.5-8) α1 (8.5-10) α2 (10.5-12) β1 (12.5-18) β2 (18.5-21) β3 (21.5-30) ω (45-125)	Cross-sectional	32-channel EEG EC 15 min	sLORETA	Intracortical lagged coherence (Ph)	Between-region	20 SZ (8/12); 38.7 ± 8.9 20 HC (8/12); 37.1 ± 7.3	CPZE 878.5 ± 614.3	Not reported	No significant differences in 4 DMN nodes (mPFC, ri/le IPL, PCC)
(Razavi et al., 2013))	δ (1-3.5) θ1 (3.5-6.25) θ2 (6.25-8.2) α1 (8.2-10.5) α2 (10.5-14) β1 (14-18.75) β2 (18.75-21.88) β3 (21.88-30)	Cross-sectional	92-channel EEG EC 9 min	EEG-informed fMRI (covariance mapping of EEG spectral amplitude with DMN and LWMN fMRI ICs) (A)		Within-region	11 SSD (4/7); 30.77 ± 6.4 11 HC (4/7); 31.16 ± 6.66	CPZE 664.73 (495.76)	AD n = 2 ACV n = 6 BZP n = 5 ACH n = 1	θ1: SSD < HC associated to LWMN *Other findings:* - ↓ α1/α2 and ↑ δ/θ power in SSD - ↓ covariance map consistency in SSD - Similar maps associated with lower frequencies in SSD than in HC - no significant medication effects
(Rutter et al., 2013)	θ (4-8) α (8-14) β (14-30) γ (30-80)	Cross-sectional	275-channel MEG EC 4 min	Synthetic aperture magnetometry beamformer	Magnitude squared coherence (MSC) (Ph)	Between-region	20 SZ & SA (6/14); 31.2 ± 10.9 20 HC (6/14); 31.3 ± 10.8	All patients medicated; dose not reported	Not reported	No significant differences after correction for multiple comparisons
(Umesh et al., 2016)	θ	Cross-sectional	192-channel EEG EC 10 min	sLORETA	Lagged linear connectivity (LLC) (A)	Between-region	20 SZ (0/20); 29.8 ± 7.68 20 HC (0/20); 29.75 ± 7.71	CPZE 443.65 (215.94)	Not reported	θ: SZ > HC between le/ri IPL & ri MFG *Other findings:* - ↑ θ LLC trendwise correlation between ri Prc-le MFG and total symptom load - ↑ θ CSD in patients in le ACC

Abbreviations: δ = delta; θ = theta; α = alpha; β = beta; ω = omega; γ = gamma; A = Amplitude-based; ACC = Anterior cingulate cortex; ACH = Anticholingergics; ACV = Anticonvulsants; AD = Antidepressants; AI = Anterior insula; BOLD = Blood-Oxygenation-Level-Dependent; BZP = Benzodiazepines; C = Central regions; CC = Cingulate cortex; Cer = Cerebellum; CPZE = Chlorpromazine equivalent; CSD = Current source density; CSI = Coherence source imaging; Cu = Cuneus; DMN = Default mode network; DS = Deficit syndrome schizophrenia (predominantly negative symptoms); EC = Eyes closed; EEG = Electorencephalography; eLORETA = exact low-resolution brain electromagnetic tomography; EO = Eyes open; f = female; F = Frontal lobe; FEP = First-episode psychosis; GFS = Global Field Synchronization; HC = Healthy controls; IC = Imaginary

coherence; ICs = Independent components; IFG = Inferior frontal gyrus; Ins = Insula; IPL = Inferior parietal lobe; LD = Long illness duration; le = left; Lim = Limbic regions; LLC = Lagged linear connectivity; lLFC = left lateral frontal cortex; lPCC = left posterior cingulate cortex; LPS = Lagged phase synchronization; LWMN = le working memory network; m = male; MEG = Magnetoencephalography; MFG = Middle frontal gyrus; MIM = Multivariate interaction measure; ML = Midline regions; MOG = Medial occipital gyrus; mPFC = medial Prefrontal cortex; MRFOCUSS = Coherence source imaging technique; MRI = Magnetic Resonance Imaging; MSC = Magnitude squared coherence; NDS = Non-deficit schizophrenia; O = Occipital lobe; P = Parietal lobe; PCC = Posterior cingulate cortex; PEC = Power envelope correlation; PFC = Prefrontal cortex; PG = Precentral gyrus; Ph = Phase-based; PP = Psychosis patients; Prc = Precuneus; ri = right; rOFC = right orbital frontal cortex; rSMA = right sensory motor areas; SA = Schizoaffective disorder; SD = Standard deviation; SFG = Superior frontal gyrus; ShD = short illness duration, sLORETA = standardized low-resolution brain electromagnetic tomography; SSD = Schizophrenia spectrum disorders; STG = Superior temporal gyrus; SZ = Schizophrenia patients; T = Temporal lobe; Th = Thalamus; *data used for final common analyses (2-center study with different recording specifications between centers); ** results reported in this table represent analyses in the medicated sub-sample; *** average connectivity of a region to all other brain regions.

healthy controls between prefrontal cortex, parietal-temporal areas and cingulate cortex using EEG lagged-phase synchronization (Di Lorenzo et al., 2015). And a third paper found connectivity increases in the occipital lobe, right prefrontal cortex, right inferior frontal gyrus and medial occipital gyrus, as well as connectivity decreases in the left middle frontal gyrus, left precentral gyrus and right superior temporal gyrus in *medicated* psychosis patients compared to healthy controls in the alpha band using MEG imaginary coherence (Hinkley et al., 2011).

In *medication-naïve* first-episode psychosis patients compared to healthy controls, one paper reported decreased EEG connectivity between fronto-parietal and fronto-temporal regions using intracortical-lagged coherence (Lehmann et al., 2014) and the other reported no significant results in EEG connectivity for the alpha band using lagged-phase synchronization (Ramyead et al., 2016).

3.2.4. Beta frequency band

A total of seven source-level papers analyzed the beta band. A slight majority reported no significant results (n = 4) in *medicated* psychosis patients compared to healthy controls using EEG (Andreou et al., 2015a; Kirino et al., 2018), MEG (Rutter et al., 2013) and simultaneous EEG-fMRI (Razavi et al., 2013). On the other hand, three papers reported connectivity changes in *medicated* psychosis patients compared to healthy controls (Baenninger et al., 2017; Di Lorenzo et al., 2015; Gjini et al., 2020). Connectivity increases were found using simultaneous EEG-fMRI between right precuneus and cuneus (Baenninger et al., 2017; a large-sample study), in parietal regions using MEG coherence source imaging (Gjini et al., 2020), and in lower beta mainly between the prefrontal cortex, occipital and parietal cortex using EEG lagged-phase synchronization (Di Lorenzo et al., 2015; a large-sample study). However, the latter authors also reported decreased EEG connectivity in *medicated* psychosis patients compared to healthy controls in the higher beta band between the left frontal cortex and left posterior cingulate cortex, as well as right orbital frontal and right sensory motor areas using EEG lagged-phase synchronization (Di Lorenzo et al., 2015).

In *medication-naïve* first-episode psychosis patients compared to healthy controls, one paper reported decreased EEG connectivity in the high beta band using lagged-phase synchronization (Ramyead et al., 2016), while another study did not find any significant results in beta band EEG connectivity using intracortical-lagged coherence (Lehmann et al., 2014).

3.2.5. Gamma frequency band

The gamma band was examined by six source-level papers. Of these, most papers again found no significant effects (n = 4) using EEG (Andreou et al., 2015a; Kirino et al., 2018) and MEG (Gjini et al., 2020; Rutter et al., 2013). Two papers (Andreou et al., 2015b; Di Lorenzo et al., 2015) reported connectivity increases in *medicated* psychosis patients compared to healthy controls mainly between bilateral frontal and insula regions and left temporal-midline regions using EEG orthogonalized power envelope correlation (Andreou et al., 2015b) and between the right occipital and right prefrontal-parietal-temporal and cingulate cortex using EEG lagged-phase synchronization (Di Lorenzo et al., 2015; a large-sample study).

The only study that compared *medication-naïve* first-episode psychosis patients to healthy controls and examined the gamma frequency found no significant results in EEG connectivity for this frequency band using lagged-phase synchronization (Ramyead et al., 2016).

(b) Longitudinal comparison: Drug-intervention versus placebo in healthy controls (Table 3)

Of all papers included in this review, only one paper was identified that compared a drug-intervention with the dopamine-agonist dexamphetamine vs. placebo in healthy controls using source-level EEG power-power coupling, orthogonalized power envelope correlation and debiased weighted phase lag index functional connectivity analysis. Connectivity decreases were found in the theta, alpha and low beta bands and connectivity increases were found in the gamma band in

Table 2
Association of dopaminergic *medication* with EEG *sensor-level* functional connectivity in cross-sectional comparisons; patients with psychotic disorders versus healthy controls.

Reference	Frequency range (Hz)	Design	Resting-state EEG	Connectivity measure (Ph/A)	Topographic analysis	Patients (f/m); mean age ± SD	Mean antipsychotic medication dose in mg (SD)	Other medication	Summary of findings
(Krukow et al., 2019)	δ (0.5-4) θ (4-8) α1 (8-10) α2 (10-12) β (13-30) γ (30-48)	Cross-sectional	21-channel EEG EC 10 min	Phase lag index (PLI) (Ph)	Between-region	35 FEP (18/17); 21.14 ± 2.95 35 HC (20/15); 21.54 ± 0.70	RE 4.37 (±1.48) Percentage of patients receiving: Olanzapine 65.62%, Risperidone 22.85%, Aripiprazole 11.53%	Not reported	θ: FEP > HC bi F/C/P/O α1: FEP < HC bi F/C/P/O
(Umesh et al., 2018))	γ (71-100)	Cross-sectional	192-channel EEG EC 10 min	Cross-spectral coherence (Welch's averaged periodogram method) (Ph)	Global coherence*	20 SZ (0/20); 29.80 ± 7.68 20 GR (20/0); 29.85 ± 7.35 20 HC (20/0); 29.75 ± 7.71	CPZE 433 ± 215.94 Typical AP n = 4; atypical AP n = 10; typical + atypical AP n = 6	Not reported	γ: SZ + GR < HC (ri T, ri F-O); significance lost with correction for multiple testing *Other findings:* γ spectral power SZ < GR < HC (ML, le P, ri T, O), negative correlation with social anhedonia Step-by-step linear discriminant function analysis accurately classified 85% of 60 cases correctly (100% SZ, 85% GR, 70%HC). Predictors: social anhedonia, ML gamma, ri-F gamma, ri F-T intrahemispheric gamma coherence
(Zaytseva et al., 2018)	δ (1.5–3.9) θ (4–7) α (8–13) β1 (13–20) β2 (20–30) γ (30–40)	Cross-sectional	16-channel EEG EC	Inter- and intrahemispheric coherence (Ph)	Within- and between-region	32 FEP (16/16) 28.91 ± 10.64 32 SA (16/16) 27.59 ± 6.93 40 HC (20/20) 27.63 ± 6.37	FEP: CPZE 227.55 ± 69.1 SA: CPZE 208.62 ± 80.9 10 patients were only medicated for the duration of 1 week at the time of EEG registration	Not reported	Inter-hemispheric α: FEP < HC (ant), β1: FEP < HC (ant), SA < HC (ant) β2: FEP < HC (ant), FEP > HC (P3-P4), SA < HC (ant) γ: FEP < HC (ant), FEP > HC (C3-P4, P3-P4), SA > HC (P3-P4) Intra-hemispheric β1: FEP < HC (ant, midline), FEP > HC (P3-T5), SA < HC (ant), SA > HC (P3- T5, T3-T5) β2: FEP < HC (ant, midline Fp2-Fz), FEP > HC (midline P4-Pz), SA < HC (ant), SA > HC (P3-T5, P4-T6) γ: FEP < HC (ant), FEP > HC (C4-Pz, P3-Pz, P4-Pz)

Abbreviations: δ = delta; θ = theta; α = alpha; β = beta; ω = omega; γ = gamma; A = Amplitude-based; AD = Antidepressant; Ant = Anterior; AP = Antipsychotic; bi = bilateral; C = Central; CPZE = Chlorpromazine equivalents; EC = Eyes closed; EEG = Electorencephalography; EO = Eyes open; f = female; F = Frontal region; FEP = First-episode psychosis; GR = Genetic risk (unaffected siblings); HC = Healthy controls; le = left; m = male; ML = Midline region; O = Occipital region; P = Parietal region; Ph = Phase-based; PLI = Phase lag index; Post = Posterior; RE = Risperidone equivalent; ri = right; SA = Schizoaffective disorder; SD = Standard deviation; SZ = Schizophrenia patients; T = Temporal region; * average connectivity of a region to all other brain regions.

bilateral frontal, central, parietal and occipital areas for the intervention timepoint compared to placebo using power-power coupling (Albrecht et al., 2016). Connectivity increases on the other hand were found in the theta and alpha band in bilateral frontal, central, parietal and occipital areas using debiased weighted phase lag index for the intervention timepoint compared to placebo (Albrecht et al., 2016).

3.3. Association of dopaminergic medication with EEG/MEG sensor-level functional connectivity

(a) Cross-sectional comparisons: Patients with psychotic disorders versus healthy controls (Table 2)

A total of three papers used sensor-level EEG functional connectivity analysis to compare *medicated* patients with psychotic disorders to healthy controls (Krukow et al., 2019; Umesh et al., 2018; Zaytseva et al., 2018) and one paper compared *medication-naïve* first-episode psychosis patients to healthy controls using sensor-level EEG (Bandyopadhyaya et al., 2011). These are reported by frequency band as follows.

3.3.1. Delta frequency band

Two large-sample studies examined the delta band at the sensor level and did not report any significant changes in *medicated* psychosis patients compared to healthy controls using the EEG phase-lag index (Krukow et al., 2019) and EEG inter- and intrahemispheric coherence (Zaytseva et al., 2018).

Table 3
Association of dopaminergic *medication* with EEG *source-and sensor-level* functional connectivity in longitudinal comparisons.

Reference	Frequency range (Hz)	Design	Resting-state EEG	Source localization method	Connectivity measure (Ph/A)	Topographic analysis	N Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
(Albrecht et al., 2016)	δ (1-4) θ (4-8) α (8-12) β1 (12-20) β2 (20-30) γ (30-45)	Longitudinal: Single-dose drug challenge vs. placebo; counterbalanced crossover design (2 sessions, 1 week apart)	32-channel EEG EO 2 min EC 4 min	sLORETA	1. Power-power coupling (PPC) (A) 2. orthogonalized power envelope correlation (PEC) (A) 3. debiased weighted phase lag index (DWPLI) (Ph)	Within- and between region	28 HC (14/14); 25	Oral Dexamphetamine (DEX) 0.45 mg/kg (average amount per person: 32 mg)		*PPC* θ: DEX < placebo bi F/C/P/O α: DEX < placebo bi F/C/P/O (sourced in P) β1: DEX < placebo bi F/C/P/O γ: DEX > placebo bi F/C/P/O *PEC* no differences *DWPLI* θ, α: DEX > placebo bi F/C/P/O *Other findings:* -DEX < placebo spectral power: δ, θ & α in F/C; δ & θ in P/O-T/O; β1 & β2 in F -DEX > placebo spectral power β2 & γ in P/O-T/O
(Cerdán et al., 2005)	δ (2-3) θ1 (4-5) θ2 (6-7) α1 (8-9) α2 (10-12) β1 (13-17) β2 (18-25)	Longitudinal: Typical neuroleptic treatment vs. 8 weeks OLZ treatment	16 channel-EEG EO/EC 1 h	None (sensor-level)	Intrahemispheric (rTRA) and interhemispheric (rTER) correlation (A)	Within- and between-region	14 TR SZ (0/14); 31.5 ± 8.39	Olanzapine after one week wash-out period: - 4 weeks 10 mg/day - 4 weeks 20 mg/day	Pre-washout CPZE 1030 ± 120 mg (haloperidol, trifluoperazine, fluphenazine) and biperiden	θ1: EO post- < pre-treatment rTER δ: EC (ant, ant-post, le F-T), EO (le F-T) post- > pre-treatment rTRA θ1: EO (ant-post, le F-T) post- > pre-treatment rTRA θ2: EO (O, F) post- < pre-treatment rTRA α1: EO (ant, ant-post), EC (ant-post) post- > pre-treatment rTRA β1: EO (ant), EC (ant-post) post- > pre-treatment rTRA β2: EO (ant, le F-T), EC (F-T) post- > pre-treatment rTRA *Other findings:* -57% (8/14) showed 30% symptom reduction after treatment -θ1, θ2 (EO) absolute power: pre-< post-treatment -α1 (EO), β2 (EO&EC)

(*continued on next page*)

Table 3 (*continued*)

Reference	Frequency range (Hz)	Design	Resting-state EEG	Source localization method	Connectivity measure (Ph/A)	Topographic analysis	N Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
										absolute power: pre- > post-treatment

Abbreviations: δ = delta; θ = theta; α = alpha; β = beta; ω = omega; γ = gamma; A = Amplitude-based; ant = anterior; bi = bilateral; C = Central regions; DEX = Dexamphetamine; DWPLI = Debiased weighted phase lag index; EC = Eyes closed; EEG = Electorencephalography; EO = Eyes open; f = female; F = Frontal lobe; HC = Healthy controls; m = male; O = Occipital lobe; P = Parietal lobe; PEC = Power envelope correlation; Ph = Phase-based; post = posterior; PPC = Power-power coupling; rTER = interhemispheric correlation; rTRA = intrahemispheric correlation; SD = Standard deviation; SZ = Schizophrenia patients; TR = Treatment refractory.

3.3.2. Theta frequency band

Overall, two large-sample, sensor-level papers examined the theta band. One paper reported connectivity increases in *medicated* psychosis patients compared to healthy controls between fontal, central, parietal and occipital areas using the EEG phase-lag index (Krukow et al., 2019) and the other reported no significant results using EEG inter- and intrahemispheric coherence (Zaytseva et al., 2018).

3.3.3. Alpha frequency band

Two large-sample sensor-level papers that examined the alpha frequency band converged by reporting connectivity decreases in *medicated* psychosis patients compared to healthy controls between fontal, central, parietal and occipital areas using EEG phase-lag index (Krukow et al., 2019) and EEG inter- and intrahemispheric coherence in anterior regions (Zaytseva et al., 2018).

3.3.4. Beta frequency band

The two papers that examined the beta frequency band at the sensor level (both assessing large samples) reported contrasting results. One of these reported no significant results in *medicated* psychosis patients compared to healthy controls using the EEG phase-lag index (Krukow et al., 2019), while the other reported a complex pattern of both connectivity increases and decreases in anterior and posterior regions using EEG intra- and interhemispheric coherence (Zaytseva et al., 2018) in the high and low beta band (see Table 2 for details).

3.3.5. Gamma frequency band

Three sensor-level papers examined the gamma frequency band in *medicated* psychosis patients compared to healthy controls. One reported no significant results using the EEG phase-lag index (Krukow et al., 2019; a large-sample study), one reported decreased EEG cross-spectral coherence in right temporal and right fronto-occipital regions which, however, did not reach significance after correction for multiple testing (Umesh et al., 2018), and the third paper assessed EEG intra- and inter-hemispheric coherence and reported connectivity increases as well as connectivity decreases in anterior, central and parietal regions (a large-sample study; Zaytseva et al., 2018; see Table 2 for details).

One paper that compared *medication-naïve* first-episode psychosis patients to healthy controls and examined the gamma frequency band, found decreased spectral cross-correlation in parietal-temporal regions in psychosis patients (Bandyopadhyaya et al., 2011).

(b) Longitudinal comparisons: Patients with psychotic disorders pre- versus post-treatment with antipsychotics (Table 3)

Of all papers included in this review, one paper compared pre- and post- antipsychotic drug treatment in treatment refractory psychosis patients using sensor-level EEG intra- and interhemispheric correlation analysis (Cerdán et al., 2005). These authors reported connectivity increases in the delta, low theta, low alpha, low and high beta bands, and connectivity decreases in the high theta band for the post- compared to the pre-treatment time-point. Connectivity increases concerned anterior, anterior-posterior and fronto-temporal regions, connectivity decreases on the other hand concerned occipital and frontal areas (Cerdán et al., 2005).

3.4. Genes affecting the dopaminergic system (*Table 4*)

Within the systematic literature search, two papers were identified that investigated genes affecting dopamine function and compared sensor-level EEG functional connectivity between groups of different allele carriers. One paper examined short vs. long-allele carriers of the dopamine receptor D4 gene (Lee et al., 2012) whereby dopamine binding to D4 receptors of long-allele carriers inhibits cyclic AMP twice as little (Asghari et al., 1995). The paper found that short-allele carriers had increased EEG functional connectivity compared to long-allele carriers in the alpha (between inferior prefrontal and parietal connections) and beta frequency range (parietal and fronto-parietal, low beta;

Table 4
Association of *genes* affecting the dopaminergic system with EEG *sensor-level* functional connectivity in cross-sectional comparisons with healthy controls.

Reference	Frequency range (Hz)	Design	Resting-state EEG	Connectivity measure (Ph/A)	Compared genes	Topographic analysis	Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
(Lee et al., 2011)	δ (1-4) θ (4-8) α (8-12) β1 (12-18) β2 (18-24)	Cross-sectional	18-channel EEG EC 3 min	mutual information (Ph & A)	Catechol-O-methyl-transferase (COMT) gene Val158Met polymorphism 1. Val/Val 2. Val/Met 3. Met/Met	Between-region	- HC Val/Val (136/0); 19-21y - HC Val/Met (104/0); 19-21y - HC Met/Met (14/0); 19-21y	None	Medication free for at least 2 weeks including birth control pill	δ: Val/Val > Val/Met > Met/Met; (le F7-T3, F7-C3) θ: Val/Val > Val/Met > Met/Met (le F3– F4, F7–T3, F7–C3, F7–P3, F3–C3, F3–F7, F4–F8) *Other findings:* -major impact of COMT Val/Met polymorphisms relevant to frontal cortex
(Lee et al., 2012)	θ (4-8) α (8-12) β1 (12-18) β2 (18-24)	Cross-sectional	20-channel EEG EC 3 min	Mutual information (Ph & A)	Dopamine receptor D4 variable number of tandem repeats (VNTR) 1. long-allele carriers (= 4-repeat/> = 4-repeat) 2. short-allele-carriers (< = 4-repeat/< = 4-repeat)	Between-region	- HC short allele (220/0); 19-21y (4/4 n = 129; 2/4 n = 70; 2/2 n = 16; other < = 4/< = 4 n = 5; < = 4/>4 n = 13) - HC long allele (13/0); 19-21y (4/5 n = 6; 4/6 n = 6; 4/7 n = 1)	None	Medication free for at least 2 weeks including birth control pill	α: short- > long-allele (C3-C4, F4-C4) β: short- > long-allele (β C3-C4, F4-C4; β1 F4-C4; β2 F7-F8, F4-T4; F4-C4) α & β aggregated: Short-allele > long-allele connectivity strength at all connections (most prominent: bi F (inf), bi P, ri-lateralized network F-T, F-P, P-T)

Abbreviations: δ = delta; θ = theta; α = alpha; β = beta; ω = omega; γ = gamma; A = Amplitude-based; bi = bilateral; C = Central; COMPT = Catechol-O-methyl-transferase; EC = Eyes closed; EEG = Electroencephalography; EO = Eyes open; f = female; F = frontal; HC = Healthy control; HN = Hippocampal network; inf = inferior; le = left; m = male; Met = Methionin; P = Parietal; Ph = Phase-based; ri = right; SD = Standard deviation; SFG = Superior frontal gyrus; Sup = Superior; T = Temporal; Val = Valin.

fronto-parietal, high beta; inferior prefrontal, fronto-temporal, fronto--parietal) using mutual information theory. No significant results were found for the theta band.

Another paper by the same authors examined the Catechol-O-methyl-transferase (COMT) gene Val158Met polymorphism (Lee et al., 2011). COMT plays an important role in the metabolism of catecholamines, such as dopamine, and was postulated to be one of the main pathways of dopamine clearance in the prefrontal cortex (Sesack et al., 1998). The Val variant is thought to lead to increased clearance and thus to reduced dopamine activity compared to the Met variant. Lee et al. (2011) found increased EEG functional connectivity measured at the sensor level using the time-frequency mutual information method in Val/Val compared to Val/Met and Met/Met carriers in the delta frequency range located at left fronto-temporal and fronto-central sensors and in the theta band located at left frontal, fronto-central and fronto-temporal sensors.

4. Discussion

In the past decades, a large body of research has collected evidence for both the dysconnectivity hypothesis and the dopamine hypothesis in psychotic disorders. The findings summarized in this systematic review focus on the association of conditions or agents affecting the dopamine system with brain spatial resting-state functional connectivity assessed with EEG and MEG. We included cross-sectional as well as longitudinal studies comparing patients with psychotic disorders to healthy controls or pre- and post-treatments. We divided the results into two distinct analysis methods, those assessing connectivity at the level of brain electrical sources (source level), and those using sensor-level methods to assess functional connectivity at the 2D surface of the scalp.

Most identified papers used cross-sectional designs comparing patients with psychotic disorders to healthy controls. We chose to include these papers in our review if they reported results from homogeneous samples regarding medication status (i.e. all patients medicated, or all medication-naïve). We did so to enable indirect comparisons of antipsychotic medication effects, given that very few papers directly addressed the effects of dopaminergic agents in cross-sectional or longitudinal designs.

A heterogeneous pattern of connectivity increases, decreases, as well as no significant effects was reported in medicated patients with psychotic disorders compared to healthy controls in all frequency bands, ranging from delta through to gamma for both source-level and sensor-level analysis methods. Reported changes in brain functional connectivity concerned widespread areas including frontal, parietal, occipital, temporal and midline regions with overlapping as well as diverging results. Similarly, heterogeneous results were found by the three papers examining medication-naïve patient groups compared to healthy controls with connectivity increases in delta and connectivity decreases in alpha in one (Lehmann et al., 2014), connectivity decreases in beta in the other (Ramyead et al., 2016), and connectivity decreases in gamma in the third paper (Bandyopadhyaya et al., 2011) in overlapping areas.

Thus, no definite conclusions can be drawn across the 16 studies that compared medicated or medication-naïve patients to healthy controls.

Table 5
EEG *sensor- and source-level* functional connectivity with cross-sectional comparisons between *medication-naïve* patients with psychotic disorders and healthy controls.

Reference	Frequency range (Hz)	Design	Resting-state EEG	Source localization method	Connectivity measure	Topographic analysis	N Patients (f/m); mean age ± SD	Mean antipsychotic medication dose (SD)	Other medication	Summary of findings
(Bandyopadhyaya et al., 2011)	γ (30-100)	Cross-sectional	128-channel EEG EC	None (sensor-level	Spectral cross-correlation (Ph)	Between-region	20 SZ (0/20); 28.56 ± 5.52 20 FDR (0/20); 33.97 ± 9.97 20 HC (0/20); 28.77 ± 5.59	None (medication naïve)	n.a.	γ: SZ < HC (P-T), FDR < HC (F- P-T), positive correlation (T) & general psychopathology / anergia *Other findings:* γ power differences (le T) FDR vs. HC, SZ > HC (C, le & ri T, ri F), positive correlation with anergia (le P), depression & activation symptoms (C ri F)
(Lehmann et al., 2014)	δ (1.5-6) θ (6.5-8) α1 (8.5-10) α2 (10.5-12) β1 (12.5-18) β2 (18.5-21)	Cross-sectional	19 channel EEG EC 3-4 min	eLORETA	Intracortical lagged coherence (Ph)	Between-region	30 FEP (12/18); 23.73 ± 5.51 67 HC (35/32); 26.28 ± 4.84	None (medication naïve)	n.a.	δ: FEP > HC ri F-P and F-T α1: FEP < HC F-P and F-T Principal differences in the antero-posterior direction
(Ramyead et al., 2016)	δ (1.5-4) θ (4-8) α1 (8-10) α2 (10-13) β1 (13-21) β2 (21-30) γ (30-50)	Cross-sectional	19-channel EEG ~ EC 20 min (clinical EEG protocol)	eLORETA	Lagged phase synchronization (LPS) (Ph)	Between-region	31 FEP (13/18); 30.8 ± 8.92 29 HC (14/15); 22.4 ± 5.02	None (antipsychotic and mood-stabilizer medication naïve)	AD n = 4 BZP n = 8	β1/β2: FEP < HC stronger decrease with increasing Euclidean distance in FEP compared to HC *Other findings:* - Stronger decrease in LPS with increasing distance in patients with high positive symptom load - CSD analyses: θ: FEP < HC in le ACC α: FEP < HC in le MFG β2: FEP > HC in bilateral SFG γ: FEP > HC in le MFG

Abbreviations: δ = delta; θ = theta; α = alpha; β = beta; ω = omega; γ = gamma; A = Amplitude-based; ACC = Anterior cingulate cortex; AD = Antidepressants; BZP = Benzodiazepines; C = Central regions; EC = Eyes closed; EEG = Electorencephalography; eLORETA = exact low-resolution brain electromagnetic tomography; EO = Eyes open; f = female; F = Frontal lobe; FDR = First degree relative; FEP = first-episode psychosis; HC = Healthy controls; le = left; LPS = Lagged phase synchronization; m = male; MFG = Middle frontal gyrus; O = Occipital lobe; P = Parietal lobe; Ph = Phase-based; ri = right; SD = Standard deviation; SFG = Superior frontal gyrus; SZ = Schizophrenia patients; T = Temporal lobe.

Table 6
Quality assessment categories, range and quality scoring.

Category / range	0	1	2
Assessment of antipsychotic medication effects	None	Cross-sectional	Longitudinal
Final sample size	<12	12-20	>20
Inclusion criteria	Not reported	Partly reported	Reported
Exclusion criteria	Not reported	Partly reported	Reported
Gender	Not reported	.	Reported
IQ/ educational level	Not reported	Parental education reported	Reported
Diagnostic instrument	Not reported	Procedure reported without instrument	Reported
Duration of illness /age of onset	Not reported	Qualitative (e.g. FEP, chronic) / n.a.*	Quantitative (months/years)
Comorbid diagnosis	Not reported	n.a.*	Reported
Other medication	Not reported	.	Reported
EEG/MEG sets/ segments used for analysis	Not reported		Reported

Quality Score: Max 22. H**igh** (80-100%) >18; **moderate-high** (60-79%) 14-17; **moderate** (40-59%) 9-13; **moderate-low** (20-39%) 5-8; **low** (0-19%) <5.
Note: *not applicable if sample consists of healthy subjects only.

We identified no studies that directly compared medicated to medication-naïve patients, and only two papers directly examined the effect of agents acting on the dopamine system in a longitudinal design with pre- and post- measurements. Their findings could not be synthesized into a coherent framework either due to large differences in their designs: One drug-challenge study assessed source-level connectivity measures in healthy participants (Albrecht et al., 2016), while the other study investigated changes in sensor-level connectivity in patients with treatment-resistant psychotic disorders following antipsychotic medication treatment (Cerdán et al., 2005).

The heterogeneity of results could be due to the wide range of methods used with different seeds and brain areas in focus. While some papers focused on specific regions like the DMN (Baenninger et al., 2017) for example, others assessed pairwise connections in whole-brain analyses (e.g., Andreou et al., 2015a, 2015b; Di Lorenzo et al., 2015; Lehmann et al., 2014), while others yet again analyzed voxel-to-whole-brain connectivity strength (e.g., Gjini et al., 2020; Hinkley et al., 2011). Given that the term 'dysconnectivity' refers to abnormal functional integration among brain regions rather than purely decreased or increased functional connections (Stephan et al., 2009), the observed difference in analysis methods could explain the heterogeneity of results.

Further methodological constraints need to be considered when assessing these heterogeneous connectivity patterns. In the following, we address the most important challenges and pitfalls throughout the 20 studies included in this systematic review.

4.1. Connectivity analysis methods

A variety of analysis methods were used for both source- as well as sensor-level estimates. Within the group of 13 papers that used source-level analysis, ten different functional connectivity measures were applied; within the group of seven papers that conducted analyses at the sensor level, the respective number of connectivity measures was five. One, but not the only, relevant distinction is between phase coherence measures and amplitude correlation measures of connectivity. These two types of connectivity measures have been suggested to serve distinct processes (He et al., 2019). Coherence measures based on the phase alignment of oscillatory waves can reflect global state changes of the brain such as sleep, are affected by stimulus context or cognitive setting and can be used to capture the communication between separate neural populations within a network (Supp et al., 2011). Such measures include for example phase locking, lagged phase coherence, imaginary coherence and multivariate interaction measures. On the other hand, correlation measures that are mainly based on the covariance of the amplitude or power envelopes of the underlying oscillatory waves are well suited to capture slow fluctuations of up to 0.1 Hz such as the BOLD signal in fMRI (Engel et al., 2013), are largely dependent on anatomical connectivity (Wang et al., 2013) and can be used to determine the availability of neural network populations.

An illustration of the potential effects on results are findings by Andreou et al., who found increased connectivity in the theta band in medicated patients compared to controls using the multivariate interaction measure (a phase-based measure of coherence) (Andreou et al., 2015a), but increased connectivity in the gamma band using a different connectivity measure (orthogonalized power envelope correlation, an amplitude-phased measure) (Andreou et al., 2015b). Similarly, Albrecht et al. (2016) found no significant effects of dexamphetamine drug challenge in healthy subjects when the measure of connectivity was orthogonalized power envelope correlation, but observed increased interactions in theta- and alpha-band following the drug challenge when using the debiased weighted phase lag index. However, it is difficult to assess to what extent the type of connectivity measure used (i.e., phase- or amplitude-based) may have driven differences in findings between studies, as studies using connectivity measures of the same type often reported quite divergent results (see Tables 1–5).

Other methodological choices may have also affected the heterogeneous findings. As outlined in the introduction, spurious connectivity patterns may emerge as a consequence of signal mixing due to volume conduction and are influenced by the use of a common reference (Nolte et al., 2004) without appropriate correction for these effects.

4.2. Methodological differences in EEG recording and preprocessing

Differences in data acquisition and preprocessing protocols in EEG analysis may further limit comparability between the included papers. Eyes open and eyes closed are two applied states during data acquisition procedures and have been shown to be a strong determinant of EEG temporal dynamics (Zanesco et al., 2020). In an fMRI study, eyes closed resting-state was associated with visual cortex activation whilst eyes open was associated with ocular motor system activity (Marx et al., 2004). In the longitudinal drug-challenge paper by Albrecht et al. (2016) changes in power-power coupling, orthogonalized power coupling and debiased weighted phase lag index through dexamphetamine were less pronounced in the eyes-open resting-state condition compared to eyes-closed. On the other hand, Cerdán et al. (2005) only found decreased interhemispheric correlation in post compared to pre-olanzapine treatment in the eyes-open, and not in the eyes-closed condition. Both eyes-closed and eyes-open measures were applied in the included studies and thus, these confounding brain activation patterns need to be taken into account when directly comparing results.

Contamination of electrophysiological signals from cranial and muscle activity (Carl et al., 2012), applied data selection and smoothing parameters (Michel and Koenig, 2018), as well as different applied filtering techniques might further seriously change the appearance of signals and affect the obtained results (Widmann et al., 2014). These preprocessing differences can therefore not be ignored to account for results heterogeneity. Additionally, the use of different reference channels has been shown to further influence connectivity measures. As Olejarczyk and Jernajczyk (2017) demonstrated, the use of different reference electrode techniques led to diverging findings in schizophrenia patients compared to healthy controls.

Furthermore, different definitions for all frequency ranges were applied across the 20 included papers. For example, delta was defined as

Table 7
Quality assessment and rating of the included studies.

Author (Year)	Assessment of antipsychotic medication effects	Sample size	Inclusion criteria	Exclusion criteria	Gender	IQ/ education	Diagnostic instrument	Duration of illness /age of onset	Comorbid diagnosis	Other medication	EEG/MEG segments used for analysis	Sum of scores	Category
(Albrecht et al., 2016)	2	2	1	2	2	0	0	n.a.	n.a.	0	2	13	Moderate
(Andreou et al., 2015a)	1	2	2	2	2	2	2	1	2	2	2	20	High
(Andreou et al., 2015b)	1	2	1	2	2	0	2	2	0	2	2	16	Moderate-high
(Baenninger et al., 2017)	1	2	0	2	2	2	2	0	0	0	2	13	Moderate
(Bandyopadhyaya et al., 2011)	1	2	2	2	2	2	2	0	0	0	0	13	Moderate
(Cerdán et al., 2005)	2	1	1	2	2	2	2	2	2	2	2	20	High
(Di Lorenzo et al., 2015)	1	2	2	2	2	2	2	2	0	2	0	17	Moderate-high
(Gjini et al., 2020)	1	1	2	2	2	0	2	0	0	0	0	10	Moderate
(Hinkley et al., 2011)	1	2	2	0	2	1	2	1	2	0	2	15	Moderate-high
(Kirino et al., 2018)	1	2	1	2	2	2	2	2	0	0	0	14	Moderate-high
(Krukow et al., 2019)	1	2	2	2	2	2	2	2	0	2	2	19	High
(Lee et al., 2011)	1	2	1	0	2	2	1	n.a.	n.a.	2	0	13	Moderate
(Lee et al., 2012))	1	2	1	2	2	0	1	n.a.	n.a.	2	2	15	Moderate-high
(Lehmann et al., 2014)	1	2	0	0	2	0	0	0	0	0	2	7	Moderate-low
(Ramyead et al., 2016)	1	2	2	2	2	2	2	1	0	2	0	16	Moderate-high
(Razavi et al., 2013)	1	2	1	2	2	0	2	2	2	2	2	18	High
(Rutter et al., 2013)	1	2	2	2	2	0	0	0	0	0	2	11	moderate
(Umesh et al., 2016)	1	2	1	1	2	0	2	2	0	0	2	13	Moderate
(Umesh et al., 2018)	1	2	1	2	2	2	2	1	2	0	2	17	Moderate-high
(Zaytseva et al., 2018)	1	2	1	1	2	2	2	2	0	0	2	15	Moderate-high

1.5−6 Hz in Lehmann et al. (2014), which overlapped with the frequency range defined as theta (3.5−6.25 Hz) in Razavi et al. (2013) and low theta (4−5 Hz) in Cerdán et al. (2005). Similarly, the definition of the alpha band (6−14 Hz) in Hinkley et al. (2011) overlapped with theta (4−8 Hz) and low beta (12−20 Hz) in e.g., Baenninger et al. (2017); Di Lorenzo et al. (2015); Lehmann et al. (2014).

A final source of variance in studies assessing source-level connectivity is the inverse method applied. It has been shown that current source density and beamforming approaches differ in terms of accuracy, sensitivity and specificity of source localization (Halder et al., 2019).

4.3. EEG vs. MEG

Whilst both electroencephalography (EEG) and magnetoencephalography (MEG) offer high temporal resolution to measure neural activity, each of these recording techniques has its distinct characteristics and advantages. EEG is better suited to measure long-range connectivity and has a more precise localization of brain sources when dipoles are radially oriented (Nunez and Cutillo, 1995). However, it is more prone to volume conduction effects than MEG (Winter et al., 2007). MEG on the other hand is better suited for short-range connectivity and identifies brain sources with tangentially oriented dipoles better (Srinivasan et al., 2007). Consequently, the exact method used may also have affected comparability of results. As such, the three included MEG studies reported either no significant results between medicated patients and healthy controls (Rutter et al., 2013) or reported only differences at the level of average brain connectivity of single regions (Gjini et al., 2020; Hinkley et al., 2011). In contrast, reported differences in EEG studies (Andreou et al., 2015a, 2015b; Baenninger et al., 2017; Di Lorenzo et al., 2015) concerned long-range connectivity between distinct brain regions (e.g., between fronto-pariental-temporal and occipital regions). With MEG and EEG being said to better capture short- and long-range connectivity respectively, the two methods might have been sensitive to different spatial distributions.

4.4. Sample sizes

Larger sample sizes lead to increased statistical power. Studies with high power are more likely to find true effects, e.g., correlation coefficients are estimated with a higher precision when sample sizes are increased (Masouleh et al., 2019). The majority of the included studies of this review suffer from small sample sizes. A total of 12 out of 20 studies used participant groups with 20 or less participants, six analyzed sample sizes between 28 and 35 and only two used large sample sizes of 42 and 78. Small, insufficiently powered studies might not be able to reveal truly existing effects and are at greater risk of bias through single outliers. Multicenter research projects allow for the inclusion of large patient samples and could solve the problem of small and inadequately powered studies.

4.5. Antipsychotic medication

Antipsychotic medication doses of patients, where reported, differed largely between the included studies from a chlorpromazine equivalent dose of 188.6 (SD 181.0) to 878.5 (SD 614.3). The heterogeneity of medication dose and possibly other aspects such as duration of treatment are likely to have influenced the presented EEG/MEG brain functional connectivity results. It has been reported that antipsychotic medication intake affects the theta frequency band in spectral qEEG (Galderisi et al., 2009) and EEG source density (Tislerova et al., 2008). fMRI studies on the other hand reported structural and functional brain alterations as a result of antipsychotic medication (Navari and Dazzan, 2009; Scherk and Falkai, 2006; Smieskova et al., 2009). In a MRI meta-analysis, patients on antipsychotic medication were more likely to show grey matter volume abnormalities in anterior cingulate and left insular clusters (Radua et al., 2012), decreases in both grey matter (Fusar-Poli et al., 2013) and white matter volumes (Ho et al., 2011), and there is evidence that a few weeks of antipsychotic medication can already modulate the anterior cingulate response (Lahti et al., 2004; Snitz et al., 2005).

A systematic review on the effects of psychotropic drugs on EEG draws to attention that individual drugs affect EEG measurements in different ways (Aiyer et al., 2016). Clozapine and its effects on EEG deserve special mention in this context: Of all typical and atypical drugs in the included studies, clozapine was shown to have the greatest effect on EEG slowing in a recent systematic review (Jackson and Seneviratne, 2019). Furthermore, increase in delta and theta frequencies (Joutsiniemi et al., 2001; Tislerova et al., 2008) and decrease in lower alpha and higher beta frequencies were found in patients receiving clozapine compared to medication-naïve patients (Tislerova et al., 2008). In the present review however, only three of the included papers listed the specific antipsychotic agents administered (Andreou et al., 2015a, 2015b; Krukow et al., 2019) and only one paper listed clozapine explicitly as an exclusion criterion (Gjini et al., 2020). Therefore, it remains unknown whether clozapine specifically might have affected the present results.

4.6. Illness duration

Duration of illness could be a further confounding factor with short-term vs. long-term illness effects besides long-term medication effects on the brain (see above). This was directly examined by an EEG study that found decreased delta and gamma with widespread distribution, increased theta in prefrontal, cingulate cortex, parietal and temporal regions and a complex pattern of increased and reduced higher beta when comparing patients with long vs. short illness durations (Di Lorenzo et al., 2015). Included papers studied first-episode psychosis patients (n = 6) as well as patients with an established psychosis (n = 11). Therefore, illness duration can be supposed to have acted as confounding factor between study populations.

4.7. Sex and age differences

The majority of papers studied samples with an unbalanced distribution of male and female participants, with female participants being largely underrepresented (with a factor 2.5 of 139 females to 346 males across all studies) or not included at all (n = 4). This seriously questions the generalizability of the included papers as epidemiological studies report clearly lower men-to-women indices risk ratios from 1.15 (van der Werf et al., 2014) to 1.4 (Aleman et al., 2003; McGrath et al., 2008). Female patients with psychotic disorders have a later age at illness onset than men, putatively due to the psycho-protective effect of estrogens (Riecher-Rossler et al., 2018). There are also sex differences in symptomatology, comorbidity, and neurocognition in patients with psychotic disorders, which appear to reflect differences in the general population (Riecher-Rossler et al., 2018). Although one of the four studies that did not include any female participants (Bandyopadhyaya et al., 2011) reasoned that such sex differences justified inclusion of male participants only, it can be conversely argued that increased homogeneity comes at a cost for generalizability and therefore, balanced sample distributions should be considered for future studies.

Moreover, large age differences were observed across the 20 included studies with reported means between 21.14–40.30 years of age in patient groups. Throughout childhood and adolescence, human brain development is characterized by increasing caliber, myelinization of axons and cortical pruning (Lebel and Deoni, 2018; Petanjek et al., 2011). Brain changes throughout development include decreases in cortical volume, thickness and surface area (Tamnes et al., 2017), changes in white matter volume and microstructure (Lebel and Deoni, 2018) in healthy individuals. Cognitive decline, which is seen to occur with increasing age, is suggested to be more prominent in patients than healthy controls for some cognitive functions (Fucetola et al., 2000).

With that, age cannot be discarded as confounding factor and ideally needs to be considered in statistical analyses.

4.8. Resting-state measure

It could also be debated whether resting-state is superior over task-based measures and valid enough to characterize changes to neural networks induced by psychopathology. However, it has been shown that spontaneous EEG activity influences the processing of incoming stimuli (Britz et al., 2009; Hipp et al., 2011). Therefore, investigation of the resting-state is a very promising complement to task-based studies, since it allows a view into the underpinnings of cognitive and perceptual disturbances in psychosis. Furthermore, well-known confounders of amotivation and impaired task performance in patients are eliminated through resting-state measurements. With the EEG resting-state research field being much younger than event-related analyses, it holds further potential for improvement and with that could have contributed to the heterogeneity of results.

5. Conclusion

Several studies report abnormalities in resting-state EEG/MEG brain functional connectivity patterns in patients with psychotic disorders compared to healthy controls. However, the evidence summarized in this systematic review does not allow for any definite conclusions regarding dopaminergic contributions to the direction, spatial pattern, or nature of these abnormalities. We observed significant heterogeneity in sample characteristics and analysis methods which limits comparability of findings across studies. Studies using longitudinal designs in large patient samples are needed to directly study and understand the association of antipsychotic medication with neural network changes over time as well as potential predictors of response, and to ultimately improve treatment response of patients with psychotic disorders. Further suggestions for future research include an increased focus on generalizability and reproducibility by systematically addressing confounding factors and the development of standard consensus analysis pipelines. The publication of data in open-access repositories might prove very valuable in this regard by allowing multiple analyses of data that may help trace the sources of heterogeneity in findings.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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2.2 Publication 2: EEG Microstate Differences in Medicated vs. Medication-Naïve First-Episode Psychosis Patients

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EEG Microstate Differences in Medicated vs. Medication-Naïve First-Episode Psychosis Patients

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There has been considerable interest in the role of synchronous brain activity abnormalities in the pathophysiology of psychotic disorders and their relevance for treatment; one index of such activity are EEG resting-state microstates. These reflect electric field configurations of the brain that persist over 60–120 ms time periods. A set of quasi-stable microstates classes A, B, C, and D have been repeatedly identified across healthy participants. Changes in microstate parameters coverage, duration and occurrence have been found in medication-naïve as well as medicated patients with psychotic disorders compared to healthy controls. However, to date, only two studies have directly compared antipsychotic medication effects on EEG microstates either pre- vs. post-treatment or between medicated and unmedicated chronic schizophrenia patients. The aim of this study was therefore to directly compare EEG resting-state microstates between medicated and medication-naïve (untreated) first-episode (FEP) psychosis patients (mFEP vs. uFEP). We used 19-channel clinical EEG recordings to compare temporal parameters of four prototypical microstate classes (A–D) within an overall sample of 47 patients (mFEP $n = 17$; uFEP $n = 30$). The results demonstrated significant decreases of microstate class A and significant increases of microstate class B in mFEP compared to uFEP. No significant differences between groups were found for microstate classes C and D. Further studies are needed to replicate these results in longitudinal designs that assess antipsychotic medication effects on neural networks at the onset of the disorder and over time during illness progression. As treatment response and compliance in FEP patients are relatively low, such studies could contribute to better understand treatment outcomes and ultimately improve treatment strategies.

Keywords: electroencephalography, resting-state, schizophrenia, antipsychotic, neuroleptic, untreated, unmedicated, pathophysiology

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INTRODUCTION

Delusions, hallucinations, disorganized speech, catatonic behavior, and negative symptoms form the core of psychotic disorders [DSM-5®, (1)]. The lifetime prevalence of psychotic disorders is estimated at 0.75% (2). Compared to the general population, patients' life expectancy is estimated to be shortened by 15–20 years due to increased physical morbidity (3). Patients' everyday functioning

such as independent living, productive activity, and social functioning is often impaired, leading to high costs beyond their medical treatment (4). Good functional outcomes were found to be related to shorter duration of untreated psychosis (5) which calls for timely and effective treatment at an early illness stage. However, discontinuation rates within 18 months of antipsychotic treatment due to inefficiency or intolerable side effects were observed to be relatively high (64–82%) in psychotic disorders (6) with a recovery rate estimated at only 13.5% (7). This clearly calls for more research on antipsychotic medication and how EEG markers and neural networks differentiate between medicated and unmedicated patients with psychotic disorders.

Electroencephalography (EEG) is one method in neuroscience research that offers several advantages. Apart from being inexpensive, non-invasive, and easy to implement, EEG can capture the fast-changing dynamics of neuronal networks with high temporal resolution in frequency bands ranging from 1 Hz to up to 200 Hz (8, 9). This allows EEG to depict coupling patterns of neural activity that might not be captured by functional Magnetic Resonance Imaging (10). There is a large body of research that has studied neuronal network disruptions in psychotic disorders using EEG methods and extensive reviews exist on the topic (11–14).

The term "resting-state" refers to intrinsic patterns of the awake state in which participants are not performing an explicit mental or physical task (15) and are postulated to show the underlying intrinsic mechanisms of the brain which influence stimulus processing as well as behavioral phenomena (16). An accumulation of evidence has shown that EEG resting-state microstates are a suitable tool to study the temporal dynamics of resting-state brain networks: EEG microstates are spatial configurations of scalp global field power that remain stable for a short period of time (60–120 ms) and occur several times per second (17, 18). These short-lasting, non-overlapping configurations of brain electric states have been divided into four prototypical microstate classes A, B, C, and D that each have a different orientation of the scalp-electric field (19): Microstate A has a left occipital to right frontal orientation, microstate B a right occipital and left frontal, microstate C a symmetric occipital to prefrontal and microstate D a symmetric frontocentral to occipital orientation (17). These four classes explain 65–84% of EEG data variance (20) and were shown to have high test-retest reliability and cross-method consistency (21). The microstate classes are described by three statistical parameters; the duration of each class in milliseconds, mean number of occurrence per second and percentage of time covered by each class (17).

Microstates were hypothesized to be the fundamental building blocks of human information processing and were found to differ across sex groups (22), over the course of development (17, 22) and between different brain states such as sleep and wakefulness (23, 24). Studies using simultaneous EEG-fMRI methods have correlated microstate classes to different resting-state networks (25, 26). Furthermore, abnormal patterns have been described in various mental conditions (27–30), most notably in psychotic disorders: Microstate differences across all classes were found for medicated (31–35), as well as medication-naïve patients with psychotic disorders (30, 36–38) compared to healthy controls, as well as patients in the high-risk state of psychosis (31, 36, 39). Two recent meta-analyses found increased occurrence of microstate C and decreased duration of microstate D to be consistently reported across studies in medicated as well as medication-naïve patients with psychotic disorders (40, 41).

So far, it is not clear whether and how antipsychotic medication treatment plays a role in EEG resting-state microstate abnormalities in patients with psychotic disorders. Antipsychotics have been shown to modulate neural networks in fMRI studies (42, 43) and to have effects on microstate parameters by increasing the mean duration of all microstate classes in healthy individuals (44). However, so far only two studies investigated the effects of antipsychotic treatment on EEG microstates in patients with psychotic disorders. A cross-sectional study from more than two decades ago with chronic schizophrenia patients reported antipsychotic treatment to be negatively correlated with microstate duration in a dose-dependent way and average microstate duration was longer in unmedicated than medicated patients (45). Moreover, increased duration of microstate classes A and D, and decreased occurrence of microstate class C was reported in responders vs. non-responder schizophrenia patients following 2–8 week treatment with antipsychotics in a longitudinal design (37). However, the latter findings were based on a small sample size ($n = 14$) and have not yet been replicated.

The present study therefore aimed to investigate the effects of antipsychotic treatment on EEG resting-state microstate parameters by comparing medicated first-episode psychosis patients (mFEP) to a control group of patients who were medication-naïve (untreated first-episode psychosis; uFEP). Our comparisons were set out to investigate differences in parameters of microstate classes A-D that might be attributed to the medication status of the two patient groups beyond the effect of the disorder. As the results of previous studies have been inconsistent so far, we based our study hypotheses on a recent study by our group (36) in which we suggested that microstate A and B may be state markers for psychotic disorders. We therefore hypothesized antipsychotics to associate with microstate A and B and these microstates to differentiate the two patient groups.

METHODS

The data used in this paper was collected in the FePsy project (***Früherkennung von Psychosen***; Early Detection of Psychoses) of the University of Basel Psychiatric Clinics (UPK) during the time period from 2000–2013. The aim of the FePsy project was to improve early detection and intervention of psychosis. The study was approved by the local ethics committee and in accordance with the Declaration of Helsinki. Riecher-Rössler et al. (46, 47) provide a comprehensive overview of the FePsy study design.

Participants

All first-episode psychosis (FEP) patients included in the present paper were help-seeking consecutive referrals to the FePsy clinic at the psychiatric outpatient department of the University of Basel Psychiatric Clinics (UPK). Upon inclusion in the FePsy study, written informed consent was given by all participating

TABLE 1 | Sample demographics.

	mFEP	uFEP			
	***n* = 17**	***n* = 30**	**t/χ2**	***p***	***d***
Sex (M:F)	13:4	19:11	0.862	0.353	–
Age at diagnosis (years) (mean [SD])	27.68 (5.1)	28.63 (7.5)	−0.517*	0.608	0.148
BPRS (mean [SD])	47.66 (7.15)	53.68 (10.84)	−1.70	0.10	0.66
Total score					
Depression/anxiety	9.45 (3.24)	11.70 (4.39)	−1.54	0.13	0.58
Psychosis/thought disturbance	10.64 (2.46)	12.13 (3.37)	−1.33	0.19	0.50
Negative symptoms	5.41 (2.20)	5.72 (2.76)	−0.34	0.74	0.12
Activation	6.73 (3.16)	7.28 (3.50)	−0.45	0.65	0.16
Duration of illness (months) (mean [SD])	24.83 (22.61)	23.77 (35.36)	0.11	0.91	0.04
Comorbidities (ICD-10)			–	0.81**	–
F10-F19[1]	0	1			
F30-F39[1]	5	7			
F40-F49[1]	1	0			
F60-F69[1]	0	1			
CPZ equivalent dose (mean [SD])	210.29 (262.71)	n/a	–	–	–
Further medication			–	1**	–
Antidepressants	2	4			
Anxiolytics	4	7			
Mood stabilizers	0	0			
Other	1	2			
Current drug use			–	0.44**	–
Yes	11	20			
No	5	4			
Current alcohol use			–	1**	–
Yes	8	12			
No	8	12			
Cannabis use			–	0.52**	–
1)Earlier					
Yes	9	18			
No	7	5			
2)Currently					
Yes	6	9			
No	11	18			
Verbal IQ* (mean [SD])	103 (16.04)	107.28 (14.34)	−0.84	0.41	0.28
School education (years) (mean [SD])	10.71 (3.25)	11.20 (3.22)	−0.50	0.62	0.15
Education level			–	0.84**	–
Education ongoing	2	1			
Primary school	1	1			
Secondary school	9	11			
Upper/specialized secondary school	1	2			
High school without completion	0	2			
High school	3	6			
Current employment			–	0.71**	–
Yes	3	6			
No	13	17			
EEG total analysis time (seconds) (mean [SD])	300.30 (74.83)	299.20 (44.72)	0.055	0.957	0.018
EEG explained variance (%) (mean [SD])	77.43 (3.36)	77.36 (3.61)	0.073	0.942	0.020

*mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients; BPRS, Brief Psychiatric Rating Scale; CPZ, Chlorpromazine; SD, standard deviation; d, Cohen's d effect size; *assessed with the German version of the multiple choice vocabulary test [Mehrfach-Wortschatz-Test; (52)]; **Fischer's exact test applied. [1]F10-F19, Mental and behavioral disorders due to psychoactive substance use; F30-F39, Mood [affective] disorders; F40-F49, Neurotic, stress-related and somatoform disorders; F60-F69, Disorders of adult personality and behavior. Significance level is 0.05.*

patients. The Basel Screening Instrument for Psychosis [BSIP; Riecher-Rössler et al. (47, 48)] was used to determine the FEP status, diagnostics were made according to ICD-10 (49), the Brief Psychiatric Rating Scale [BPRS; (50, 51)] was applied to assess patients' symptom severity, and the German version of the multiple choice vocabulary test [Mehrfach-Wortschatz-Test; (52)] was used to assess verbal IQ. The status of medication-naïve was defined by the absence of any lifetime antipsychotic treatment and illness duration for both groups was calculated based on the patient's reports in hindsight of the very first occurrence of psychotic symptoms with sufficient severity. As **Table 1** displays, intake of other medication did however occur in the uFEP group.

Exclusion criteria were applied as follows; (1) age < 18 years; (2) insufficient knowledge of German; (3) IQ < 70; (4) serious medical or surgical illness; (5) previous episode of psychosis due to substance abuse, and (6) psychotic symptomatology within a clearly diagnosed affective or borderline personality disorder.

EEG Recording and Pre-processing

A standard clinical EEG protocol of 20 min (incl. resting-state, eyes opening, photostimulation, and hyperventilation) was recorded by a trained lab assistant using 19 gold cup electrodes (Nicolet Biomedical, Inc.) of the International 10–20 system and referenced to linked ears. Participants were comfortably seated in a quiet room. The first 8 min of the entire clinical EEG recording corresponded to a resting-state eyes-closed recording which was used for the present analysis. During this, participants were asked to open their eyes for 6 s every 3 min to avoid drowsiness. When behavioral or EEG signs of drowsiness (e.g., slow rolling eye movements, alpha drop-out, increased beta, or theta activity) occurred, participants were asked to open their eyes. The sampling rate was 256 Hz and electrode impedances were always kept below 5 kΩ.

Brain Vision Analyzer (Version 2.0, Brain Products GmbH, Munich, Germany) was used for offline pre-processing. After bandpass (IIR; 0.5–70 Hz) and notch (50 Hz) filters were

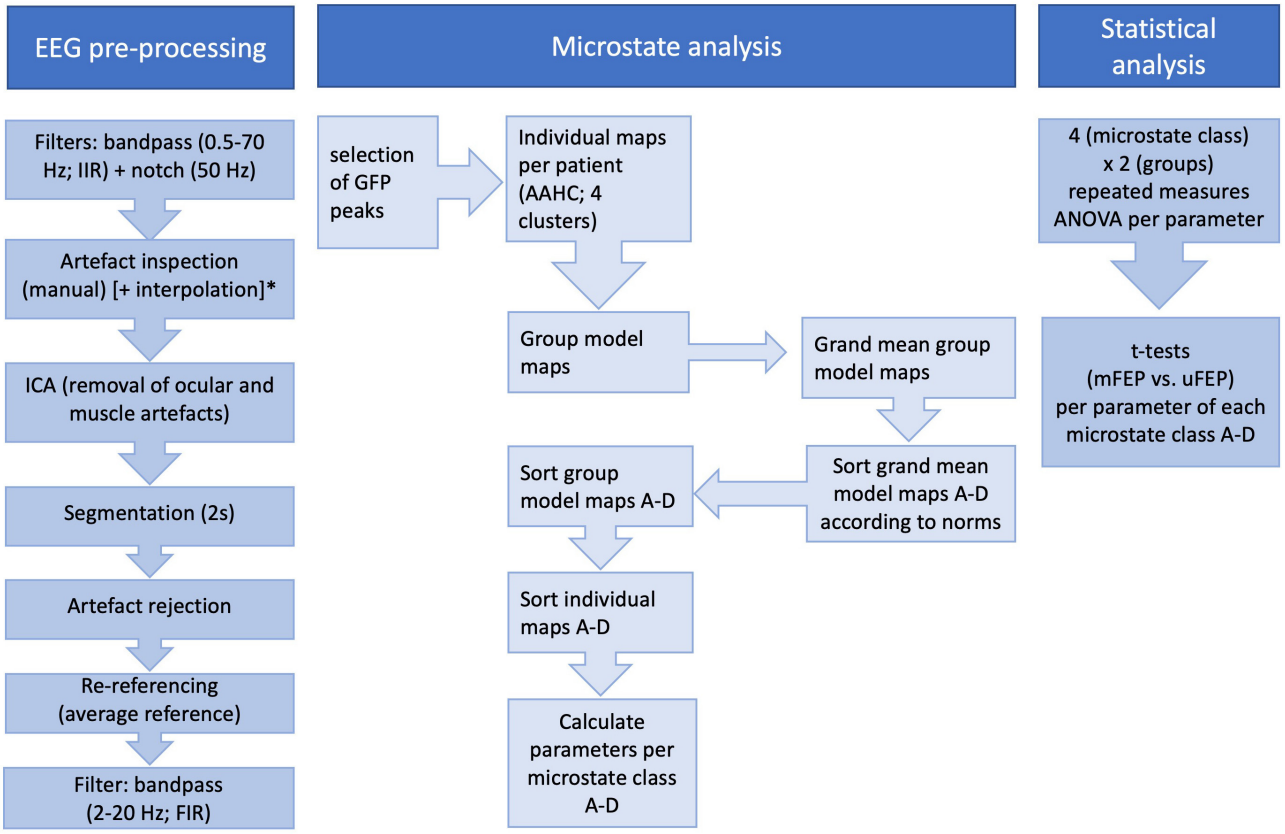

FIGURE 1 | All performed steps of EEG pre-processing, microstate analysis, and statistical analysis. ICA, Independent Component Analysis; GFP, Global Field Power; AAHC, Atomize-Agglomerate Hierarchical Clustering; *Interpolation was only performed for channels with severe artifacts across the whole recording.

applied, eyes-open epochs and epochs with prominent muscle artifacts or bad EEG signals were removed manually upon visual inspection by trained staff. After that, interpolation was applied for channels with severe artifacts across the whole recording and Extended Infomax ICA was used to remove ocular muscle artifacts. The continuous EEG recording was then divided into 2s segments and segments with residual artifacts were removed semi-automatically and by means of visual inspection based on consensus between at least two independent reviewers. Re-referencing was applied with a common average reference and the data was finally bandpass filtered (FIR; 2–20 Hz).

Microstate Analysis

The Microstate Analysis plug-in (Version 0.3; downloaded from http://www.thomaskoenig.ch/Download/EEGLAB_Microstates/) for EEGLAB (53) version 13.6.5b in Matlab (54) was used for the microstate analysis. First, the Global Field Power (GFP) was calculated for each time point of the recording. Since the signal-to-noise ratio is the highest for GFP peaks, microstate configurations remain stable around these peaks (17). Using Atomize-Agglomerate Hierarchical Clustering (AAHC), individual microstate maps for GFP peaks only were calculated for each participant based on the original momentary maps (55). Four microstate classes have been described to explain 65–84% (20) of the EEG variances. Based on this and for comparability with previous studies on psychotic disorders, the number of microstate clusters for the present study was also pre-set to four.

Group model maps were calculated separately for both patient groups using a permutation algorithm that minimized common variance across subjects (19). Based on these group models, a "grand-mean" model was calculated. The grand-mean model was then class-labeled into microstates A–D by using minimal Global Map Dissimilarity and model map norms from Koenig et al. (17). Next, the class-labeled "grand-mean" model maps were used as a template to assign the group model maps to the four class-labeled grand-mean maps. As a final step, the individual microstate maps were sorted according to the class-labeled group model maps. Three parameters were then extracted per microstate class: coverage (percentage of analysis time covered by each microstate class), duration (the average duration of a microstate class in milliseconds), and occurrence per second (total number of each microstate class per second). As the microstate toolbox ignores the first and last segment of the EEG data, only non-truncated microstate parameters are calculated. In addition, microstate transition probabilities (observed minus expected) were calculated. **Figure 1** depicts all analysis steps.

Statistical Analysis

A 4 (microstate class) × 2 (group) repeated measures ANOVA was applied to assess the interactional effect for each microstate parameter. Independent *t*-tests between the two groups (mFEP vs. uFEP) were conducted in order to determine group differences per parameter for each microstate class and demographic variables.

All analyses were carried out using SPSS 25 and R (56). Statistical tests in the present study are two-sided tests and the statistical level was set at $\alpha = 0.05$. When equal variances could not be assumed, the Greenhouse-Geisser correction for ANOVAs and the Welch-Satterthwaite method for the *t*-tests was applied. Microstate results were corrected for multiple comparisons within each parameter (57).

RESULTS

Group Characteristics

From a total of 59 FEP patients with available EEG data, 12 patients were excluded ex post facto due to unclear medication status. Thus, a total of 47 participants were included in the present analysis, consisting of 30 untreated, medication-naïve patients with first-episode psychosis (uFEP) and 17 medicated patients with first-episode psychosis (mFEP). There were no statistically significant differences between the two groups in age at diagnosis, sex distribution, illness duration (months), and symptom severity score as assessed with the Brief Psychiatric Rating Scale (51). **Table 1** displays the demographics of the two study groups and **Table 2** gives an overview of the ICD-10 diagnosis types per group which did not significantly differ between the two groups either. Approximately, a mean of 5 min resting-state recording per subject were used for further analysis (mFEP mean 300.3 s, and uFEP mean 299.2 s, respectively) which equals ∼150 epochs of 2 s length per subject of each patient group. If channels were interpolated, these did not exceed a maximum of 4 channels per participant (mean 0.61, SD 1.00; range 1–4 channels).

TABLE 2 | Overview of diagnosis types per group.

Type of psychotic disorder	ICD-10 Code	mFEP	uFEP	*p*
		***n* = 17**	***n* = 30**	**0.154**
Paranoid schizophrenia	F20.0	10 (58%)	14 (47%)	
Hebephrenic schizophrenia	F20.1	0	2 (7%)	
Undifferentiated schizophrenia	F20.3	1 (6%)	0	
Other schizophrenia	F20.8	1 (6%)	0	
Schizophrenia unspecified	F20.9	1 (6%)	4 (13%)	
Persistent delusional disorders	F22.0	2 (12%)	1 (3%)	
Acute and transient psychotic disorders	F23.x	1 (6%)	7 (23%)	
Schizoaffective disorder, depressive type	F25.1	0	2 (7%)	
Unspecified non-organic psychosis	F29	1 (6%)	0	

mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients. Significance level is 0.05.

Microstate Parameters: Overall Results

Class-labeled group model maps were calculated separately for each participant group and are shown in **Figure 2**. The average global explained variance across both groups was 77.4% and the EEG total analysis time (seconds) did not significantly differ between groups (see **Table 1**).

Microstate Parameters: Between-Group Differences

The microstate class x group interactions were significant for all microstate parameters: coverage [$F_{(3,135)} = 11.603$, $p < 0.001$, $\eta_p^2 = 0.205$]; duration [$F_{(2.414,108.616)} = 7.698$, $p < 0.001$, $\eta_p^2 = 0.146$]; and occurrence [$F_{(3,135)} = 14.417$, $p < 0.001$, $\eta_p^2 = 0.243$]. Follow-up *t*-tests indicated significant decreases of mFEP compared to uFEP for microstate A coverage [$t_{(39.8)} = -3.87$, $p = 0.001$, $d = -1.14$], and occurrence [$t_{(44.5)} = -3.51$, $p = 0.003$, $d = -1.00$]. No significant group differences were found for microstate A duration [$t_{(34.3)} = -2.24$, $p = 0.094$, $d = -0.68$]. Significant increases in the mFEP compared to uFEP group were found for microstate B coverage [$t_{(44.5)} = 7.58$, $p < 0.001$, $d = -2.16$], duration [$t_{(25.5)} = 2.78$, $p = 0.040$, $d = 0.88$], and occurrence [$t_{(35.6)} = 7.39$, $p < 0.001$, $d = 2.22$]. No significant results were found for microstate C coverage [$t_{(38.1)} = -1.69$, $p = 0.198$, $d = -0.50$], duration [$t_{(45.0)} = -1.83$, $p = 0.146$, $d = -0.52$], and occurrence [$t_{(27.5)} = -0.79$, $p = 0.876$, $d = -0.25$], as well as microstate D coverage [$t_{(35.8)} = 0.22$, $p = 0.827$, $d = 0.07$], duration [$t_{(35.4)} = -0.23$ $p = 0.817$, $d = -0.07$], and occurrence [$t_{(31.5)} = 0.63$, $p = 0.876$, $d = 0.19$]. **Figure 3** and **Supplementary Table 1** display means for all microstate parameters. The transition probabilities from class A to B [$t_{(32.0)} = 3.97$, $p = 0.004$, $d = 1.21$] and class C to B [$t_{(44.9)} = 5.97$, $p < 0.001$, $d = 1.68$] were increased in mFEP compared to uFEP. The transition probabilities from class A to C [$t_{(34.2)} = -3.40$, $p = 0.016$, $d = -1.03$] and class C to A [$t_{(43.7)} = -4.69$, $p < 0.001$, $d = -1.35$] were decreased in mFEP compared to uFEP. Detailed results are displayed in **Supplementary Table 2**.

DISCUSSION

We compared EEG microstate dynamics in medicated and medication-naïve first-episode psychosis patients (mFEP and uFEP, respectively). The microstate parameters coverage (%), duration (ms) and occurrence/s of four microstate classes (A–D) were compared between the two patient groups. We were able to confirm the hypothesis of an association between antipsychotics and microstate classes A and B.

We observed decreased microstate A coverage, and occurrence in mFEP compared to uFEP. This finding is underlined by a decrease of transitions from microstate C to A in mFEP compared to uFEP. Previous studies in unmedicated patients have reported an increase in microstate A compared to healthy controls (19, 30, 36, 38). Here, we show a decrease in this class in medicated patients, suggesting a beneficial association of antipsychotics with microstate A. Converging with our results, a decrease of microstate A was observed in medicated first-episode

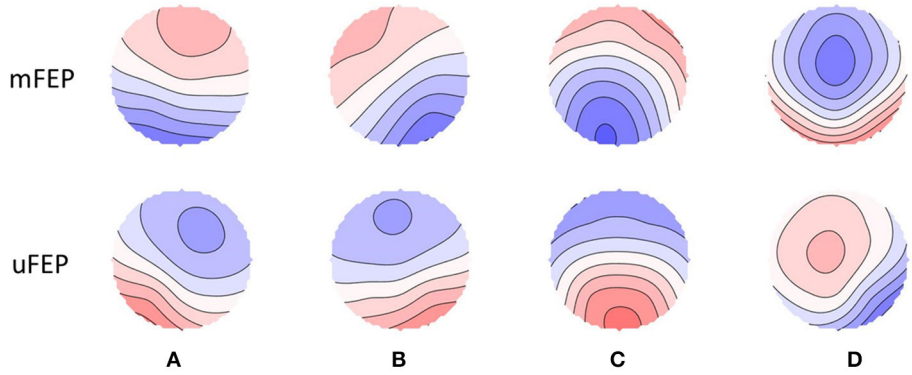

FIGURE 2 | Spatial configuration of the four microstate classes. Each row displays the four microstate classes **(A–D)** for both groups. Polarity is ignored. mFEP, medicated first-episode psychosis patients; uFEP, untreated, medication-naïve first-episode psychosis patients.

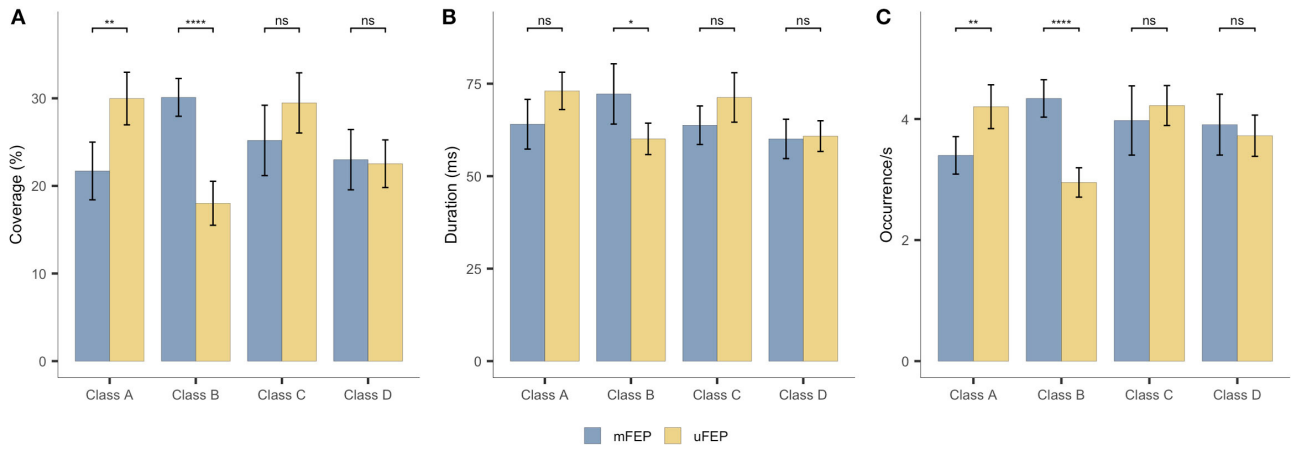

FIGURE 3 | Microstates statistics. Group averages of the temporal parameters: **(A)** coverage, **(B)** duration and **(C)** occurrence. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$.

patients compared to healthy controls (34) and microstate A was positively correlated with psychopathological symptoms such as depression (28) and negative symptoms of the avolition-apathy domain (33) in patients with psychotic disorders.

Interestingly, another study observed an increase in the same microstate class in more chronic medicated patients with schizophrenia spectrum disorder with up to 10.5 years of illness duration (SD 8.7) (32). Thus, illness progression (first-episode vs. more chronic) may be an important factor to consider in future studies of medication effects. Another modulatory aspect of microstate A was demonstrated by Kikuchi et al. (37): Although there was no pre- vs. post-effect after 2–8 weeks of antipsychotic treatment—possibly due to the small sample size of $n = 14$ and relatively short follow-up intervals—they observed increased microstate A in responders vs. non-responders.

Further between-group differences were observed for microstate B in which coverage, duration, and occurrence were increased in mFEP compared to uFEP. In addition, we observed more transitions from microstates A and C to microstate B in mFEP compared to uFEP. Compared to healthy controls, previous studies in unmedicated patients showed a decrease in microstate B (30, 38, 58). Again, the present study shows an opposite effect in medicated patients which could be an indication of a positive treatment effect for this class. This is further underlined by Andreou et al. (31) in which medicated first-episode patients also showed an increase in coverage of microstate B. On the other hand, Baradits et al. (32) found a decrease in all parameters of microstate B. However, inclusion of medicated schizophrenia patients with an average illness duration of 10.5 years in the latter study could again explain the difference in findings. This is in line with the recent suggestion that microstate B might be a specific state biomarker for psychotic illness progression (36).

Despite the fact that several studies found changes in microstate C between unmedicated (30, 37, 38) and medicated patients with psychotic disorders (33, 34, 37, 59) compared to healthy controls, we did not observe any significant differences between mFEP and uFEP in the present study. The absence of a difference might be explained by the fact that previous studies have reported the same finding, i.e., increase in microstate C compared to healthy controls, regardless of whether they assessed medicated or medication-naïve patient samples. Therefore,

it is conceivable that microstate C changes in patients are independent of medication status; however, larger studies are warranted to confirm our negative finding.

No significant differences in microstate D were observed between the two groups either. This is somewhat surprising, given that changes in microstate D are a central finding of studies comparing (both medicated and unmedicated) patients with psychotic disorders to healthy controls (19, 30, 32, 37, 38, 40, 59). Microstate D has further been associated with (positive) psychotic symptoms: a decrease was observed during periods of auditory hallucinations (60) and an increase in patients who responded well to antipsychotic medication (37). However, a study by Andreou et al. (31) comparing patients with FEP to a high-risk group with a similar symptom profile observed no differences in microstate D. The symptom severity scores of the patients in the present study did not significantly differ, with both groups being within the "markedly ill" range (61). This could explain why no differences in microstate D were observed. However, there is also an alternative explanation: We previously suggested that microstate D serves as a trait marker for psychotic disorders (36) in which case no effects of medication would be expected. Furthermore, a study by da Cruz et al. (40) suggested microstate D as endophenotype for psychosis in non-affected siblings of schizophrenia patients. To this end, studies with larger sample sizes are needed to further investigate medication effects on microstate D in patients with psychotic disorders.

Response status is an important issue to be considered in future studies investigating antipsychotic medication effects since it differs between individual patients (62, 63). As already mentioned, Kikuchi et al. (37) reported differences between patients that were classified as responders vs. non-responders to antipsychotic medication. However, their finding warrants replication, given that it was based on a small sample size ($n = 7$ per group). Unfortunately, it was not possible to trace response history for patients included in the present study; further studies should therefore investigate this issue. In addition, studies with longitudinal within-subject designs should explore the effects of antipsychotic medication treatment on EEG resting-state microstates, their association with individual response trajectories, as well as the role of patient baseline characteristics on medication effects. Ultimately, such studies could set the first steps into personalized medicine. This approach has been suggested for major depressive disorders and attention deficit disorders [for a review see Olbrich et al. (64)]. EEG resting-state microstates are particularly suited for this purpose, given that they have been suggested to be promising candidate biomarkers in psychotic disorders (32, 36, 40).

Further limitations of the present study have to be considered as well. Although the changes observed in medicated patients are in the expected direction, i.e., in the opposite direction of changes reported in previous studies comparing unmedicated patients to healthy controls, the inclusion of a matched healthy control sample would have been advantageous in completing the picture. Besides a healthy control group, a longitudinal design would have enabled us to confirm that the observed effects in medicated patients indeed correspond to a "normalization" of microstate parameters. A larger sample size than the one used here would have further increased statistical power of the results. Studies with high power are more likely to find true effects, e.g., correlation coefficients are estimated with a higher precision when sample sizes are increased (65). Moreover, it is due to the small sample size that we could not explore correlations between the four factors of the BPRS (with which the patients' symptom severities were measured) and the three parameters coverage, duration and occurrence of each microstate class A, B, C, and D. This could therefore be considered as a further limitation of this study.

In addition, cautiousness is warranted in the interpretation of our results, as a decrease or increase of a given parameter does not necessarily correspond to a "good" or "bad" outcome. Previous studies comparing first-episode patients (FEP), ultra-high-risk for psychosis patients and/or unaffected siblings of patients, and healthy controls have demonstrated that microstate changes do not always follow a linear pattern across different stages of psychotic disorders (31, 36, 40). Moreover, it has been suggested that some of the observed changes may reflect compensatory mechanisms rather than a deficit (31, 40). A further limitation of our study regards information which was not known for our sample and could have acted as confounding factor. This includes potentially different effects of individual antipsychotics (i.e., first vs. second generation antipsychotics) on EEG, medication duration, antipsychotic side effects, medication compliance, markers of socio-economic functioning, nicotine use, as well as the time of day of the EEG recording. Further confounding factors could have been age and sex distributions, as well as illness duration, drug consumption or other medication. However, all these variables did not significantly differ between groups.

Furthermore, two methodological points should be considered as well. First, based on previously established norms by Koenig et al. (17) the present study assessed four microstate classes. However, as suggested by Custo et al. (26) an increased number of microstates with a 7-map model might improve the explained global variance (20). Nevertheless, using four microstate classes has the important advantage of allowing direct comparisons of our results with previous studies in patients with psychotic disorders and high psychosis risk. Together with our relatively high global explained variance of 77%, we therefore deem our current method appropriate. As a second methodological limitation, it should be kept in mind that different pre-processing strategies, data selection methods and smoothing parameters (20) as well as differences in microstate analysis steps [e.g., the template used for microstate class assignment (21)] may influence microstate temporal parameters. In our study, we chose pre-processing and analysis parameters such as to ensure maximum comparability with a previous study by our group (36) but there may be differences compared to other studies. For future research in the field of EEG microstates, it would be very useful to harmonize methods in order to promote comparability.

CONCLUSION

Our findings suggest an association of antipsychotic medication with microstates A and B in first-episode psychosis patients. Further studies with large sample sizes and longitudinal designs are needed that directly compare medicated and medication-naïve patients as well as healthy controls, in order to

investigate antipsychotic medication effects on neural networks over time and throughout illness progression.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by EKNZ Basel. The patients provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AR-R was responsible for the conception and design of the FePsy study. CA and SB contributed to the acquisition of data. CA, RB, and AM were responsible for the conception and design of the current microstate analysis whilst. AM, RB, and ES performed the statistical analysis. AM and RB wrote the first draft of the manuscript. All authors contributed to critical revision for important intellectual content and final approval of the submitted manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.600606/full#supplementary-material

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2.3 Publication 3: EEG microstates as biomarker for psychosis in ultra-high-risk patients

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EEG microstates as biomarker for psychosis in ultra-high-risk patients

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Abstract

Resting-state EEG microstates are brief (50–100 ms) periods, in which the spatial configuration of scalp global field power remains quasi-stable before rapidly shifting to another configuration. Changes in microstate parameters have been described in patients with psychotic disorders. These changes have also been observed in individuals with a clinical or genetic high risk, suggesting potential usefulness of EEG microstates as a biomarker for psychotic disorders. The present study aimed to investigate the potential of EEG microstates as biomarkers for psychotic disorders and future transition to psychosis in patients at ultra-high-risk (UHR). We used 19-channel clinical EEG recordings and orthogonal contrasts to compare temporal parameters of four normative microstate classes (A–D) between patients with first-episode psychosis (FEP; $n = 29$), UHR patients with (UHR-T; $n = 20$) and without (UHR-NT; $n = 34$) later transition to psychosis, and healthy controls (HC; $n = 25$). Microstate A was increased in patients (FEP & UHR-T & UHR-NT) compared to HC, suggesting an unspecific state biomarker of general psychopathology. Microstate B displayed a decrease in FEP compared to both UHR patient groups, and thus may represent a state biomarker specific to psychotic illness progression. Microstate D was significantly decreased in UHR-T compared to UHR-NT, suggesting its potential as a selective biomarker of future transition in UHR patients.

Introduction

Psychotic disorders are complex and debilitating mental illnesses, affecting multiple domains of everyday life with potential for chronic outcomes[1]. However, timely treatment in the early stages of the illness can substantially improve clinical and functional outcomes[2,3]. Among patients with psychotic disorders, it has long been observed that a prodromal phase may precede the onset of first psychotic symptoms by several years[4]. Based on this observation, operationalized clinical criteria were developed to detect individuals at risk for psychotic disorders. The most prevalent among them are the ultra-high-risk (UHR) criteria, consisting of the presence of either (a) attenuated positive symptoms; (b) brief limited psychotic symptoms; or (c) genetic vulnerability accompanied by functional decline[5,6]. About 22–29% of UHR patients will transition to psychosis, with most transitions occurring in the first 3 years following diagnosis[7,8]. To optimize transition prediction, and thereby treatment in UHR patients, a large body of research has been devoted to identifying biomarkers that may be used to improve predictive accuracy[9–11].

Reliable biomarkers have adequate discriminatory capacity, are present at a sufficiently early (ideally preclinical) illness stage, are selective for an illness, and are reproducible across different patient samples[12]. Moreover, to improve clinical applicability, biomarkers need to incur reasonable costs and minimal patient discomfort. One method that offers several advantages in biomarker research is resting-state electroencephalography (EEG). Apart from being inexpensive and easy to implement, resting-state EEG can capture the fast-changing dynamics

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of neuronal networks with high temporal resolution. Studying these networks is extremely relevant in psychosis and UHR research since multiple studies have demonstrated altered network properties in affected individuals[13–15].

A compelling tool for studying the temporal dynamics of (eyes-closed) resting-state brain networks are EEG microstates. EEG microstates are brief (about 50–100 ms) periods in which the spatial configuration of scalp global field power remains quasi-stable before rapidly shifting to another configuration[16,17]. These spatial configurations can be clustered into a pre-defined number of configurations or classes. Four common classes, labeled A, B, C and D, explain 65–84% of EEG data variance[17]. These classes are present across different sex and age groups,[18,19] different neuropsychiatric diseases[20], and show cross-method consistency and high test–retest reliability[21]. Simultaneous functional magnetic resonance imaging (fMRI)-EEG studies have linked microstate classes to specific resting-state functional networks[22,23].

Microstate classes can be characterized by a set of temporal parameters: coverage, duration, and occurrence. Previous research has identified several differences in these temporal parameters between medication-naïve patients with schizophrenia and healthy controls[24–29]. While these studies have reported changes across all microstate classes, recent meta-analyses only reported increased occurrence of microstate C and decreased duration of microstate D in patients with psychotic disorders[30,31]. Although less pronounced, some of these changes are already present in individuals with a clinical or genetic high risk for schizophrenia[32,33], indicating that microstate alterations already occur at an early stage of psychotic disorders. The above findings suggest that EEG resting-state microstates might be a valuable candidate biomarker for the prediction of psychotic transition in UHR patients. However, no studies have yet assessed microstates in UHR patients with respect to future transition to psychosis.

The present study aimed to investigate microstate dynamics with respect to their suitability as biomarker for psychosis and transition to psychosis. To this end, we included UHR patients with and without a future psychotic transition (UHR-T and UHR-NT, respectively), first-episode-psychosis (FEP) patients and healthy controls (HC). Our comparisons were set out to examine state differences unspecific for illness progression (by comparing FEP, UHR-T, and UHR-NT to HC), state differences selective for developed psychosis (by comparing FEP to UHR-T and UHR-NT), and trait differences that reflect later transition to psychosis (UHR-T vs. UHR-NT). Based on previous studies that report microstate changes in patients with (high risk for) psychotic disorders, we expected to find both state and trait differences using EEG microstates, thereby showing the potential of EEG microstates as biomarker.

Methods

The data presented here were collected in the context of the FePsy (*Früherkennung von Psychosen*; Early Detection of Psychoses) project, which was conducted from 2000 to 2017 with the aim to improve early detection of psychosis. The FePsy project was approved by the local ethics committee and in accordance with the Declaration of Helsinki. A detailed description of the project can be found elsewhere[34].

Participants

Patients were help-seeking consecutive referrals to the FePsy clinic at the psychiatric outpatient department of the University Psychiatric Clinics (UPK) Basel. Healthy controls (HC) were recruited from the same geographical area as the FEP and UHR groups. All participants gave written informed consent for participation in the project.

FEP and UHR status was determined based on the Basel Screening Instrument for Psychosis (BSIP)[35]. Participants were assigned to the FEP or UHR groups according to the respective criteria set by Yung et al.[36]. UHR participants were followed-up at regular intervals to identify those who later transitioned to psychosis (UHR-T) and those who did not (UHR-NT). The definition of transition to psychosis was made using the Brief Psychiatric Rating Scale (BPRS)[37] according to the criteria set by Yung et al.[36]. Assessments for transition were performed monthly in the first year of follow-up, every 3 months in the 2nd and 3rd year, and yearly in the following years. The minimal follow-up duration before assigning a patient to the UHR-NT group was 3 years.

Exclusion criteria for patients were age <18 years, insufficient knowledge of German, IQ < 70, serious medical or surgical illness, previous episode of psychosis due to substance abuse, and psychotic symptomatology within a clearly diagnosed affective or borderline personality disorder. For the present analysis, we additionally excluded patients with UHR status based solely on BSIP unspecific criteria (as these criteria are associated with a lower risk of transition than the UHR criteria[38]), as well as all patients who had received antipsychotic treatment prior to the EEG recording. For healthy controls, exclusion criteria were age <18 years, current or past psychiatric disorder, family history of any psychiatric disorder, head trauma, neurological illness, serious medical or surgical illness, or substance abuse.

EEG recording and pre-processing

Clinical EEG (20 min) was recorded by a trained lab assistant while participants were comfortably seated in a quiet room. The first 8 min of the recording, which

correspond to resting-state eyes-closed EEG, were used in the present study. Every 3 min, participants were asked to briefly open their eyes for 6 s to avoid drowsiness. Additionally, participants were asked to open their eyes when behavioral (e.g., relaxation of face and neck muscles) and/or EEG signs of drowsiness (e.g., slow rolling eye movements, alpha drop-out, increased beta or theta activity) were observed. EEG was recorded with 19 gold cup electrodes (Nicolet Biomedical, Inc.), referenced to linked ears and attached according to the International 10–20 system. Impedances were always kept below 5 kΩ and sampling rate was 256 Hz.

Offline pre-processing was performed with Brain Vision Analyzer (Version 2.0, Brain Products GmbH, Munich, Germany). Raw EEG data were filtered with a bandpass (IIR; 0.5–70 Hz) and a notch (50 Hz) filter. Eyes-open epochs were removed based on marker positions and epochs with severe artefacts due to movement or poor signal were removed upon visual inspection. Channels with severe artefacts across the whole recording were interpolated. Ocular muscle artefacts were removed by means of Extended Infomax ICA. Subsequently, data were divided into 2 s segments and segments with residual artefacts were removed by means of visual inspection based on consensus between at least two independent reviewers. Finally, the data were re-referenced to the common average reference and bandpass filtered (FIR; 2–20 Hz).

Microstate analysis

Microstate analysis was performed with the Microstate Analysis plug-in (Version 0.3; http://www.thomaskoenig.ch/Download/EEGLAB_Microstates/) for EEGLAB[39] in Matlab 2015b. Individual microstate maps for each participant were calculated from original momentary maps using Atomize-Agglomerate Hierarchical Clustering (AAHC)[40]. The number of clusters was pre-set to four because four microstate classes have been reported to explain a large part of EEG data variance in healthy subjects[17] and for comparability with previous studies in patients with psychotic disorders. Group model maps were calculated separately for each participant group (HC, UHR-NT, UHR-T, FEP) using a permutation algorithm that minimized common variance across subjects[26] and class-labeled into microstates A–D by using minimal Global Map Dissimilarity and model map norms from Koenig et al.[18]. The class-labeled group model maps were then used as templates to assign individual microstate maps to the four class-labeled group maps. The microstate toolbox ignores the first and last segments and thereby only calculates non-truncated microstate parameters. The following parameters were extracted from microstate data: coverage (percentage of analysis time covered by the microstates of a given class), duration (the average duration of a microstate class in milliseconds), and occurrence/second (total number of the microstate of a given class per second).

Table 1 Orthogonal contrasts.

Contrast	Group 1		Group 2
I	FEP, UHR-T, UHR-NT	vs.	HC
II	FEP	vs.	UHR-T, UHR-NT
III	UHR-T	vs.	UHR-NT

Statistical analysis

Group differences for each microstate parameter were investigated by means of separate 4 (microstate class) × 4 (group) repeated measures analysis of variances (ANOVAs). Since the goal of the present study was to investigate microstate dynamics with respect to their suitability as biomarker for psychosis and transition to psychosis, we carried out specific contrasts. The contrasts were planned in an orthogonal manner in that a group once split off was not brought back into a next contrast (Table 1). By comparing FEP & UHR-T & UHR-NT vs. HC (i.e., all patient groups combined compared to healthy controls), contrast I assessed changes in microstates that might reflect general illness state irrespective of diagnosis. Contrast II compared FEP vs. combined UHR-T & UHR-NT, thereby assessing state markers of established psychosis. The last contrast (contrast III) was set to examine differences that might be predictive of later transition to psychosis (UHR-T vs. UHR-NT).

All analyses were carried out using SPSS 25. Statistical tests in the present study are two-sided tests wherever applicable and the statistical level was set at $\alpha = 0.05$.

Comparisons of class topography

A challenge in microstate analyses is that the class topographies used for the assignment of individual momentary maps and extraction of temporal characteristics may systematically differ between groups. To assess for such group differences in microstate class topographies, we used the Matlab tool Ragu (downloaded from www.thomaskoenig.ch/Ragu_src.zip[41]) to perform topographic analysis of variance (TANOVA). TANOVA uses the global field power of difference maps and non-parametric randomization statistics to quantify and assess between-group differences in scalp topography. Separate TANOVAs (5000 randomizations, L2-norm normalization of scalp field variance across sensors) were carried out for each contrast and results were Bonferroni-corrected for the total number of microstates ($n = 4$).

Vigilance

During eyes-closed resting-state conditions, it is possible that participants exhibit changes in arousal especially when participant groups are different clinical populations with some of them medicated. We therefore carried out an analysis assessing different stages of vigilance. We used VIGALL 2.0 (downloaded from https://research.uni-leipzig.de/vigall/) as add-in in Brain Vision Analyzer. For each participant, alpha center frequency was detected, as well as adaptations of absolute power thresholds. The different vigilance stages are: states A (1–3; alertness, relaxed wakefulness), state B (1–2/3; drowsiness), and state C (sleep) (see also Olbrich et al.[42]). Each 1-s segment was assigned to one of the states. For each state, the relative number of segments was calculated.

Subsidiary analyses: age mediation and moderation

As reported further below (see "Results"), between-group comparisons at baseline indicated significant differences in age between groups, with FEP being the oldest group (Table 2). As microstate parameters have been reported to variate with age[18], we investigated whether age mediated or moderated the significant planned contrasts. The age mediation and moderation analyses were carried out using the PROCESS macro version 3.1 for SPSS[43].

Results

Group characteristics

From a total of 162 participants with available EEG data initially recruited in the project, 53 participants were excluded ex post facto due to antipsychotic medication criteria ($n = 18$), definition of risk state based on other criteria than UHR criteria ($n = 8$), insufficient EEG quality ($n = 24$), insufficient follow-up time, or missing information on diagnosis ($n = 3$). A total of 108 participants were thus included in the analysis, consisting of 29 patients with first-episode psychosis (FEP), 20 ultra-high-risk (UHR) patients with (UHR-T) and 34 UHR patients without (UHR-NT) later transition to psychosis, and 25 healthy controls (HC). Table 2 displays group characteristics on the four study groups.

Microstate parameters: overall results

Class-labeled group model maps were calculated separately for each participant group and are shown in Fig. 1. The average global explained variance for all groups was 77% and did not significantly differ between groups ($F(3, 107) = 1.293$, $p = 0.281$, $\eta^2 = 0.036$) (Table 2).

Table 2 Sample demographics.

	HC	UHR-NT	UHR-T	FEP			
	n = 25	*n* = 34	*n* = 20	*n* = 29	*F*/χ2	*p*	Post-hoc
Sex (M:F)	12:13	26:8	11:9	19:10	5.69	0.128	
Age (mean [SD])	22.39 (5.24)	25.32 (8.14)	25.80 (7.20)	28.68 (7.64)	3.41	0.020	FEP > HC
BPRS (mean [SD])							
Total score	–	41.62 (11.70)	41.84 (9.67)	53.81 (11.02)	10.60	<0.001	FEP > UHR-T, UHR-NT
Depression/anxiety	–	9.59 (4.32)	10.69 (2.87)	11.79 (4.44)	2.09	0.131	
Psychosis/thought disturbance	–	6.30 (2.35)	6.52 (2.12)	12.09 (3.42)	38.68	<0.001	FEP > UHR-T, UHR-NT
Negative symptoms	–	6.43 (2.51)	5.76 (2.70)	5.75 (2.81)	0.58	0.562	
Activation	–	5.80 (2.38)	5.22 (1.46)	7.21 (3.55)	3.34	0.041	FEP > UHR-T
Comorbidities (ICD-10)							
F10–F19[a]	–	1	3	1			
F30–F39[a]	–	9	16	7			
F40–F49[a]	–	3	9	0			
F60–F69[a]	–	0	0	1			
EEG total analysis time (mean [SD])	299.72 (41.16)	296.74 (48.57)	309.35 (48.14)	296.71 (45.24)	0.38	0.768	
EEG explained variance (%) (mean [SD])	76.92 (2.77)	76.75 (2.95)	75.42 (4.00)	77.25 (3.68)	1.29	0.281	

HC healthy controls, *UHR-NT* ultra-high-risk without transition to psychosis at follow-up, *UHR-T* ultra-high-risk with transition to psychosis at follow-up, *FEP* first-episode psychosis, *BPRS* Brief Psychiatric Rating Scale, *SD* standard deviation.
[a]F10–F19 = Mental and behavioral disorders due to psychoactive substance use; F30–F39 = Mood [affective] disorders; F40–F49 = Neurotic, stress-related, and somatoform disorders; F60–F69 = Disorders of adult personality and behavior. Significance level is 0.05; only significant differences between groups (Games-Howell corrected) are presented for post-hoc comparisons.

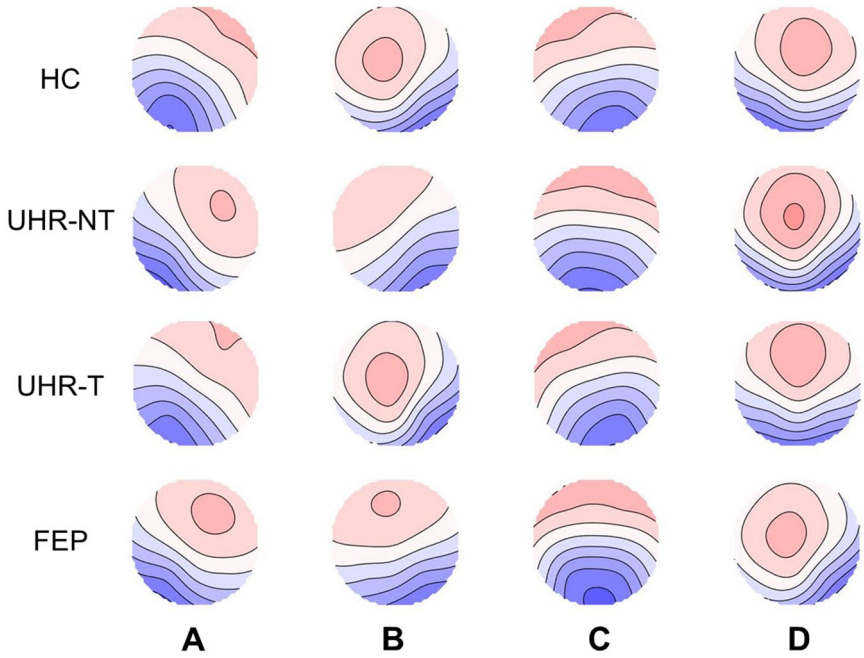

Fig. 1 Spatial configuration of the four microstate classes. Each row displays the four topographic configurations (A-D) for each group. HC healthy controls, UHR-NT ultra-high-risk without transition, UHR-T ultra-high-risk with transition, FEP first-episode psychosis.

Microstate parameters: between-group differences

We found significant class x group interactions for all microstate parameters: coverage ($F(8.291, 287.434) = 4.186$, $p < 0.001$, $\eta^2 = 0.108$); duration ($F(7.280, 252.370) = 2.130$, $p = 0.039$, $\eta^2 = 0.058$); and occurrence ($F(8.671, 300.603) = 6.334$, $p < 0.001$, $\eta^2 = 0.154$). We next performed separate one-way ANOVAs to further investigate group differences in specific microstate classes. These follow-up tests revealed significant between-group differences for microstate A coverage ($F(3, 107) = 10.582$, $p < 0.001$, $\eta^2 = 0.234$), duration ($F(3, 107) = 4.305$, $p = 0.007$, $\eta^2 = 0.110$) and occurrence ($F(3, 107) = 6.149$, $p = 0.001$, $\eta^2 = 0.151$), microstate B occurrence ($F(3, 107) = 2.756$, $p = 0.046$, $\eta^2 = 0.740$), and microstate D coverage ($F(3, 107) = 3.561$, $p = 0.017$, $\eta^2 = 0.093$) and occurrence ($F(3, 107) = 5.980$, $p = 0.001$, $\eta^2 = 0.147$). There were no significant results for microstate C. Table 3 displays means for all microstate parameters.

Microstate parameters: planned contrasts

By comparing FEP & UHR-T & UHR-NT vs. HC (i.e., all patient groups combined compared to healthy controls), contrast I assessed changes in microstates that might reflect general illness state irrespective of diagnosis. We found a significant increase of microstate A coverage ($t(104) = 2.889$, $p = 0.005$, $d = 0.580$) and occurrence ($t(104) = 2.390$, $p = 0.019$, $d = 0.514$) in all patient groups compared to HC.

In order to specifically assess state markers of established psychosis, we compared FEP vs. combined UHR-T & UHR-NT (contrast II). FEP showed significantly increased microstate A coverage ($t(104) = 4.239$, $p < 0.001$, $d = 1.006$), duration ($t(104) = 2.509$, $p = 0.014$, $d = 0.605$) and occurrence ($t(104) = 3.293$, $p = 0.001$, $d = 0.814$) compared to the two UHR groups. In addition, we observed significantly decreased microstate B coverage ($t(104) = -2.484$, $p = 0.015$, $d = -0.557$) and occurrence ($t(104) = -2.671$, $p = 0.009$, $d = -0.632$) in FEP compared to UHR-T and UHR-NT combined.

The last contrast (contrast III) was set to examine differences that might be predictive of later transition to psychosis (UHR-T vs. UHR-NT). The UHR-T group showed significantly decreased microstate D coverage ($t(104) = -3.043$, $p = 0.003$, $d = -0.840$) and occurrence ($t(104) = -4.109$, $p < 0.001$, $d = -1.244$) compared to UHR-NT.

Topographic analysis of variance (TANOVA)

Contrast I

The TANOVA group main effect was significant ($p = 0.001$); significant differences in topography were observed in microstates A ($p = 0.006$), B ($p = 0.02$), and D ($p = 0.002$), while the group effect for microstate C was non-significant ($p = 0.19$).

Contrast II

The TANOVA group main effect was significant ($p = 0.04$); differences in topography reached marginal significance in the case of microstate D ($p = 0.05$), while they

Table 3 Means for all microstate parameters.

	HC	UHR-NT	UHR-T	FEP	*F*	*p*	Post-hoc
Coverage (%) (mean [SD])							
A	22.74 (5.38)	23.27 (5.08)	26.27 (6.14)	30.77 (7.50)	10.58	<0.001	FEP > UHR-NT, HC
B	20.85 (4.32)	21.46 (4.85)	21.11 (7.08)	18.04 (6.26)	2.28	0.084	
C	32.23 (6.41)	30.64 (8.64)	34.30 (5.33)	29.18 (9.28)	1.88	0.138	
D	24.18 (6.62)	24.63 (7.38)	18.32 (7.73)	22.03 (7.65)	3.56	0.017	UHR-T < UHR-NT, HC
Duration (ms) (mean [SD])							
A	66.69 (7.47)	65.49 (7.75)	70.48 (8.95)	73.71 (13.50)	4.30	0.007	FEP > UHR-NT
B	65.12 (13.98)	62.89 (8.81)	63.50 (11.10)	59.58 (11.23)	1.17	0.326	
C	77.29 (15.92)	72.94 (19.28)	76.74 (9.16)	70.84 (18.46)	0.88	0.456	
D	66.68 (15.19)	64.28 (13.00)	60.82 (14.24)	60.18 (11.55)	1.33	0.268	
Occurrence/s (mean [SD])							
A	3.47 (0.83)	3.60 (0.67)	3.79 (0.72)	4.29 (0.89)	6.15	0.001	FEP > UHR-NT, HC
B	3.31 (0.59)	3.45 (0.61)	3.34 (0.80)	2.99 (0.60)	2.76	0.046	FEP < UHR-NT
C	4.33 (0.68	4.31 (0.76)	4.60 (0.61)	4.21 (0.88)	1.08	0.361	
D	3.69 (0.64)	3.86 (0.69)	2.97 (0.76)	3.68 (0.96)	5.98	0.001	UHR-T > HC, UHR-NT, FEP

Significance level is 0.05; only significant differences between groups (Games-Howell corrected) are presented for post-hoc comparisons.
HC healthy controls, *UHR-NT* ultra-high-risk without transition, *UHR-T* ultra-high-risk with transition, *FEP* first-episode psychosis.

were non-significant for microstates A ($p = 0.50$), B ($p = 0.08$), and C ($p = 1.0$).

Contrast III

The TANOVA group main effect was significant ($p = 0.007$); significant differences in topography were observed for microstates B ($p = 0.02$) and C at a trend level ($p = 0.06$), while the group effect was non-significant for microstates A ($p = 0.14$) and D ($p = 0.11$).

Vigilance

On average, participants spent 71% in state A (awake), and 29% in state B (drowsiness). No significant interaction (group x state) ($F(15, 624) = 0.471$, $p = 0.955$) or main effect of group ($F(3, 624) = 0.000$, $p = 1.000$) was observed.

Subsidiary analyses: age mediation and moderation

In the mediation analysis, there was no significant mediation effect of age in any of the previously significant contrasts. In moderation analyses, significant interactions between age and group were observed for microstate A contribution ($F(1,104) = 4.132$, $p = 0.045$) in contrast I (FEP & UHR-T & UHR-NT vs. HC). More specifically, this microstate parameter was increased in the patient groups FEP & UHR-T & UHR-NT compared to HC, but only in younger subjects. In addition, there were significant age x group interactions for microstate D contribution ($F(1, 50) = 8.672$, $p = 0.005$) and occurrence ($F(1, 50) = 4.143$, $p = 0.047$) in contrast III (UHR-T vs. UHR-NT), with the microstate parameters being decreased in UHR-T compared to UHR-NT only in younger subjects. The main effect of group in contrast III remained significant after controlling for age, while this was not the case for contrast I. Age did not significantly moderate contrast II (FEP vs. UHR-T & UHR-NT).

Discussion

The aim of this study was to investigate resting-state EEG microstates as biomarker for psychotic disorders and transition to psychosis in high-risk individuals. To this end, we investigated microstate parameters in patients with first-episode psychosis (FEP), patients with ultra-high-risk for psychotic disorders (UHR), and healthy controls (HC). Moreover, we were able to directly compare EEG microstate parameters in patients with (UHR-T) and without (UHR-NT) a subsequent transition to psychosis, which makes this paper unique in EEG microstate literature.

We found increased microstate A coverage and occurrence to differentiate the three patient groups (FEP, UHR-T, and UHR-NT) from HC, as well as increased microstate A coverage, occurrence and duration to differentiate FEP from the two combined UHR groups. Previous studies have reported increased microstate A occurrence[26,27] and coverage[26–28] in schizophrenia patients compared to controls, but also increased microstate A coverage and duration in drug-naïve patients with panic disorders

compared to healthy controls[25] and a positive correlation of microstate A parameters with depression severity[44]. Given the high rates of non-psychotic psychiatric comorbidity in all patient groups (60%; see symptom profiles presented in Table 2), we suggest that the observed microstate A parameter increase might represent an unspecific state marker of general psychopathology.

Decreased microstate B coverage and occurrence was found to additionally differentiate FEP from the combined UHR groups. Decreased microstate B duration has been consistently reported in unmedicated schizophrenia patients compared to healthy controls[24,27,28] (with a single exception[25]). With microstate B successfully differentiating between FEP and UHR-T & UHR-NT, who at time of the measurement were experiencing psychosis-like symptoms but had not (yet) transitioned to psychosis, these results suggest that microstate B might represent a state biomarker specific to psychotic illness progression. Interestingly, previous research by Andreou et al.[32] found differences in the opposite direction between medicated, stable FEP and high-risk patients with respect to microstates A (decreased coverage in FEP) and B (increased coverage in FEP), suggesting a modulatory role for antipsychotic medication on these two microstates and thus providing support for their view as state markers.

The present study is the first to directly compare UHR-T to UHR-NT regarding resting-state EEG microstates at baseline. We found decreased microstate D coverage and occurrence in UHR-T compared to UHR-NT. In previous research, decreased microstate D coverage, occurrence and duration were observed in patients with 22q11 deletion syndrome, a genetic syndrome associated with high psychosis risk[33]. Microstate D coverage was also found to be decreased in unmedicated schizophrenia patients compared to healthy controls[25–27], which was confirmed by two recent meta-analysis, including medicated and unmedicated patients with psychotic disorders[31]. Dynamics of microstate D were further suggested as candidate endophenotype by a study that compared medicated schizophrenia patients and their siblings to healthy controls and found decreased microstate D in both the patient group, as well as their siblings[30]. Our results expand upon these previous findings, indicating that decreased microstate D could be a selective trait marker that potentially predicts later transition to psychosis in UHR patients. This is in line with a previous suggestion that microstate D is associated with reality testing due to its reduction in schizophrenia[27], hypnosis[45], and sleep[46]. Further, microstate D was found to have shortened duration during periods of hallucinations[47] and had increased duration at follow-up for patients that responded well to antipsychotic medication[25]. This function might be mediated by attentional processes, as microstate D has been associated with the frontoparietal attention network[48], and suggested to be dominant during focus switching and reorientation of attention[22], during no-task resting[49], and involved in error-monitoring[47].

Surprisingly, we did not find any microstate C differences in any of the studied contrasts. Microstate C was suggested to predominantly occur during activation of the salience network[22], and would have therefore been expected to be abnormal in patients with psychotic disorders based on the aberrant salience account of psychosis[50]. On the other hand, although both aforementioned meta-analyses[30,31] reported microstate C to be increased (coverage and occurrence) in schizophrenia patients, this effect is not very consistent across single studies, with approximately half of existing studies reporting differences in this microstate between unmedicated schizophrenia patients and healthy controls[25,27,28], while the other half failed to observe significant differences[24,26,29]. This inconsistency may be explained by a recent observation that the optimal number of microstate maps to describe resting-state EEG data may be higher than the original four (A–D). Custo et al.[48] have proposed a 7-map model and suggested that microstate C in the original 4-map model may, in fact, result from two spatially correlated but separate microstate topographies corresponding to different resting-state networks, which might explain the above discrepant results across studies. Further research is warranted to confirm this hypothesis, as there have not been any studies using the 7-map model in patients with psychotic disorders so far.

FEP being the oldest participant group might raise the question whether the significant age difference between HC and FEP partially accounted for our results. However, age was not a significant mediator of group differences in our subsidiary analysis. Interestingly however, differences in microstate A between HC and patient groups as well as differences in microstate D between UHR-T and UHR-NT were more pronounced in younger subjects, thus revealing age as moderator for these microstates. As Koenig et al.[18] and Tomescu et al.[19] demonstrated, microstate temporal parameters change throughout developmental stages from early childhood to late adulthood. This suggests that microstate differences found in this study might be influenced by altered maturation processes in patients compared to healthy controls. Indeed, recent publications have suggested that UHR patients exhibit an altered structural maturation process compared to healthy controls[51], which was shown to be predictive of greater risk of transition to psychosis and poor functional outcomes only in younger UHR patients[52].

To our knowledge, this is the first study investigating microstates in patients at high risk for psychotic disorders under consideration of later transition status. Its strengths

include (a) the inclusion of only antipsychotic-naïve patients to ensure sample homogeneity (see Stevens et al.[53] and Yoshimura et al.[54] for effects of antipsychotic medication on microstate parameters), and (b) the fact that transition status for UHR patients was determined based on a sufficiently long follow-up time leaning on reported transition trajectories[34,55,56] to minimize the amount of potential unnoticed late transitions in the UHR-NT group.

However, certain methodological points should be considered as well. First, based on previously established norms by Koenig et al.[18], the present study assessed four microstate classes. As mentioned above, an increased number of microstates might improve the explained global variance[17]. Nevertheless, using four microstate classes has the important advantage of allowing direct comparisons of our results with previous studies in patients with psychotic disorders and high psychosis risk. Altogether with our relatively high global explained variance of 77%, we deem our current method appropriate. As a second limitation, it should be kept in mind that different pre-processing strategies, data selection methods and smoothing parameters[17], as well as differences in microstate analysis steps (e.g., the template used for microstate class assignment[21]) may influence microstate temporal parameters. In our study, we chose pre-processing and analysis parameters such as to ensure maximum comparability with a previous study of UHR patients by our group[32] but there may be differences compared to other studies. For future research in the field of EEG microstates, it would be very useful to harmonize methods in order to promote comparability.

Conclusion

In sum, the present results suggest microstates A and B as state markers, respectively, for general psychopathology and psychotic symptoms, and microstate D as a trait marker that selectively identifies those UHR patients that make a future transition to psychosis. Overall, the search for robust biomarkers for transition to psychosis from the high-risk state is still a key challenge in the field of early detection research, although multiple variables have been suggested to increase predictive accuracy[57] since the early starting points of research on prediction of psychosis transition[58] beyond the genetic risk approach[59]. With the present study, we demonstrate the potential of EEG microstates parameters as a valuable biomarker psychosis transition in the wake of a recently published article that found microstates to successfully (accuracy 82.7%) differentiate between patients with psychotic disorders and healthy controls[60]. Further research is warranted to establish the robustness of these results in order to enhance predictive accuracy, ideally in a combined multiple variable approach.

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Conflict of interest
The authors declare that they have no conflict of interest.

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3. Discussion

3.1 Evaluation of results

Little is known about how the two pathophysiological models of psychotic disorders, the dopamine hypothesis and the dysconnectivity hypothesis, are associated. This dissertation focusses on filling that knowledge gap by investigating the association of dopaminergic agents with resting-state EEG/MEG functional connectivity measures. Existing research is complemented by three publications: A systematic review on the topic and two publications that investigate the association of resting-state EEG microstates with antipsychotic medication, psychosis illness progression and transition to psychotic disorders.

An association of the dysconnectivity and the dopamine hypotheses could indeed be shown. As summarized in Figure 2, the results of this dissertation demonstrate an association of resting-state EEG microstates with antipsychotic medication in a sample of FEP patients (publication 2) and with psychotic illness progression in FEP and transition to psychosis in UHR patients (publication 3). However, systematic evidence on the association of dopaminergic agents with resting-state EEG/MEG brain functional connectivity across 20 studies published since 2000 could not be found (publication 1).

In the following, the results of each publication, and how the respective research questions were answered, will be discussed in more detail. The significance of each publication for the field of research on psychotic disorders and their implications will be discussed. This will be followed by a summary on strength and limitations across all three publications, an outlook for future research and will close with a conclusion.

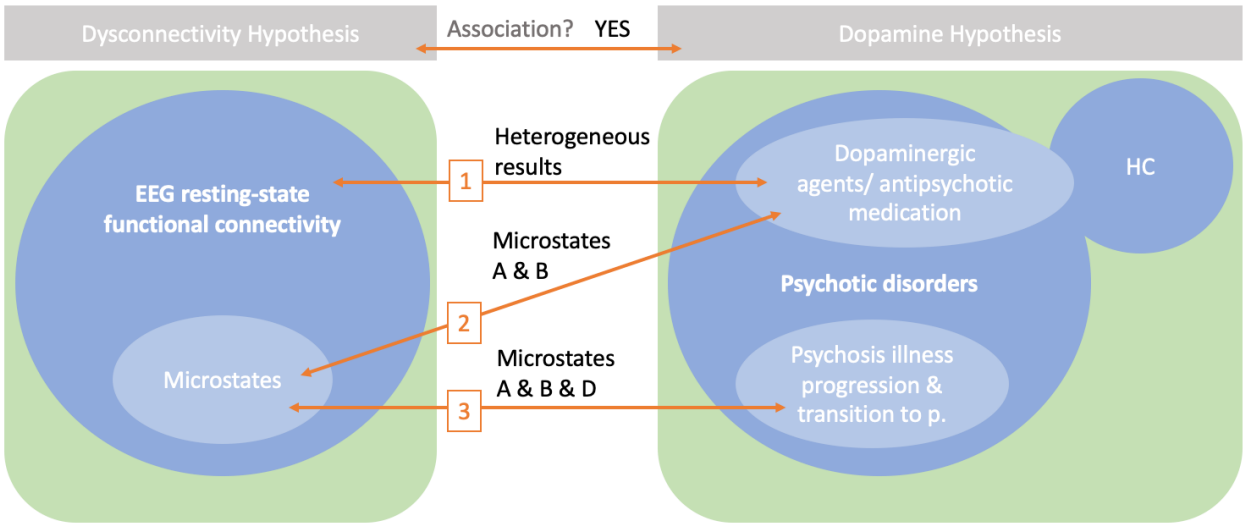

Figure 2: Results of the three publications 1) Mackintosh et al., 2021; 2) Mackintosh et al., 2020; and 3) de Bock et al., 2020 depicted above the orange arrows of each research question.

3.1.1 *First research question: Does systematic evidence exist on the association of dopaminergic agents with resting-state electro- and magnetoencephalographic (EEG/MEG) brain functional connectivity assessed by sensor- as well as source-level measures?*

The first research question of this dissertation was tackled by a systematic review that researched the existing evidence on dopaminergic association with resting-state EEG/MEG functional connectivity published since 2000. Both pharmacological agents acting on and genes associated with the dopamine system were explored for the comparisons outlined in the introductory chapter (see 1.4.1).

A heterogeneous pattern of resting-state EEG/MEG connectivity increases, decreases and non-significant results were found in widespread areas across all frequency bands in the 16 included studies that compared medicated patients with psychotic disorders to healthy controls or medication-naïve patients with psychotic disorders to healthy controls. Only two papers compared medication effects in a pre-post design. These examined completely different participant groups (chronic patients with psychotic disorders vs. healthy controls) which is why their results were not conclusive either.

With that, the systematic review could not clearly answer the first research question of this thesis as no systematic evidence was found. The results of the included publications were inconsistent as to the direction and spatial pattern of the resting-state EEG/MEG abnormalities. A wide range of methods was applied across all included studies for source- and sensor-level functional connectivity measures. These included phase as well as amplitude correlations, different recording and preprocessing methods, different frequency-range definitions and small sample sizes in the majority of studies. Further confounding factors between studies were; different antipsychotic medications applied with a wide range of dosages, participant groups with different illness durations, as well as different sex and age distributions. In line with these findings, systematic reviews by Maran and colleagues (2016) and Perrottelli and colleagues (2021) on functional connectivity abnormalities across different frequency bands in patients with psychotic disorders found considerable inconsistencies concerning the direction of effects.

When pondering on why no systematic evidence could be found for the first research question, it becomes apparent that there is a great gap in studies in EEG/MEG research able to answer the question. First of all, most studies compared a group of patients who were medicated with antipsychotics to a group of healthy controls that were not medicated. This means that the comparisons were mainly between-subject instead of within-subject which brings along further confounding factors. Studies that follow up patients throughout their treatment over a long period of time with pre-post measurements that compare patients medication-naïve and after treatment onset would have answered the research question more clearly. Such longitudinal studies would have eliminated confounding factors of the disorder and between subjects. However, there was a striking lack of longitudinal designs with the desired outcome measures of EEG/MEG functional connectivity per frequency band. Recently for example, a longitudinal resting-state fMRI randomized control trial was published that revealed dysconnectivity differences in medicated FEP patients compared to medication-naïve FEP patients who were treated with placebo and psychosocial interventions

(Chopra et al., 2021). This is the type of study design desperately needed in the field of research on psychotic disorders, ideally with multiple outcome measures.

Secondly, for the between-subject comparisons it would have been valuable to compare medicated patients to medication-naïve patients directly, as well as to healthy controls in order to limit the effects of the disorder. In the search process of the systematic review however, there was not a single paper that compared those two groups of patients which is a shortcoming of this field of research. Publication 2 of this thesis (discussed in the following chapter) attempts to close this gap.

Thirdly, only one included paper of the systematic review conducted a drug-challenge with healthy controls (Albrecht et al., 2016). This was a further lack identified by the review. Drug-challenges with healthy controls that investigate the association between dopamine and dysconnectivity independent of any psychiatric disorder would be helpful to complete the picture.

Fourth, antipsychotics can only serve as approximations of dopamine-antagonists as they target other neurotransmitter systems as well (Stahl, 2013) and with that do not answer the research question to the full extent. Only one included paper applied a dopamine-agonist dexamphetamine (Albrecht et al., 2016) whereas in all other studies participants were medicated with a variety of first and second generation antipsychotics. In order to stringently disentangle the question of how the dopamine and the dysconnectivity hypotheses are associated, studies are needed that apply dopamine agents that do not target other receptors (albeit to the cost of external validity as antipsychotic medication represent the clinical standard in the field of psychiatry).

Fifth and last, psychotic disorders are a heterogeneous group of psychiatric conditions with positive as well as negative symptoms (DSM-5®, American Psychiatric Association, 2013; ICD-10, World Health Organization, 2004). All psychotic disorder types were included in the reviewed studies from delusional and schizoaffective disorders, over to the various types of schizophrenia disorders, acute and transient psychotic disorders, and psychotic disorder not further specified. As symptoms overlap between different diagnoses subtypes, they can also vary greatly between patients with the same diagnosis (Stephan et al., 2016; Tamminga, 2014). This problem has been stated previously by other authors who saw various schizophrenia spectrum disorders to be a potential source of between-study heterogeneity for systematic reviews (Belbasis et al., 2018).

The research question however remains essential as extensive reviews have postulated resting-state EEG/MEG functional connectivity changes in patients with psychotic disorders (Alamian et al., 2017; Maran et al., 2016; Radua et al., 2012; Uhlhaas and Singer, 2013). It has been suggested that antipsychotic medication may normalize dysconnectivity in patients with psychotic disorders in an fMRI study (Guo et al., 2017) and more functional connectivity increases than decreases were found at follow-up in medicated compared to medication-naïve patients (Chopra et al., 2021). As intolerable side-effects, treatment discontinuation and relapse rates after medication discontinuation remain relatively high for antipsychotic medication (for reviews see Bowtell et al., 2018; Gentile, 2019; Kaar et al., 2019), there is a clear need to

improve pharmacological and non-pharmacological treatment options with expanded efficacy and reduced side-effects.

New avenues of complementary treatment models which are non-pharmacological are already being explored for psychotic disorders that include dietary supplementation such as D-serine (Li et al., 2018) and omega-3 fatty acids (Hsu and Ouyang, 2021), vitamin supplements (Adamson et al., 2017; Firth et al., 2017), mineral supplementation (Firth et al., 2017), and probiotic supplementation (Ng et al., 2019) for example. Besides pharmacological treatment at onset of a psychotic disorder, increased focus could be put on improving coping mechanisms (Riera-López de Aguileta et al., 2020) for psychological and environmental stress factors that have been postulated to increase the risk for psychotic disorders as well as later relapses (Fusar-Poli et al., 2017; McGrath et al., 2004; Morgan et al., 2008; O'Donoghue et al., 2015; Varese et al., 2012). To date, this is still a shortcoming in clinical practice.

3.1.2 Second research question: Are differences in parameters of resting-state EEG microstate classes A-D associated to antipsychotic medication in FEP patients?

The second research question investigated whether resting-state EEG microstates are associated to antipsychotic medication intake in a sample of FEP patients. Publication 2 answered this question by comparing mFEP patients (n = 17) to a control group of uFEP patients (n = 30). As hypothesized, significantly decreased microstate class A coverage and occurrence and significantly increased microstate class B coverage, duration and occurrence were found in mFEP compared to uFEP. No significant differences in microstate classes C and D were found.

These results are in accordance with previous studies that found the same effects in samples of medicated patients with psychotic disorders compared to healthy controls for microstate A (Murphy et al., 2019) and microstate B (Andreou et al., 2014). Not surprisingly, changes in the opposite direction were found in samples of medication-naïve patients with psychotic disorders compared to healthy controls for microstate A (de Bock et al., 2020; Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013), as well as microstate B (Irisawa et al., 2006; Lehmann et al., 2005; Nishida et al., 2013). Microstate classes A and B were associated to visual processing and verbalization (Britz et al., 2010; Milz et al., 2016), two cognitive processes disrupted in psychotic disorders which could indeed be differently affected in medicated and medication-naïve patients.

The fact that we did not find microstate classes C and D to differentiate the two patient groups might tie back to the lack of a healthy control group (i.e., that differences in these microstates only show up when compared to healthy controls). A further reason could have been the small sample size, as studies with higher power are more likely to find true effects. However, the lack of significant results for microstate D is underlined by the third publication of this thesis (de Bock et al., 2020) that suggests microstate D as a trait marker for psychotic disorders in UHR-T patients and a recent study suggesting microstate classes C and D as endophenotypes for psychotic disorders in unaffected siblings compared to healthy controls (da Cruz

et al., 2020). In that wake, microstate classes C and D might not differentiate between the two included FEP patient groups that did not differ in their symptom severity scores (measured by the Brief-Psychiatric-Rating-Scale (BPRS); Maß et al., 1997; Overall and Gorham, 1962; for a description see overview of Appendix B).

There are only two studies so far that researched resting-state EEG microstates in relation to antipsychotic medication in patients with psychotic disorders. Both studies were conducted over a decade ago. The first compared chronic schizophrenia patients to healthy controls and found antipsychotic treatment to be negatively correlated to microstate duration in a dose-dependent way and the average microstate duration to be longer in unmedicated than medicated patients (Stevens, 2009). The second study compared responder vs. non-responder schizophrenia patients in a longitudinal design following 2-8 weeks treatment with antipsychotics and found increased duration of microstate classes A and D and decreased occurrence of microstate class C to differentiate the two groups (Kikuchi et al., 2007).

The association of resting-state EEG microstates to antipsychotic medication found by publication 2 are further supported by EEG studies that found EEG modifications (sharp or epileptiform activities) associated to atypical antipsychotics in a dose-dependent way (Dias Alves et al., 2018). Further support comes from other brain imaging modalities: Grey-matter volume decrease was found by two meta-analyses to be negatively correlated with the exposure to antipsychotic treatment (P. Fusar-Poli et al., 2013; Radua et al., 2012) and progressive decrement of white matter and gray matter volume reduction was found by a longitudinal MRI study (Ho et al., 2011).

The association of dopamine dysregulation and antipsychotic medication effects with changes of the brains functional networks however is still poorly understood. Further studies with resting-state EEG/MEG functional connectivity measures are needed that directly compare medicated to medication-naïve patients and follow them up in longitudinal and pre-post designs. This knowledge will ultimately lead to improving treatment plans and ensure better functional outcomes for patients with psychotic disorders.

3.1.3 Third research question: Are differences in parameters of resting-state EEG microstate classes A-D associated with psychosis illness progression and transition to psychosis in FEP and UHR patients?

The third research question of this thesis investigated whether resting-state EEG microstates are associated to psychosis illness progression and transition to psychosis, as already researched by EEG task-based studies (Danjou et al., 2019; and for reviews see Lepock et al., 2018; Perrottelli et al., 2021). To answer this, publication 3 of this thesis found the following results: Increased microstate class A coverage and occurrence was found to differentiate the three included patient groups (FEP, UHR-T and UHR-NT) from HC and was postulated to be an unspecific state marker for general psychopathology. Further comparing FEP to the combined UHR groups (UHR-T and UHR-NT), significantly increased microstate class A coverage, duration and occurrence and significantly decreased microstate class B coverage and occurrence was found. Microstate class B was thus postulated as state marker specific for psychotic illness

progression. Decreased microstate class D coverage and occurrence was found at baseline in UHR patients with (UHR-T) compared to patients without (UHR-NT) later transition to a psychotic disorder. Microstate class D was therefore suggested as a potential biomarker for future transition to a psychotic disorder.

The results are in line with publication 2 that found microstate classes A and B to differentiate medicated from medication-naïve FEP patients. However, the results are in the opposite direction (increase vs. decrease of microstate parameters). This is not surprising, as the two papers cover different comparisons between patient groups. Whilst publication 3 included medication-naïve FEP patients only and compared them either to the combined UHR patient group or together with the UHR patient group to HC, publication 2 compared medicated to medication-naïve FEP patients and did not compare them to HC. However, the direction of change in microstate parameters, i.e., increases vs. decreases, does not signify either a good or a bad outcome and thus no specific direction was hypothesized in both papers.

Further support for microstate class A as a state marker for general psychopathology comes from studies that found microstate class A to be associated to depression severity (Damborská et al., 2019), patients with panic disorders (Kikuchi et al., 2011), as well as patients with psychotic disorders (Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013) compared to healthy controls. Microstate class B on the other hand was found to be decreased in medication-naïve patients with psychotic disorders compared to healthy controls (Irisawa et al., 2006; Lehmann et al., 2005; Nishida et al., 2013) which supports the findings of microstate class B as state marker for psychosis illness progression. However, there is only one other study that directly compared FEP to UHR patient groups (Andreou et al., 2014) and found microstate A and B in the opposite direction of the present findings. This might be attributed to the medication status, as Andreou and colleagues (2014) analyzed a partly medicated patient sample which stands in contrast to the purely medication-naïve patients of publication 3.

Microstate class D was also found to differentiate a sample of patients with 22q11 deletion syndrome (a genetic high-risk factor for psychotic disorders) from healthy controls (Tomescu et al., 2014). These were the only other authors besides Andreou and colleagues (2014) who compared high-risk patients to healthy controls. Furthermore, a few studies found parameters of microstate class D to differentiate medication-naïve patients with psychotic disorders (instead of UHR patients) from healthy controls (Kikuchi et al., 2007; Koenig et al., 1999; Lehmann et al., 2005; Nishida et al., 2013) which is further supported by a meta-analysis on medication-naïve patients with psychotic disorders (Rieger et al., 2016).

The question arises whether resting-state EEG microstates can be implemented as biomarker as suggested by publication 3. Biomarkers have been defined as ‘biological’ markers including imaging measures that are useful to confirm diagnosis or predict treatment outcomes (for a review see Perlis, 2011). However, for biomarkers to be implemented in widespread clinical practice, they are requested to provide clinical information reliably (Holland, 2016). The first step to establish a biomarker is to show an association between the marker and a clinical condition (Holland, 2016) and this is fulfilled by publication 3. The second step has been suggested to take years and decades. It includes to replicate and confirm the findings of the association and to develop clinically meaningful quantifications or cut-offs (Holland, 2016). In the case of

resting-state EEG microstates, this would mean that for one, the present findings need to be replicated by further studies, and for two, robust effects need to be demonstrated on the level of meta-analyses (such as by Rieger and colleagues, 2016) and umbrella reviews.

Holland and colleagues (2016) further suggested that a new biomarker needs to provide information not yet available to clinicians and should be capable to change the outcome for patients in a meaningful way. Clinical management of major psychiatric disorders have been described to still be based mainly on psychopathological knowledge and their treatment to rely on 'trial and error' (for an umbrella review see Carvalho et al., 2020). An established state marker for psychosis illness progression and trait marker for the transition to psychosis could support clinicians in making a precise diagnosis. As EEG measures are non-invasive and easy to implement at low costs, the implementation to clinical practice is feasible. Transition rates of UHR patients were found to be relatively low (36% after 3 years follow-up; Fusar-poli et al., 2012) which further emphasizes the need for better prediction tools. This is in the wake of the emerging framework of precision psychiatry that sets out to develop tools to help clinicians make psychiatric diagnosis objectively (Vieta, 2015).

To account for the wide heterogeneity of mental illnesses as they manifest clinically, biomarkers will need to be combined as no single biomarker will probably define any psychiatric disorder (Fernandes et al., 2017). For that, multiple units of analysis have been suggested within the biological system including physiological recordings, brain imaging, 'omics' biomarkers (such as genomics, epigenomics, metabolomics, proteomics etc.), environmental exposures and self-reported experience to be combined with ecological momentary assessments (Fernandes et al., 2017). Such multi-domain approaches are in the wake of the Research Domain Criteria (RDoC) framework launched by the National Institute of Mental Health in 2009 (Cuthbert and Insel, 2013) that promotes the integration of multiple measures to study psychological phenomena. Multi-domain computational modeling approaches have for example been shown to outperform one single domain in predicting diagnosis of schizophrenia and bipolar disorders (Fernandes et al., 2020). Brain imaging data, such as the present resting-state EEG microstates results, would therefore need to be combined with further units of analysis in a multi-domain approach in order to form a robust prediction and diagnosis system for clinical application.

3.2 Strengths and Limitations

In researching the association of the dopamine and the dysconnectivity hypotheses, this dissertation stands out in novelty with the following three aspects:

a) A systematic research of existing studies published since 2000 (publication 1)

b) A comparison of medicated to medication-naïve FEP patient groups (publication 2)

c) A comparison of UHR-T to UHR-NT patients at baseline with the information of future transition to psychotic disorders (publication 3).

All three publications come with a set of shortcomings that limit the generalizability of their results. The following limitations will be highlighted as they are deemed the most important:

a) Confounding factors that weaken the comparisons: These include distribution differences of sex, age, illness duration; differences in medication duration, medication compliance and side effects; socio-economic functioning; nicotine and caffeine use; lack of patient baseline characteristics such as pre-treatment symptom severity levels and response status (publications 1-3)

b) Small sample sizes (publication 1-3)

c) Resting-state EEG pre-processing and analysis steps that could limit comparability to other studies (publications 1-3)

d) Methodological limitations of microstate analysis with four instead of seven topographies included (publications 2-3)

e) Lack of healthy control group (publication 2).

3.3 Outlook

Replication of the resting-state EEG microstates results are warranted and are ideally expanded to other resting-state EEG/MEG functional connectivity measures. As resting-state EEG microstates assess sensor-level functional connectivity at the global level of brain topography, measures that assess functional connectivity between single brain regions at the source level of the brain will be further informative. Longitudinal and pre-post designs that include within- and between-subject comparisons are needed, as well as drug challenges. These will contribute to better understanding treatment trajectories and fill the knowledge gap on the association of dopaminergic agents with neuronal network changes of the brain (dysconnectivity).

In order to establish resting-state EEG microstates as robust biomarker, further research is needed to establish consistent analysis methods across studies and sites. Making study data publicly available

(including unused data or null findings) will further support this endeavor and allow for a more conclusive picture on the pathophysiology of psychotic disorders.

Different subgroups of patients with psychotic disorders might need different treatment plans. Patient baseline characteristics, as well as reliable genetic, neuroimaging, electrophysiological and neurochemical biomarkers could therefore inform clinicians in treatment choice and predict response more reliably in a multi-domain approach.

With ongoing effort, the results of this dissertation could lead to a more biological than phenomenological approach for the diagnosis of psychiatric disorders. This would consequently lead to watering down the current diagnostic categories which is supported by authors who suggest that the underlying biology is poorly mapped by current diagnostic categories (Owen, 2014; Stephan et al., 2016) and by findings of biomarkers that do not respect diagnostic borders (Fernandes et al., 2009). By combining a wide set of different biomarkers, a more biologically-lead diagnosis system could be established (Cuthbert and Insel, 2013; Morris et al., 2015).

As treatment response and compliance in FEP patients are relatively low due to undesirable side-effects, there is a clear need to understand the interplay between antipsychotic medication and neuronal networks changes better. New approaches for treatment of psychotic disorders are needed. In a study with healthy controls for example, microstate class D could be successfully up-regulated using a neurofeedback-paradigm (Diaz Hernandez et al., 2016). These results indicate that resting-state EEG microstates can be modulated in a specific training program and that, once well established, could offer a further non-pharmacological treatment option.

Comprehensive individualized treatment plans will contribute towards improved functional outcomes for patients with psychotic disorders. Psychotherapeutic interventions, social and vocational support, self-management skills, cognitive remediation, as well as family interventions have been suggested by the American Psychiatric Association Practice Guidelines to complement pharmacological treatment (Keepers et al., 2020). These first-line therapies offered in many specialized care programs however could be extended towards more holistic treatment approaches including other research areas. To name a few, mindfulness-based interventions (for reviews and meta-analyses see Hodann-Caudevilla et al., 2020; Khoury et al., 2013), art therapy for psychotic disorders (Montag et al., 2014), positive self-development approaches (for a meta-analysis see Gleeson et al., 2020), and self-help and peer-based interventions (for a meta-analysis see Scott et al., 2015) could further enrich comprehensive individualized treatment plans. The outcome of these could then be measured by robust, multi-domain biomarkers to which resting-state EEG microstates ideally contribute to in future.

3.4 Conclusion

The results of this dissertation reveal resting-state EEG microstate classes A and B to differentiate mFEP from uFEP patients and suggest microstate class A as potential state marker of general psychopathology (FEP & UHR vs HC), microstate class B as potential state marker of psychosis illness progression (FEP vs. UHR) and microstate class D as potential trait marker for future transition to a psychotic disorder in UHR patients. With that, an association of the two pathophysiological models of psychotic disorders, the dopamine and the dysconnectivity hypotheses, could be shown. However, systematic evidence for the association of antipsychotic medication with resting-state EEG/MEG functional connectivity could not be found across studies published in the last twenty years. Methodological differences and differences in sample characteristics between the included studies of the systematic review contributed to the heterogeneity of results.

Further research is needed to assess the association of the dopamine and the dysconnectivity hypotheses. Confounding factors of inter- and intra-individual differences need to be addressed systematically, analysis methods need to be harmonized across sites and ideally, datasets are combined for heterogeneous analysis across studies. More studies with longitudinal designs are needed to rule-out between-subject differences and to track response trajectories, as well as pre-post effects of antipsychotic medication. Individualized, precise and holistic treatment options are needed for patients with psychotic disorders to ensure better functional outcomes beyond the first-line psycho-pharmacological treatments applied to date. Further research is needed to establish resting-state EEG microstates as robust biomarker in order to inform clinicians for the diagnosis, treatment and outcome prediction of psychotic disorders in a multi-domain approach.

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Appendix A: Model of the early course of psychosis

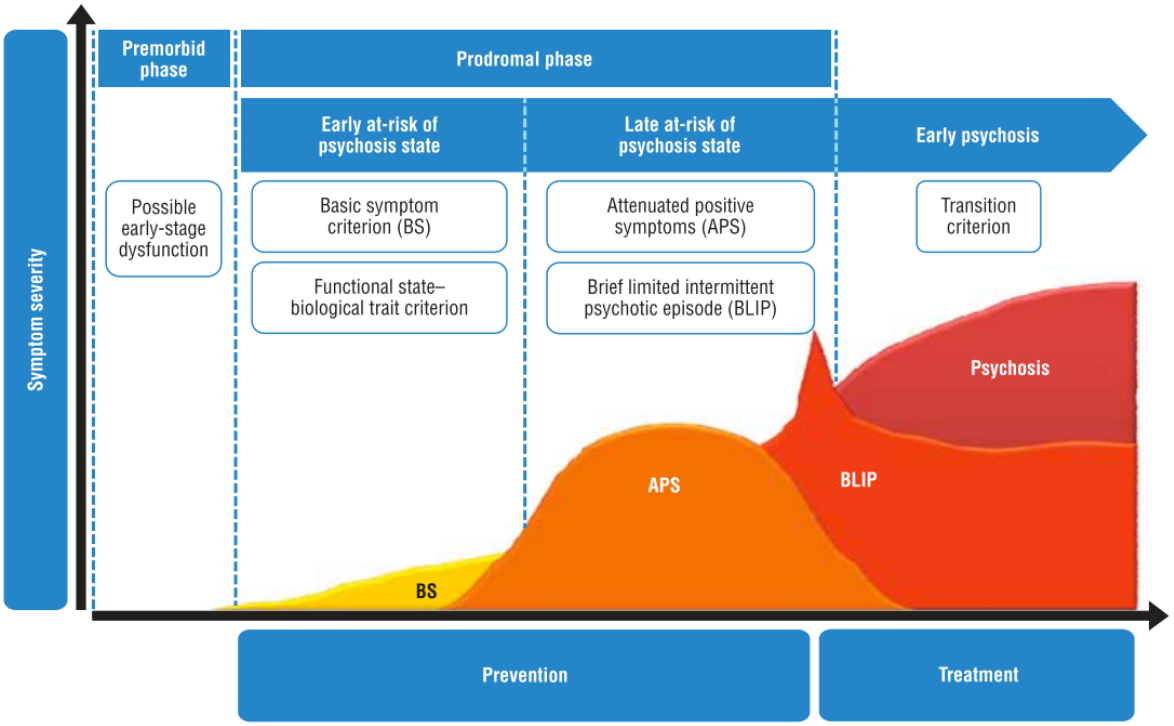

Figure 3: Model published in a comprehensive state-of the art review on the psychosis high-risk state by Fusar-Poli and colleagues (2013). The course of psychosis develops on the x-axis, the symptom severity increases on the y-axis.

Appendix B: Overview of instruments used for the assessment of the ultra-high-risk (UHR) state

Instrument	Structure and subscales relevant in the rating of APS and BLIPS
SIPS: Structured Interview for Psychosis-Risk Syndromes [64]	Modelled on the 'Positive and Negative Syndrome Scale' (PANSS) [41] Contains 4 subscales: positive, negative, disorganized, and general symptoms Five positive symptoms are used for the assessment of APS and BLIPS: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, disorganized communication/speech
CAARMS early (before 2006) versions: Comprehensive Assessment of At-Risk Mental States [130]	Modelled on various scales including the 'Brief Psychiatric Rating Scale' (BPRS) [82] Contains 8 subscales: disorders of thought content, perceptual abnormalities, conceptual disorganization, motor changes, concentration and attention, emotion and affect, subjectively impaired energy, and impaired tolerance to normal stress Three subscales are used for the assessment of APS and BLIPS: disorder of thought content, perceptual abnormalities, disorganized speech
CAARMS 2006 version: Comprehensive Assessment of At-Risk Mental States [131]	Modelled on earlier versions of CAARMS [130] Contains 7 subscales: positive symptoms, cognitive change attention/concentration, emotional disturbances, negative symptoms, behavioural change, motor/physical changes, and general psychopathology Four positive symptoms are used for the assessment of APS and BLIPS: unusual thought content, non-bizarre ideas, perceptual abnormalities, and disorganised speech
BSIP: Basel Screening Instrument for Psychosis [86]	Modelled on the BPRS [82] 46-item checklist used in combination with the BPRS Three symptoms of the BPRS are used for the assessment of APS: hallucinations, unusual thought content, and suspiciousness Four symptoms of the BPRS are used for the assessment of BLIPS: hallucinations, unusual thought content, suspiciousness, and conceptual disorganisation
ERIraos: The Early Recognition Inventory [63]	Modelled on the 'Instrument for the Retrospective Assessment of the Onset of Schizophrenia' (IRAOS) [33] Consists of a symptom list with 110 items, which is further structured into 12 sections Five sections include items used for the assessment of APS, BLIPS and also COPER: thought disorder, disorders of self and delusions, impaired bodily sensations, abnormal perceptions, and observation-based items
PANSS: Positive and Negative Syndrome Scale [41]	Contains 3 subscales: positive, negative and general psychopathology Four positive symptoms are used for the assessment of APS and BLIPS: delusions, hallucinations, suspiciousness, and conceptual disorganization
BPRS: Brief Psychiatric Rating Scale [82]	Contains 24 subscales: somatic concern, anxiety, depression, suicidality, guilt, hostility, elated mood, grandiosity, suspiciousness, hallucinations, unusual thought content, bizarre behaviour, self-neglect, disorientation, conceptual disorganisation, blunted affect, emotional withdrawal, motor retardation, tension, uncooperativeness, excitement, distractibility, motor hyperactivity, mannerisms and posturing Four subscales of the BPRS are used for the assessment of APS and BLIPS: unusual thought content, hallucinations, suspiciousness, and conceptual disorganisation

APS: Attenuated Psychotic Symptoms; BLIPS: Brief Limited Intermittent Psychotic Symptoms; COPER: Cognitive-Perceptive basic symptoms.

Table 1: Overview of assessment instruments published in the EPA-guidance on the early detection of clinical high risk states of psychoses by Schultze-Lutter and colleagues (2015).