In search of the self

On self-disturbances and social cognition in schizophrenia

Brain Center Rudolf Magnus

Merel Prikken

In search of the self

On self-disturbances and social cognition in schizophrenia

Merel Prikken

In Search of the Self

The research described in this thesis was funded by a VIDI grant from the Netherlands Organization for Scientific Research (NWO) to dr. N.E.M. van Haren. Financial support for the publication of this thesis was kindly provided by the Brain Center Rudolf Magnus.

ISBN: 978-94-6299-957-2

Cover design: Iris Bos
Lay-out: Ridderprint BV – www.ridderprint.nl
Printing: Ridderprint BV – www.ridderprint.nl

In search of the self

On self-disturbances and social cognition in schizophrenia

Op zoek naar het zelf
Over zelfstoornissen en sociale cognitie bij patiënten met schizofrenie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
vrijdag 22 juni 2018 des middags te 12.45 uur

door

Merel Prikken

geboren op 19 november 1988 te Havelte

Promotoren:
Prof. dr. N.E.M. van Haren
Prof. dr. H. Aarts

Copromotor:
Dr. A. van der Weiden

Contents

Chapter 1
General introduction 7

Chapter 2
Self-other integration and distinction in schizophrenia : A theoretical analysis and a review of the evidence 17

Chapter 3
Multisensory integration underlying body ownership in schizophrenia and offspring of patients: A study using the Rubber Hand Illusion paradigm 51

Chapter 4
Impaired self-agency inferences in schizophrenia: The role of cognitive capacity and causal reasoning style. 73

Chapter 5
Abnormal agency experiences in schizophrenia patients: Examining the role of psychotic symptoms and familial risk. 93

Chapter 6
The role of the self-reflection network in cognitive and affective empathy in schizophrenia and healthy individuals 111

Chapter 7
Summary and general discussion 133

Chapter 8
References 141

Chapter 9
Nederlandse samenvatting 163

Chapter 10
Dankwoord 171
List of publications 177
Curriculum Vitae 179

General introduction

1

For most patients with schizophrenia it is difficult to sufficiently participate in the community, largely due to deficits in social interaction. These problems in social interaction can have a profound impact on patients' relationships with family and friends and their ability to maintain a job, which can consequently lead to poor quality of life. The decreased ability to interact with other people and understand them is affected by the way patients perceive them*selves*. Schizophrenia has been recognized as a disorder of self-disturbances long ago and these disturbances might pose problems for the integration and distinction between patients' own and other people's intentions, thoughts, and emotions. This thesis aims to investigate how these problems in self-other distinction might be manifested in patients with schizophrenia. Specifically, a series of studies explore how schizophrenia is related to components that are crucial for making a distinction between oneself and others. This introductory chapter will first provide a framework for the understanding and examination of the role of self-disturbances in schizophrenia in the ability to understand and to distinguish oneself from others.

Schizophrenia as a disorder of self-disturbance

Schizophrenia is a disease that affects 15 per 1000 individuals each year and has a lifetime prevalence of 0.7% (Tandon, Keshavan, & Nasrallah, 2008). The main diagnostic criteria are positive symptoms, i.e., behavior or experiences that are normally absent, negative symptoms, i.e., behavior or experiences that are normally present, and disorganized speech or behavior (American Psychiatric Association, 2013). Positive symptoms can either be delusions or hallucinations: a delusion is a *belief* that persists despite of conflicting evidence (e.g., the thought of being persecuted), whereas a hallucination is a *perception* that is experienced in the absence of external stimuli (e.g., seeing people that are not there). Although these are the symptoms that characterize a patient with schizophrenia, disruptions in neurocognition (e.g., attention, memory, executive functioning, etc.) and social cognition also co-occur and often persist after positive symptoms faded (Bora, Yucel, & Pantelis, 2009a; M. F. Green, Horan, & Lee, 2015; Kahn & Keefe, 2013; Klingberg, Wittorf, Sickinger, Buchkremer, & Wiedemann, 2008).

Additionally, the presence of self-disturbances has long been recognized to be part of the disease. Already in 1911 Eugene Bleuler introduced the term *schizophrenia*, which can be translated as 'split mind' or 'split personality', and recognized that the self was never intact in these patients (Bleuler, 1911). More recently, disruptions of the self have been a topic of interest in empirical research and they are seen as a core feature of schizophrenia (Parnas & Handest, 2003; Sass & Parnas, 2003). Importantly, these disruptions are clearly manifested in the symptoms patients suffer from. For example, psychotic experiences such as hearing voices that are not audible for other people or having the idea that some external source controls your thoughts indicate that in patients with schizophrenia the boundaries between the self and the outside world are faded.

Understanding self and others

Understanding the self is essential for social cognition, which defined as 'the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior' (Adolphs, 2001, p.231). Distortions in understanding the relation between self and other can be described in terms of integration and distinction (van der Weiden, Prikken, & van Haren, 2015). For example, when *integration* between self and other goes wrong, we might not be able to understand other people's thoughts, emotions, or actions. On the other hand, problems in making a *distinction* between self and others might cause us to confuse other people's bodies, emotions, or actions with our own. Importantly, integrating and distinguishing represent a spectrum and cannot be treated separately. For example, feeling upset when seeing someone in pain can be described as excessive integration, but also as a lack of distinction between other people's emotions and our own. **Chapter 2** elaborates on disturbances in self-other integration and distinction in schizophrenia and describes them in terms of understanding the *self* and understanding *others*.

Also, chapter 2 provides a framework for chapters 3 to 6, in which I report empirical data on three social cognitive processes that are relevant to schizophrenia within the context of self and other processing: body ownership, self-agency, and empathy. Definitions of these topics are given in Box 1.

Box 1. Definitions of body ownership, self-agency, and empathy

Understanding the self

• Body ownership: the feeling of being the subject of one's own actions and thoughts
e.g., *I feel that it is **my** arm that is reaching for a glass.*
• Self-agency: the feeling of being the author of one's own actions and thoughts
e.g., *I feel that **I** am the one that caused my arm to reach for a glass.*

Understanding others

• Empathy: the ability to understand and interpret other people's intentions and thoughts (cognitive empathy) or emotions (affective empathy)

The feeling of body ownership and self-agency are considered the most important aspects for basic, minimal, intuitive, or primitive self-experience (Gallagher, 2000; Sass & Parnas, 2003). That is, they contribute to the feeling of presence, consciousness about our own sensations, and a sense of *being*. Although the two concepts are closely related, it is important to note

that disturbances can occur independently. For example, a psychotic patient might have the feeling that some *external* source is in control over his/her arm movement (impaired feeling of self-agency), but that this arm is part of his/her *own* body (intact feeling of body ownership).

To increase understanding of these concepts and its relevance for schizophrenia, I included different populations in the studies that are described in this thesis. First, in order to examine self-disturbances in established illness, adult patients with schizophrenia were recruited. Second, as the presence of self-disturbance might be a vulnerability marker for psychosis (Nelson, Thompson, & Yung, 2012), familial high-risk populations were included. The first sample was a subsample of a longitudinal cohort of children and adolescents with first- or second-degree family member with a psychotic or bipolar disorder (Brain Imaging, Development, and Genetics (BRIDGE)). Studying the development of this population provides the opportunity to assess whether deficits in established illness might be present before disease onset. For analyses in the current thesis, data from a single time point, rather than longitudinal data, was available. Nevertheless, demonstrating that certain symptoms of established illness are present in this population can aid in identifying those that are at increased risk to develop psychopathology at a later age. A second familial high-risk sample (from Genetic Risk and Outcome in Psychosis (GROUP); Korver et al., 2012) consisted of unaffected (adult) siblings of patients with schizophrenia in order to further investigate a potential familial vulnerability to self-disturbances.

Body ownership

Impaired integration and distinction of self and others in schizophrenia is manifested in for example abnormal bodily experiences. More specifically, patients may feel that the borders of the body are faded or that bodily parts do not feel like their own (Stanghellini, 2009; Stanghellini et al., 2014). The latter example describes a decreased sense of body ownership. Impairments herein have been confirmed empirically by using an experiment which is called the Rubber Hand Illusion (RHI; Ferri et al., 2014; Graham, Martin-Iverson, Holmes, Jablensky, & Waters, 2014; Lev-Ari, Hirschmann, Dyskin, Goldman, & Hirschmann, 2015; Peled, Pressman, Geva, & Modai, 2003; Peled, Ritsner, Hirschmann, Geva, & Modai, 2000; Thakkar, Nichols, McIntosh, & Park, 2011). In this experiment, originally described by Botvinick & Cohen, the real right hand and a fake rubber left hand are visible to an individual, whereas the own left hand is covered up and remains invisible (Botvinick & Cohen, 1998; see Figure 1 for the experimental set-up used in the current study). When an experimenter applies simultaneous stroking of the fake left hand *and* the invisible real left hand (using a brush), a sense of body ownership over the fake hand can be induced. Although evidence from RHI-paradigms shows that patients have disturbances in experiences of body ownership, this evidence is scarce and the use of different experimental procedures on small sample sizes impedes drawing definite conclusions.

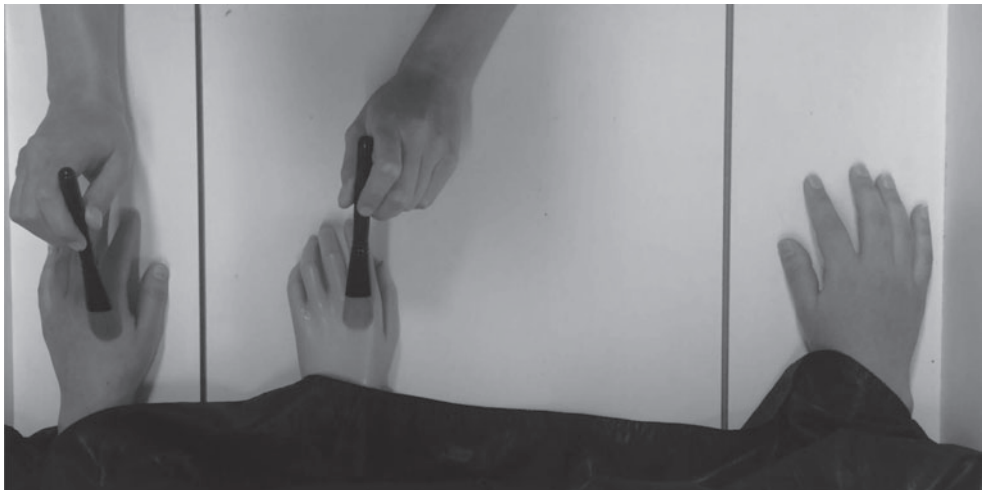


Figure 1. Rubber Hand Illusion set-up in the current study

To arrive at illusory experiences of ownership, information from different sensory modalities such as visual, tactile, and proprioceptive sources is integrated by different parts of the brain (Botvinick, 2004; Ehrsson, 2012; Graziano & Botvinick, 2002). This multisensory integration of information underlies a feeling of body ownership, as shown by the RHI. Also, evidence suggests that this experience of illusory ownership influences how the self is perceived in relation to others (Tsakiris, 2017). As an example, the degree of ownership over a fake rubber hand with a different racial color has been found to be positively related to a decrease in racial bias (Maister, Sebanz, Knoblich, & Tsakiris, 2013). These findings suggest that multisensory integration underlying body ownership is relevant for perception of the self, as well as social perception.

Chapter 3 describes a study on multisensory integration in schizophrenia, using a well-controlled RHI paradigm. Furthermore, to gain insight in the *development* of potential disturbances, this chapter examines multisensory integration in children and adolescents with and without increased familial risk to develop psychotic or mood disorders.

Self-agency

The experience of oneself being the author of one's own actions and the resulting consequences, i.e., the sense of self-agency, is an essential part of self-perception and social interaction. The sense of self-agency results from perceiving effects of one's own actions as being caused by oneself; an action-perception process that has been explained by two different models: the motor prediction model and the cognitive inference model. First, the motor prediction model explains agency experiences over actions through the motor control system (Frith, Blakemore, & Wolpert, 2000a; Wolpert & Flanagan, 2001). That is, when

an efference copy of an intended action matches the sensory consequences of that action, a feeling of self-agency arises. However, motor predictions become less reliable in more complex, for example social situations. In these cases the cognitive inference model comes into play (Aarts, Custers, & Wegner, 2005; Wegner, 2002). According to this model, self-agency can also be *inferred* based on prior beliefs or knowledge about the action-effects. The literature review in chapter 2 describes both models in detail and explains how they are impaired in patients with schizophrenia. The cognitive inference model in particular is thought to be relevant for social behavior, and therefore it has potential to explain some of the variance of impaired social functioning in schizophrenia. As this model is underexposed in the schizophrenia literature despite its potential relevance, it is the focus of the studies on self-agency in this thesis.

Intuitively, self-agency inferences seem closely related to other terms of personal causation, such as locus of control, free will, or attributional style. Interestingly, attributional style, defined as the tendency to explain events by internal or external causes, was previously found to be impaired in schizophrenia (e.g., Janssen et al., 2006; Mehl et al., 2014; Mehta, Thirthalli, Bhagyavathi, et al., 2014). Aiming to increase understanding of the origin of disturbances of self-agency inferences in schizophrenia, **Chapter 4** examines whether impairments in attributional style are related to these inferences.

It is not surprising that experiences of self-agency are widely investigated in patients with schizophrenia. That is, the first-rank or passivity symptoms of the disease, i.e., symptoms in which patients experience diminished or even no control over their actions or thoughts, have been identified long ago (Schneider, 1939). According to this definition, passivity symptoms can be interpreted as *decreased* experiences of self-agency (i.e., underattribution of agency). Conversely, some other psychotic symptoms can be interpreted as *increased* experiences of self-agency (i.e., overattribution of agency). As an example of overattribution of agency, patients with delusions of grandiosity might hold the belief that they are able to cause events that are actually out of their control. Box 2 depicts how under- and overattribution of agency is reflected in symptoms of schizophrenia.

Although there is evidence for impaired self-agency inferences in schizophrenia (Renes, van der Weiden, et al., 2015; Renes, Vermeulen, Kahn, Aarts, & van Haren, 2013), the question remains *how* it is related to the disease, as both symptoms of over- and underattribution can occur simultaneously. Therefore, **Chapter 5** describes how self-agency inferences might be related to these specific symptom groups. Also, it describes whether impaired self-agency experiences are specific to patients with established illness or whether they are also present in individuals with a familiar risk to develop the disease.

Box 2. Symptoms of over- and underattribution of agency.

Overattribution:
agency attribution to the self

- Grandiosity
- Guilt delusions
- Ideas of reference

Underattribution:
agency attribution to external sources

- Delusions of control
- Thought insertion
- Thought withdrawal
- Auditory (verbal) hallucinations

Empathy

A widely studied domain of social cognition concerns empathy, which is usually described from a cognitive and an affective perspective (Shamay-Tsoory et al., 2007). Whereas cognitive empathy involves understanding and integrating other people's *thoughts and intentions*, affective empathy involves understanding and integrating other people's *emotions*. Previous studies showed that patients with schizophrenia experience problems in understanding other people's cognitive as well as affective states (Abu-Akel & Shamay-Tsoory, 2013; Bora, Yucel, & Pantelis, 2009c; Derntl et al., 2009), which is in turn associated with poor (social) functioning (Bora, Eryavuz, Kayahan, Sungu, & Veznedaroglu, 2006; Fett et al., 2011; Smith et al., 2012). According to the simulation theory, other people's thoughts, emotions, or intentions are understood and interpreted by incorporating knowledge about the self (Gallese & Goldman, 1998). Consequently, as patients with schizophrenia have problems in reflecting on the self, this might explain the alterations in empathic abilities.

Patients' impairments in self-reflection have been repeatedly shown by fMRI studies that pointed towards alterations in underlying neural networks (e.g., Murphy et al., 2010; Pankow et al., 2016; Van Buuren, Gladwin, Zandbelt, Kahn, & Vink, 2010; van der Meer, de Vos, et al., 2013; Zhang et al., 2016). Several studies found differential activation levels in the cortical midline structures in patients compared with healthy controls, mainly in the mPFC (e.g., Bedford, Surguladze, Giampietro, Brammer, & David, 2012; Liu, Corbera, & Wexler, 2014; Murphy et al.,

2010; Pankow et al., 2016). **Chapter 6** examines whether impaired empathic behavior in patients might be affected by these alterations in the neural network of self-reflective processing.

Chapter overview

To summarize, this thesis provides insight into self-disturbances and social cognitive functioning in schizophrenia. **Chapter 2** provides a selective literature review regarding self-other integration and distinction in health and schizophrenia and provides a framework for chapters 3-6. In **Chapter 3**, multisensory integration processes underlying body ownership experiences, and its relation with psychotic symptoms, are described in patients with schizophrenia and individuals at increased risk to develop the disease. **Chapter 4** elaborates on the relationship between (impaired) self-agency inferences on one hand and attributional style and neurocognitive functioning on the other hand. Building on this topic, **Chapter 5** provides insight into the relationship between impaired self-agency inferences and symptoms of over- and underattribution in schizophrenia. Also, it describes inferences of self-agency in individuals at increased familial risk to develop psychosis. Last, **Chapter 6** focusses on how decreased empathic abilities in schizophrenia might be related to functional brain abnormalities during self-reflection.

Self-other integration and distinction in schizophrenia: a theoretical analysis and a review of the evidence

Anouk van der Weiden
Merel Prikken
Neeltje E.M. van Haren

2

Reference:
van der Weiden, A., Prikken, M., & van Haren, N. E. M.(2015). Self–other integration and distinction in schizophrenia: A theoretical analysis and a review of the evidence. Neuroscience & Biobehavioral Reviews, 57, 220-237.

Abstract

Difficulties in self–other processing lie at the core of schizophrenia and pose a problem for patients' daily social functioning. In the present selective review, we provide a framework for understanding self–other integration and distinction, and impairments herein in schizophrenia. For this purpose, we discuss classic motor prediction models in relation to mirror neuron functioning, theory of mind, mimicry, self-awareness, and self-agency phenomena. Importantly, we also discuss the role of more recent cognitive expectation models in these phenomena, and argue that these cognitive models form an essential contribution to our understanding of self–other integration and distinction. In doing so, we bring together different lines of research and connect findings from social psychology, affective neuropsychology, and psychiatry to further our understanding of when and how people integrate versus distinguish self and other, and how this goes wrong in schizophrenia patients.

Introduction

In daily life people rarely act in social isolation. To ensure fluent and efficient social interaction people have to coordinate and *integrate* other people's thoughts, emotions, and behavioral intentions with their own (e.g., representing both one's own and another person's movements and grip when passing the salt). A prerequisite for doing this is the ability to *distinguish* between self and other. After all, when confusing self and other, one may project one's own intentions and emotions onto others, or take over the intentions and emotions of others. As such, it becomes challenging to develop a personal identity, regulate behavior, or hold one another responsible for certain behavior.

As social beings, our brain seems to be designed to integrate our own and other people's intentions and emotions, as well as to distinguish between self and other. In most individuals integration and distinction of self and other is a well-balanced process, which occurs without effort or conscious attention. However, not everyone is blessed with the capacity to balance self-other distinction and integration. Specifically, schizophrenia patients often experience no control over their behavior and exhibit difficulties in distinguishing their own feelings, intentions, actions and their outcomes from those of others. Accordingly, recent literature has focused on self-disturbances as a possible explanation for both positive (i.e., extra thoughts, feelings, and behaviors not seen in healthy controls, e.g., delusions of control, auditory hallucinations, grandiosity, and delusions of reference) and negative symptoms of schizophrenia (i.e., absence of normal thoughts, feelings, and behaviors, e.g., affective flattening, apathy, anhedonia, and avolition; Sass, 2014; Sass & Parnas, 2003). Moreover, recent work shows that self-other disturbances (e.g., externalizing action control, aberrant self-awareness, and misunderstanding other people's intentions and emotions) are already present in early stages of the disease (Amminger et al., 2012; An et al., 2010; Parnas et al., 2011; Thompson et al., 2012; Thompson, Papas, Bartholomeusz, Nelson, & Yung, 2013) and might even be predictive of schizophrenia onset in symptomatic and genetically high risk individuals (Nelson et al., 2012; Parnas, Carter, & Nordgaard, 2014). Such findings indicate that self-disturbances lie at the core of the disease (Bleuler, 1911; Hemsley, 1998; Mishara, Lysaker, & Schwartz, 2014; Sass & Parnas, 2003).

With regard to self-other processing, evidence shows that, although schizophrenia patients are able to *integrate* their own and others' (sometimes misinterpreted) behaviors and emotions (Abu-Akel & Shamay-Tsoory, 2013), they typically exhibit difficulties in *distinguishing* their own behaviors and emotions from those of others (Asai, Mao, Sugimori, & Tanno, 2011; Ford, Gray, Faustman, Roach, & Mathalon, 2007; Jardri et al., 2009, 2011). For example, some patients hear voices which they actually (sub vocally) produce themselves (Gould, 1948; M. F. Green & Kinsbourne, 1990; van der Gaag, 2006), feel their limb movements being controlled by aliens (Frith, 2005), or think they caused events that are actually caused by someone else, as in delusions of reference (Synofzik, Vosgerau, & Voss, 2013). In addition, a lack of self-other distinction may explain why patients get more easily distressed when confronted with the

distress of others (i.e., emotional contagion; Montag, Heinz, Kunz, & Gallinat, 2007).

Thus, abnormal processing of self and other is reflected in clinical symptoms, but also in an array of neural, social cognitive, and behavioral dysfunctions (Nelson, Whitford, Lavoie, & Sass, 2014). As such, it may be an important factor in explaining impaired social functioning in schizophrenia patients. Indeed, schizophrenia patients often struggle in social interactions (T. L. Patterson, Moscona, McKibbin, Davidson, & Jeste, 2001; Pinkham & Penn, 2006; Pinkham, Penn, Perkins, Graham, & Siegel, 2007) and this is an outcome of the disease that patients find extremely difficult to cope with (Gorwood et al., 2013; Świtaj et al., 2012). The difficulties patients encounter in social interaction are usually explained by impairments in social cognition (Fett et al., 2011), for example in theory of mind (Brown, Tas, Can, Esen-Danaci, & Brüne, 2014). As social cognition is defined as 'the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior' (Adolphs, 2001), self-other processing is a crucial aspect of social cognition, and is thus essential to social functioning.

Research on social cognition in schizophrenia has so far mainly focused on patients' ability to understand or *integrate* their own and others' intentions and emotions (e.g., emotion recognition, theory of mind). Surprisingly, little attention has been devoted to problems in self-other *distinction*. Distinguishing between the two concepts is complicated though, as integration and distinction of self and other are inextricably intertwined. That is, some processes underlying self-other integration may also affect self-other distinction, and vice versa. In this review article, we address the difficulties patients face when it comes to integrating as well as distinguishing self and other, and zoom in on mechanisms that may underlie self-other integration and distinction.

We can distinguish two major mechanistic models. So far, most work proposes that self-other processing crucially relies on the extent to which our motor control system is able to predict our own as well as others' actions and outcomes. However, people cannot always rely on motor predictions to integrate or distinguish self and other (i.e., when one has no clear prediction of one's own or others' actions, for example when actions may result in a variety of outcomes). In line with this notion, a second model has been proposed that takes into account, and emphasizes, the role of people's cognitions about their own and others' action-outcomes.

First, we will review research that was initially developed to map the perception and understanding of behaviors, intentions, and emotions of *others* (other-perspective). This research mainly focused on self-other integration, but we will show that it also provides insight into self-other distinction. Specifically, we will discuss the role of motor prediction as reflected in mirror neuron function and its implications for theory of mind and mimicry. Next, we will review research that was initially developed to map the perception and understanding of *one's own* behaviors, intentions, and emotions as distinct from those of others (self-perspective). Here, we specifically focus on the role of motor prediction in self-awareness and self-agency

phenomena. In addition, we will discuss more recent research that suggests that self-other distinction does not always arise from motor prediction processes, but may also result from cognitive expectation processes that deal with information pertaining to one's own and others' behaviors, beliefs, and emotions. Figure 1 shows a heuristic model depicting how the different motor prediction and cognitive expectation processes that will be discussed aid self-other integration and distinction.

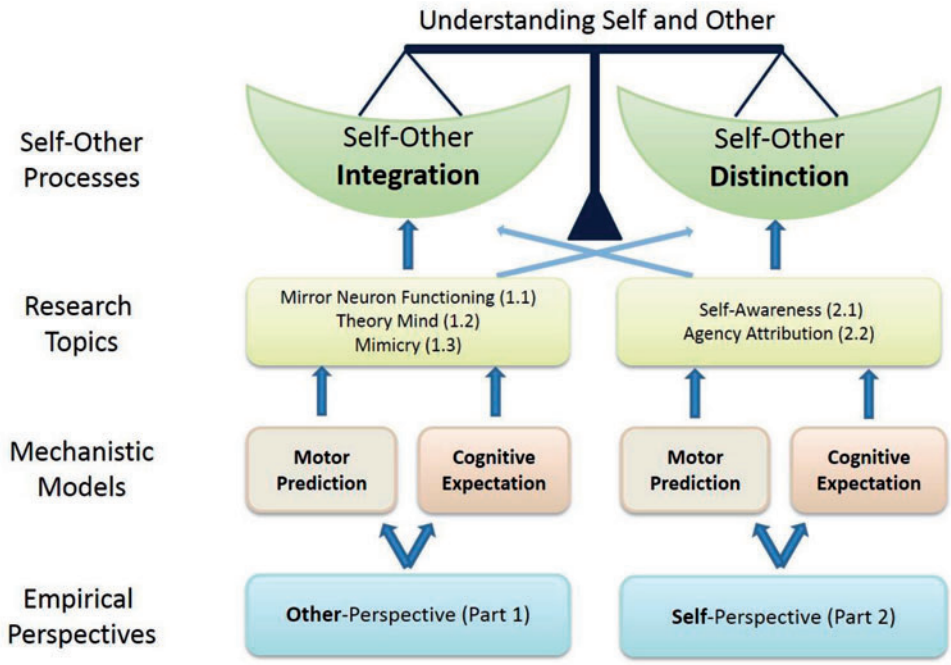


Figure 1. This figure depicts how cognitive and motor processes aid self-other integration and self-other distinction.

Essentially, we propose that motor prediction and cognitive expectation processes are both affected in schizophrenia, and may each explain disturbances in self-other integration and distinction depending on the requirements of the task or context. Thus far, research on cognitive models of self-other integration and distinction evolved independently of research on motor prediction models, although recent studies have emerged investigating the interaction between cognitive and motor processes in self-awareness and agency attribution (Gentsch & Schütz-Bosbach, 2011; Moore, Wegner, & Haggard, 2009; Sato, 2009; van der Weiden, Aarts, & Ruys, 2013). Furthermore, research on self-other *integration* mainly focused on the role of motor prediction in understanding *other people's* intentions and emotions (other-perspective),

whereas research on self-other *distinction* mainly focused on the role of motor prediction in understanding *one's own* intentions and emotions (self-perspective). Our aim is two-fold. First, we show that processes underlying self-other integration and self-other distinction are associated and may influence each other. Second, we show that in situations where motor prediction cannot inform self-other integration and distinction self-other processing is crucially affected by cognitive expectations.

Our goal is not to provide a complete overview of the available studies. Rather, we give a selective review in order to bring together these different lines of research to further our understanding of when and how people integrate or distinguish self and other, and how this is impaired in schizophrenia patients. Finally, we will briefly discuss how self-other integration and distinction as resulting from motor prediction and cognitive expectation processes may affect social functioning in healthy controls and schizophrenia patients, and as such pave the way for promising and exciting directions for future research.

Part 1: Perception and Understanding of Others (Other-Perspective)

There is consistent and convincing evidence that the motor prediction system plays an important role in the representation of the behavior of others (i.e., other-perspective). Hence, motor prediction is often proposed as a model explaining self-other integration. We will integrate findings from studies on mirror neurons, theory of mind, and mimicry in healthy controls and schizophrenia patients, and explain them in the context of motor prediction. Specifically, we discuss how, at the neural level, mirror neurons not only facilitate people's understanding of others' behaviors and emotions, but also play a key role in distinguishing their own behaviors and emotions from those of others (see section 1.1). In addition, we will discuss how theory of mind (section 1.2) and mimicry (section 1.3) may be affected by impairments in mirror neuron functioning. Also, in the latter two sections we will discuss the role of cognitive biases in theory of mind and mimicry in situations where motor predictions are less reliable (e.g., when actions can have multiple different consequences, or when it is unclear who performed the action).

1.1. Mirror Neurons

Self-other integration. In the past decade, researchers have identified specific neurons that are involved in the processing of both one's own actions and those of others. This so-called mirror neuron network consists primarily of the inferior parietal lobe (guiding sensorimotor action and perception; Mattingley, Husain, Rorden, Kennard, & Driver, 1998) and the ventral premotor cortex (involved in action planning and control; Hoshi & Tanji, 2006; Króliczak, McAdam, Quinlan, & Culham, 2008) plus the caudal part of the inferior frontal gyrus (associated with inhibition and attentional control; Hampshire, Chamberlain, Monti, Duncan, & Owen,

2010), but may also include other areas depending on the characteristics of the observed or performed action (e.g., the primary auditory cortex for actions producing sounds; see Cattaneo & Rizzolatti, 2009; Molenberghs, Cunnington, & Mattingley, 2012 for an overview). This network may be a fundamental feature of the brain, which enables implicit action understanding during interactions with the outside world (Gallese, 2003). The first studies on mirror neurons were conducted in macaque monkeys and showed that these neurons fired not only when macaques were grasping for an object themselves, but also when they observed another macaque or a human being grasping for an object (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). This pre-reflective action simulation demonstrates a link between self and other (Gallese, 2003), and reflects the integration of one's own and others' actions.

Recently, similar findings have been demonstrated in humans (Cochin, Barthelemy, Lejeune, Roux, & Martineau, 1998; Cochin, Barthelemy, Roux, & Martineau, 1999; Hari et al., 1998; Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010). However, in contrast to early conceptions of the mirror neuron system that have been extensively debated (Hickok, 2009; Hickok & Hauser, 2010; Steinhorst & Funke, 2014), recent studies suggest that mirror neurons do not simply activate an identical (i.e., mirroring) motor representation of the physical properties of the observed behavior. Rather, mirror neuron responsiveness is goal-dependent (Bonini, Ferrari, & Fogassi, 2013; Ocampo & Kritikos, 2011), highlighting the central role of mirror neurons in higher level action understanding. That is, mirror neurons are equally responsive to a variety of actions (e.g., grasping or scooping) aimed at the same goal (e.g., eating), while mirror neurons are differentially activated for identical actions (e.g., grasping) with different goals (e.g., eating or placing). Furthermore, brain activation in the mirror neuron network is more pronounced when one observes another person's incomplete actions (grasping a cup in order to drink), rather than observing past action phases (Urgesi et al., 2010). Specifically, both during the planning of one's own actions and during the observation of others' actions, the same (mirror) neurons are activated in the premotor cortex. In other words, the observed ongoing action corresponds with an action that is familiar to the observer, enabling the observer to predict the actor's action-outcomes (Kilner, Friston, & Frith, 2009).

Furthermore, mirror neurons do not only serve to understand or anticipate simple hand actions, but are also involved in understanding and anticipating more subtle emotional expressions (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Iacoboni, 2009; Rizzolatti & Craighero, 2005). Specifically, overlapping brain areas (including the mirror neuron network and the limbic system) are activated when imitating or merely observing facial expressions (Carr et al., 2003; Molenberghs et al., 2012). Also, mirror neuron activity has been related to emotional empathy, indicating that mirror neurons play a key role in the understanding of other people's emotions (Kaplan & Iacoboni, 2006). Thus, the mirror neuron system is essential and fundamental for social interaction where people have to coordinate their behavior with

others and anticipate and integrate the behavioral and emotional consequences of their own and others' actions (see also Sobhani, Fox, Kaplan, & Aziz-Zadeh, 2012). As such, the mirror neuron network has been primarily associated with understanding and integrating people's own and other's behaviors and emotions.

Self-other distinction. The mirror neuron network is also crucially involved in distinguishing between one's own and others' behaviors or emotions. That is, a subset of mirror neurons in the hippocampus, parahippocampal gyrus, and entorhinal cortex show patterns of inhibition during action observation, while patterns of excitation were found during action performance, and this has been proposed to be one of the fundamental mechanisms underlying self-other distinction (Mukamel et al., 2010). Mirror neurons thus allow one to simulate, anticipate, and understand the behavior of others (i.e., self-other integration), while at the same time they facilitate the distinction between one's own and others' actions (Veluw & Chance, 2013).

Mirror neuron function in schizophrenia. Studies in schizophrenia patients have shown that, similar to what happens in healthy people, the mirror neuron network is activated both in case of observing and performing an action (Jardri et al., 2011; McCormick et al., 2012; Thakkar, Peterman, & Park, 2014). However, patients show abnormalities in the extent to which mirror neuron networks are activated when performing or observing actions. Specifically, compared with healthy controls, patients show overall reduced activity in the mirror neuron network (i.e., inferior parietal lobe, (pre)motor cortices, and inferior frontal gyrus), and this reduction has been related to negative symptoms and impaired social cognition (Mehta, Thirthalli, Aneelraj, et al., 2014). This suggests that schizophrenia patients may be capable of understanding and anticipating (and thus integrating) the behavior of others, but possibly do this to a lesser extent than do healthy controls.

In addition, mirror neuron activity in schizophrenia patients does not differentiate between self-performed and other-performed actions (Jardri et al., 2011; McCormick et al., 2012; Thakkar et al., 2014), making it more difficult to distinguish between self and other. For example, in the study by Jardri and colleagues participants had to listen to their own recorded voice while mentally repeating the words (i.e., self-generated voice), and passively listen to unfamiliar voices (i.e., other-generated voice) and reverse-taped voices (i.e., control condition) (Jardri et al., 2011). Results revealed that when comparing self- versus other-generated voice, patients showed increased neural overlap in terms of space and amplitude in the medial frontal, medial parietal, and right middle temporal cortices as well as the right inferior parietal lobule. The increased overlap in the right inferior parietal lobule was due to increased activation in this area for self-produced voice compared with healthy controls, which may explain for example why some patients perceive their own voice as being externally generated (i.e., auditory hallucinations). In line with this notion, the level of activity in the right inferior parietal lobule positively correlated with positive symptoms.

Reduced activation and differentiation in the mirror neuron network may thus explain part of the negative and positive symptoms of schizophrenia, respectively. The lack of activation and/or self-other distinction at the mirror neuron level may further complicate the planning, monitoring, performance, and regulation of actions (see also part 2 of this review). Alternatively, as mirror neuron activation in the premotor cortex reflects the prediction and anticipation of the behavior of others, it may be that patients' impairments in motor prediction lead to less precise and thus more overlapping mirror neuron activation for their own and other's behavior. There may even be a bi-directional relationship between mirror neuron function and motor prediction (see Figure 2). Future research may be able to identify the direction of causality in this respect.

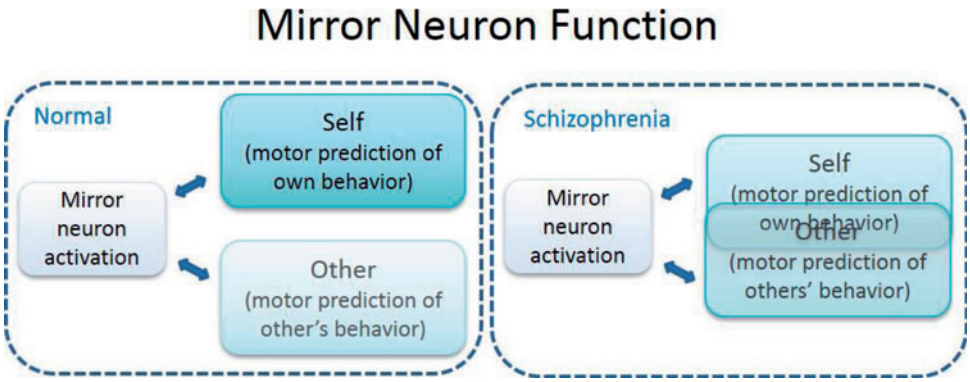


Figure 2. This figure illustrates how mirror neuron function may be related to the prediction of one's own and other people's behavior. Specifically, mirror neuron activation in the motor cortex is usually higher when predicting one's own behavior compared with predicting other people's behavior. However, in schizophrenia, the prediction of other people's behavior results in the same amount of neural activation as predicting or planning one's own behavior. This may be a consequence of imprecise motor predictions, and could lead to the perception of illusory relations between one's own and other people's behavior.

1.2. Theory of mind

Current directions in social neuroscience suggest that mirror neuron functioning is crucial for an adequate theory of mind (Gallese & Goldman, 1998; Goldman, 1989, 2009), commonly defined as the understanding of other people's intentions and behavior (i.e., cognitive theory of mind) and other people's emotions (Abu-Akel & Shamay-Tsoory, 2013). Indeed, according to simulation theory, a basic recognition (Bora et al., 2005) and understanding of other people's behaviors and emotions can result from the motor *simulation* of these behaviors and emotions by the mirror neuron system (Gallese & Goldman, 1998; Goldman, 1989, 2009). However, in complex social situations where the understanding of other people's behaviors and emotions

requires an appreciation of social rules, motor simulation is not sufficient. These situations additionally require people to rely on cognitive *theories* or beliefs (cf., theory theory; Gopnik & Wellman, 1992; Perner & Howes, 1992). For example, people have to draw upon cognitive beliefs and theories in order to understand whether people in the direct social environment are laughing with or at you, or to understand why someone says to find something tasty while her face expresses disgust (e.g., lying, being polite, or being sarcastic), or why someone who just won the lottery is crying (i.e., tears of joy). The understanding of such complex intentions and emotions requires the integration of different (sometimes conflicting) messages that are difficult to understand when merely simulating a person's facial or bodily expressions.

Theory of mind in schizophrenia. So far, the evidence regarding schizophrenia patients' theory of mind is inconsistent. Some studies suggest that theory of mind is intact (Abu-Akel, 1999; Bora et al., 2006; Brüne, 2003; Pousa et al., 2008; Sarfati, Hardy-Baylé, Brunet, & Widlöcher, 1999; Walston, Blennerhassett, & Charlton, 2000; Walter et al., 2009), while others indicate impairments in theory of mind in schizophrenia (Brüne, 2005a; Derntl et al., 2009; M. F. Green et al., 2012; Haker & Rössler, 2009; Langdon, Coltheart, & Ward, 2006; Varcin, Bailey, & Henry, 2010) as well as in populations at high risk to develop schizophrenia (Chung, Kang, Shin, Yoo, & Kwon, 2008; Marjoram et al., 2006). Based on the above, there are several possible explanations for the inconsistent findings. First, theory of mind may be differentially affected by patients' ability to *integrate* others' intentions and emotions, and their ability to *distinguish* others' intentions and emotions from their own. Second, as theory of mind is informed by motor simulation (cf. simulation theory) as well as cognitive belief processes (cf. theory theory) that may each rely on different neural processes (Mahy, Moses, & Pfeifer, 2014), abnormalities in either one may be present in schizophrenia. Integration and distinction of self and other within both motor and cognitive processes will be described below.

Motor simulation and theory of mind in schizophrenia. According to simulation theory, the mere simulation of other people's behaviors and emotions is sufficient to arrive at a basic recognition and integration of those behaviors and emotions. In line with the notion that schizophrenia patients are able to simulate other people's behaviors and emotions (Jardri et al., 2011; McCormick et al., 2012; Thakkar et al., 2014), there is converging evidence that patients perform equally well as controls in attributing basic mental states (Brüne, 2003; Pousa et al., 2008; Shamay-Tsoory et al., 2007). That is, patients perform equally well as healthy controls on first order theory of mind tasks, which require a basic understanding of how someone else feels or what the other person is thinking.

However, because schizophrenia patients show a lack of differentiation in the simulation versus expression of behaviors and emotions (Jardri et al., 2011; McCormick et al., 2012; Thakkar et al., 2014), they may experience difficulty distinguishing the behaviors and emotions of others from their own. As a consequence, patients may mistake other people's intentions or emotions for their own (e.g., emotion contagion). Indeed, ample studies suggest that patients

typically become more easily distressed when observing someone else in distress (Corbera, Wexler, Ikezawa, & Bell, 2013; Decety & Lamm, 2011; McCormick et al., 2012; Montag et al., 2007; Ruby & Decety, 2004; Smith et al., 2014). Similarly, one may speculate that patients may also be more likely to experience others' intentions as their own, a phenomenon also referred to as goal contagion (Aarts, Gollwitzer, & Hassin, 2004). Such emotion (and possibly goal) contagion provides additional support for the notion that patients are able to form a basic understanding of others' intentions and emotions.

Cognitive beliefs and theory of mind in schizophrenia. It is only when situations get more complicated or demanding (and motor simulation becomes less informative) that schizophrenia patients struggle to understand other people's intentions, and especially emotions (Abu-Akel & Shamay-Tsoory, 2013; Corcoran, Mercer, & Frith, 1995; de Achával et al., 2010). In line with this notion, patients perform worse than healthy controls on more complex (second order) theory of mind tasks (Brüne, 2005a), and this impairment has partly been explained by individual differences and task demands in IQ and working memory load (Brüne, 2003; Pousa et al., 2008), as well as processing speed (Brennan, Harris, & Williams, 2014). Specifically, this latter study showed that while patients initially (within 70ms) show reduced facial and emotional processing compared with controls, they do show enhanced later processing (Brennan et al., 2014). In dynamic social interactions, this slowed emotion processing may hinder emotion identification and integration (Derntl et al., 2009; M. F. Green et al., 2012; Haker & Rössler, 2009; Kring & Elis, 2013), as emotional expressions are very dynamic in nature and may rapidly change from one moment to another (Scherer, 2009).

Another consequence of patients' increased processing time is that they have less time to consider the social context. Perhaps as a consequence, patients have been shown to pay less attention to the social context when inferring mental states of others (M. J. Green, Waldron, Simpson, & Coltheart, 2008), and may fail to perceive, or may misperceive causal relationships between the social context and other people's intentions, actions, or emotions (M. J. Green, Williams, & Hemsley, 2010; Hemsley, 2005a, 2005b). Such misperceptions may be further exacerbated by neural abnormalities (Bosia, Riccaboni, & Poletti, 2012; Walter et al., 2009), diminished executive functioning (e.g., reduced working memory capacity, or difficulty filtering relevant from irrelevant information; Hemsley & Zawada, 1976; J. Lee & Park, 2005), and/or cognitive biases (M. J. Green et al., 2010; Langdon, Corner, McLaren, Ward, & Coltheart, 2006). Indeed, patients are generally less accurate in identifying other people's mental states (e.g., happy or embarrassed) when embedded in a social context (M. J. Green et al., 2008; Kring & Campellone, 2012; Kring & Elis, 2013).

Patients' failure to take into account the social context may further explain why schizophrenia patients typically show difficulties understanding and integrating more *complex* intentions as communicated through lies or sarcasm (Derntl et al., 2009; M. F. Green et al., 2012), or as seen in faux pas tests that require people to detect and interpret violations of social rules

(de Achával et al., 2010; Zhu et al., 2007). That is, in complex and dynamic situations where motor simulation is less informative, patients may develop and draw upon cognitive theories and beliefs about the mental states of others, devoid of social contextual nuances or based on a false, biased perception of the social context. Consequently, patients may experience particular problems with social functioning. Indeed, research indicates that theory of mind functioning in schizophrenia patients is an important contributor to social behavior in clinical settings (Brüne, 2005a; Brüne, Abdel-Hamid, Lehmkämper, & Sonntag, 2007), community functioning (Roncone et al., 2002), and interpersonal skills (Pinkham & Penn, 2006).

In order to gain more insight in how people arrive at a theory of mind, and to enhance our understanding of impairments herein, future research should appreciate that in line with abnormalities in mirror neuron activation, impairments in theory of mind may result from both reduced integration (e.g., misperception of others' intentions and emotions) and distinction (e.g., emotional contagion) of self and other, and these processes may sometimes be difficult to disentangle. For instance, patients may adopt misperceived emotions of others, reflecting difficulties in integration as well as distinction of self and other. Furthermore, future research should take into consideration whether theory of mind performance results primarily from motor simulation processes or from cognitive theories or beliefs, and how these processes interact. For example, it would be interesting to assess to what extent patients benefit from motor simulation when cognitively inferring the mental states of others (e.g., happy) by manipulating motor simulation ability (e.g., blocking the smiling muscles by biting a pen or wearing a mouthguard; Oberman, Winkielman, & Ramachandran, 2007; Rychlowska et al., 2014; Strack, Martin, & Stepper, 1988).

1.3 Mimicry

Mirror neuron activity does not only contribute to understanding other people's behaviors and emotions through motor simulation, it may even trigger the same behavioral or emotional expressions in the observer (Iacoboni, 2009). That is, people often subtly mimic (anticipated) behaviors and emotional expressions of others (Chartrand & Bargh, 1999; Frijda, 2010) and this functions as a 'social glue' by facilitating empathy (Maurer & Tindall, 1983; Stel & Vonk, 2010), helping behavior (Fischer-Lokou, Martin, Guéguen, & Lamy, 2011; Guéguen, Martin, & Meineri, 2011; Stel, van Baaren, & Vonk, 2008), feelings of closeness (Ashton–James, Baaren, Chartrand, Decety, & Karremans, 2007; Lakin & Chartrand, 2003), and by reducing prejudice (Inzlicht, Gutsell, & Legault, 2012).

Self-other integration and distinction. Similar to theory of mind, mimicry does not simply result from motor simulation, but is conditional to the social context. Specifically, people only mimic others when it serves an affiliative purpose (Bourgeois & Hess, 2008; Chartrand, Maddux, & Lakin, 2005; Cheng & Chartrand, 2003; Hess & Fischer, 2013; Lakin, Chartrand, & Arkin, 2008). For example, one would mimic the fear of friends, but laugh at the fear of foes. Hence,

mimicry, just as theory of mind, is crucially affected by cognitive theories or beliefs about the other person's personality (e.g., friendly versus unfriendly) or background (e.g., in-group versus out-group). In essence then, cognitive processes promote self-other integration (e.g., with friendly people), as well as self-other distinction (e.g., from unfriendly people), depending on the other person's identity and on the social context.

Mimicry in schizophrenia. As schizophrenia patients have more difficulty taking the context in consideration (M. J. Green et al., 2008; Hemsley, 2005a, 2005b; Penn, Ritchie, Francis, Combs, & Martin, 2002), they may be more likely to show abnormal mimicry behavior. Indeed, research suggests that schizophrenia patients show either excessive mimicry (Kring, Kerr, & Earnst, 1999), or a lack of (or atypical) mimicry (Haker & Rössler, 2009; Park, Matthews, & Gibson, 2008; Varcin et al., 2010). Such abnormal mimicry behavior reflects patients' difficulties in self-other integration as well as self-other distinction. However, little is known about the underlying mechanisms responsible for patients' abnormal mimicry behavior. There is some evidence that mimicry is negatively related to negative symptoms and poor social functioning (Haker & Rössler, 2009; Matthews, Gold, Sekuler, & Park, 2013; Park et al., 2008). However, it often remains unclear whether patients' abnormalities in mimicry behavior result from an inability to take the social context into account (resulting in excessive or atypical mimicry), from a decreased affiliative motivation of the mimicker (resulting in a lack of mimicry), or from cognitive theories or beliefs the mimicker has about the (anticipated) intentions or emotions of the mimickee (resulting in atypical mimicry, which may also be misinterpreted as a lack of mimicry when expressions identical to those expressed by the mimickee are expected but not seen). By taking these factors into account, future research may unravel the processes that contribute to patients' abnormalities in mimicry behavior.

Summary Part 1

In summary (see also Table 1), we discussed how motor predictions and mirror neuron activation are involved in the anticipation and understanding of other people's behaviors and emotions (theory of mind). Crucially, based on the presence of mirror neuron activation, schizophrenia patients are able to integrate self and other. However, the lack of differentiation in activation for self-produced versus other-produced actions causes patients to integrate the intentions and emotions of others too much (reflected in abnormal theory of mind). We further showed that impairments at the motor level makes patients more dependent on less reliable cognitive theories and beliefs regarding the intentions and emotions of others. This not only impairs their understanding (i.e., integration) of others (i.e., theory of mind), but also their behavioral reactions (mimicry), which is detrimental for social functioning.

Table 1. Summary of motor and cognitive processes involved in schizophrenia patients' impairments in the perception of other people's behaviors and emotions, and their implications for normal (in italic) versus abnormal (in bold) self-other integration and self-other distinction.

Model	Normal	Schizophrenia	Implications for self-other integration	Implications for self-other distinction
		MOTOR		
1. Mirror neurons	Activation when grasping and when seeing someone else grasping	Activation when grasping and when seeing someone else grasping	Intact ability to integrate self and other	
	Difference in activation for self-produced versus other-produced actions	No differentiation of self-produced and other-produced actions		**Less distinction of one's own and others' actions**
2. Theory of mind				
Basic intentions	Understanding others' intentions	Understanding others' intentions	Normal identification and integration of others' intentions	*Possibly less distinction between one's own and others' intentions (e.g. goal contagion)*
Basic emotions	Understanding others' emotions	Too much simulation	**too much integration**	**Less distinction between one's own and others' emotions (e.g. emotion contagion)**
		COGNITIVE		
Complex intentions	Understanding others' intentions	Impaired understanding of complex intentions (e.g., lies, sarcasm)	**Cognitive deficits affect identification and integration of intentions**	
Complex emotions	Understanding others' emotions	Impaired understanding of emotions within a social context	**Cognitive deficits affect identification and integration of emotions**	
3. Mimicry	Mimicry of others' (anticipated) behaviors and emotions depending on the social context	Inappropriate mimicry	**Inappropriate bonding with others**	**Inappropriate distancing from others**

Part 2: Perception and Understanding of Self (Self-Perspective)

In addition to processes that are involved in understanding *other* people's behavior, people also crucially rely on basic motor prediction processes that are associated with understanding their *own* behavior when distinguishing and integrating self and other. Actually, the very same notion that motor predictions are differentially associated with our own and others' actions and emotions inspired researchers to study the role of motor prediction processes

in the awareness of our own actions (e.g., in terms of effectiveness, intensity, or duration; see section 2.1) and attributions of self-agency (i.e., the explicit distinction between self and other as the cause of behavior; see section 2.2). We will argue that, in addition to the role of motor predictions, cognitive expectations also play a crucial role in action-awareness and agency attributions. Furthermore, although the literature on these topics primarily focused on self-other distinction, we will also discuss implications for self-other integration.

2.1 Action Awareness

According to the classic comparator model (Frith, 2012; Frith & Done, 2013), the motor system stores copies of each outflowing action signal (i.e., efference copies) that carry predictive information about the sensory consequences of the action. The motor system continuously compares these internally predicted outcomes with actual perceived outcomes and, if necessary, updates the predictions based on the received sensory feedback (see also Sober & Sabes, 2003). As such, the motor system plays a crucial role in the planning and regulation of one's own behavior. Although such action monitoring and regulation can take place without conscious awareness (Fourneret & Jeannerod, 1998), people usually become aware of their actions when distortions (i.e., a mismatch between prediction and sensory feedback) reach a certain threshold and become noticeable.

Action awareness in schizophrenia. Schizophrenia patients show impairments in the motor prediction processes that are involved in the monitoring and regulation of action (see Farrer & Franck, 2007 for an overview). Specifically, a recent study revealed that although schizophrenia patients show relatively normal brain activation during sensory feedback processing (but see Horan, Foti, Hajcak, Wynn, & Green, 2012 for a more complex picture), they do show reduced sensorimotor activation preceding action execution, which reflects reduced motor prediction. Furthermore, in contrast to healthy controls, motor prediction and sensory feedback processing did not correlate in patients (Bender et al., 2012), indicating an interruption in the formation and updating of motor predictions. As a consequence, patients with schizophrenia have more difficulty learning associations between their actions and subsequent outcomes (Jones, Hemsley, & Gray, 1991; Serra, Jones, Toone, & Gray, 2001), and are typically less sensitive to behavioral distortions (Hommes et al., 2012; Malenka, Angel, Hampton, & Berger, 1982; Synofzik, Thier, Leube, Schlotterbeck, & Lindner, 2010). For example, Synofzik and colleagues had participants perform out-of-sight pointing movements while observing false movement feedback (i.e., rotated to a certain extent) (Synofzik et al., 2010). Compared with healthy controls, schizophrenia patients showed a larger threshold for detecting inconsistencies between their actual movement and the visual feedback (21.4˚ vs. 13.1˚ distorted in angle). Interestingly, there is suggestive evidence that this impaired sensitivity is specific to certain psychotic symptoms. That is, impaired error detection has been related to paranoid-hallucinatory syndrome or formal thought disorders (Knoblich, Stottmeister, &

Kircher, 2004), and even to subclinical positive symptoms in unaffected siblings of patients with schizophrenia (Hommes et al., 2012).

Action awareness may also be affected by action monitoring in a more indirect manner. Specifically, evidence shows that motor predictions as well as cognitive expectations affect a) the intensity of action awareness through a process called sensory attenuation, and b) the temporal awareness of action events through a process called temporal binding. We will discuss how sensory attenuation and temporal binding contribute to the distinction, but also integration, of one's own and other's actions.

Sensory attenuation. Because people are able to predict quite precisely the sensory consequences of their own actions, they already experience to some extent what the action will feel like before actually performing the action. As a consequence, if the sensory consequences match one's internal predictions, the actual experience feels less intense (Roussel, Hughes, & Waszak, 2013; Timm, Sanmiguel, Keil, Schröger, & Schönwiesner, 2014; Waszak, Cardoso-Leite, & Hughes, 2012). This so-called sensory attenuation is a fundamental phenomenon and is even witnessed in lower order species such as crickets (Poulet & Hedwig, 2002) and weak electric fish (C. C. Bell, 2001).

The attenuation of predicted sensations is an essential mechanism that enables people to distinguish between actions and outcomes they produced themselves and actions and outcomes that are caused by others. That is, people are generally better at predicting the sensory consequences of their own actions as compared with those of other people's actions (see Figure 3), causing self-produced sensations to feel less intense than other-produced sensations. This is, for example, why it feels much more intense when one is tickled by someone else, compared with when one tickles oneself (Blakemore, Wolpert, & Frith, 1998).

Sensory attenuation for one's own versus others' actions resembles the differentiation in activation of one's own and others' actions in the mirror neuron network. This is not surprising as both sensory attenuation and mirror neuron activation rely on the precision of internal motor predictions. Also, there is suggestive evidence that sensory attenuation correlates with activation in the frontoparietal network, which is part of the mirror neuron network (Hughes & Waszak, 2011). Perhaps there is also a direct relationship between mirror neuron activation and sensory attenuation, such that increased activity in the mirror neuron network for one's own actions results in increased sensory attenuation for one's own actions, and hence an increased ability to distinguish one's own from others' actions.

Interestingly, recent research suggests that sensory attenuation is specifically attuned to distinguish self and other, as the attenuation of behavioral outcomes increases when interacting with other people (Weiss, Herwig, & Schütz-Bosbach, 2011). Specifically, this research suggests that other people's action-outcomes are attenuated when produced upon one's own request compared with when they are produced by the other person individually. Thus, as long as one is at least partly responsible for an action, performed by either self or

other, sensory attenuation is present. Crucially however, in such interactive social contexts, one's own actions performed upon the other's request also become more attenuated than usual, possibly due to an increased attention to one's own actions in order to prevent self-other confusion.

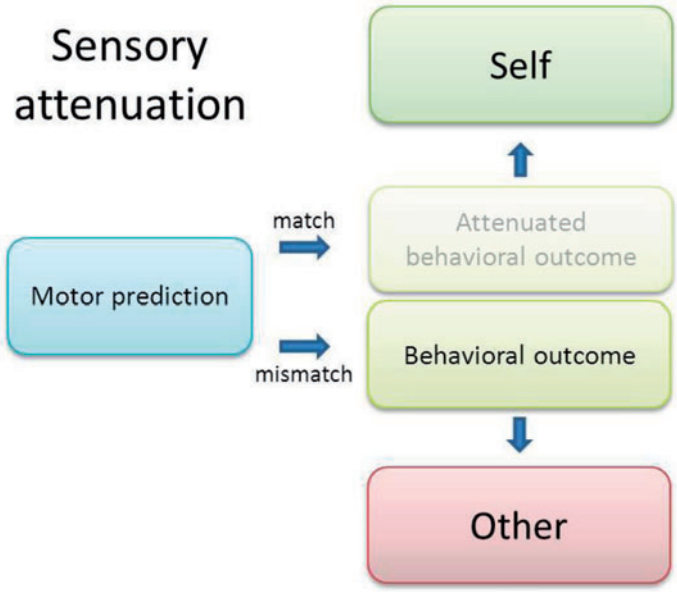


Figure 3. This figure depicts the sensory attenuation of internally predicted behavioral outcomes, and how this sensory attenuation may inform self-other distinction.

Sensory attenuation in schizophrenia. Schizophrenia patients are impaired in the motor prediction processes that are involved in the awareness of action, which significantly undermines their ability to distinguish between self and other. Specifically, recent electroencephalography (EEG) research has demonstrated that schizophrenia patients show impairments in the efference copies that are generated by the motor system (Bender et al., 2012; Ford, Palzes, Roach, & Mathalon, 2013; Ford, Roach, Faustman, & Mathalon, 2008). This manifests itself in less motor activation before action performance (i.e., less anticipation), and increased sensory activation (i.e., less attenuation) of action outcomes (Ford et al., 2013, 2008). Because of this lack of sensory attenuation, self-produced outcomes feel similar as other-produced outcomes, making it more difficult to distinguish one's own action-outcomes from those of others.

Indeed, in an inventive study by Blakemore and colleagues (Blakemore, Smith, Steel, Johnstone, & Frith, 2000), investigating sensory attenuation in schizophrenia, bipolar, and depressed patients, participants had to rate the intensity of a tactile stimulation on the palm of

their left hand. This stimulation was either self-produced or externally induced. Healthy control subjects rated the self-produced tactile stimulation as less intense than externally produced stimulations (Blakemore et al., 1998). Interestingly, however, patients suffering from auditory hallucinations and/or passivity phenomena failed to notice a difference in perception between self-produced and externally induced stimulation. This decreased sensory attenuation was crucially depended on the presence of these symptoms, and were independent of the diagnosis of schizophrenia or (bipolar) depression. Reduced tactile sensory attenuation has also been found in patients with paranoid symptoms (Bulot, Thomas, & Delevoye-Turrell, 2007) and predominantly positive symptoms (Shergill, Samson, Bays, Frith, & Wolpert, 2005). Furthermore, a single case-study showed reduced sensory attenuation in a patient with verbal auditory hallucinations and delusions of control (Jardri et al., 2009).

The deviant perception of externally generated touch may not only be related to psychotic symptoms, but may also play a role in patients' social functioning. That is, research in healthy subjects has shown that another person's touch increases compliance (M. L. Patterson, Powell, & Lenihan, 1986; Willis & Hamm, 1980) and strengthens interpersonal relationships (Gallace & Spence, 2010). Future research may investigate whether patients' failure to differentiate between self-produced and other-produced touch makes them insensitive to such social influences.

This failure to attenuate self-produced outcomes has also been replicated in the auditory (Ford et al., 2007; Ford & Mathalon, 2012; Heinks-Maldonado et al., 2007) and visual (Leube, Knoblich, Erb, Schlotterbeck, & Kircher, 2010) domain. For example, Ford and colleagues (Ford et al., 2007) examined the attenuation of speech in patients with schizophrenia. Attenuation was measured by suppression of the auditory event-related EEG potential N1. The results showed that whereas controls attenuated their own speech compared with recorded speech, schizophrenia patients did not. In addition to an increased awareness of aspects of experience that are normally tacit or implicit (Kapur, Mizrahi, & Li, 2005; Sass & Parnas, 2003), the failure to differentiate between self-produced and externally produced sensory experiences may explain symptoms such as auditory hallucinations where patients experience self-produced speech as externally controlled (Nelson et al., 2014). Indeed, there is some evidence that patients with auditory hallucinations show less attenuation when hearing an alien voice compared with patients without auditory hallucinations (Heinks-Maldonado et al., 2007).

Temporal binding. Another way in which the internal prediction of action-outcomes affects action awareness is by changing the temporal perception of actions and outcomes. In order to make sense of our actions and the effects they have on the outside world, our brain has to integrate multiple sensory signals (i.e., multisensory integration). That is, as was also addressed in the classic comparator model of motor prediction, the brain integrates predictive action signals with signals accompanying observed action-outcomes, involving visual, auditive, tactile, and olfactory modalities. However, some signals take longer than others

to reach the brain. For example, sound takes longer than vision, which is why we perceive lightning to precede thunder. Likewise, the visual perception of touching one's toe arrives sooner than the tactile perception on one's toe. To assure a coherent perception of events that happened at the same time, but reach the brain at different points in time, the brain waits a couple of milliseconds for the slowest signal to arrive before integrating the different signals (Vroomen & Keetels, 2010). This waiting period is also referred to as the 'temporal binding window' (Colonius & Diederich, 2004).

Although this temporal binding window is crucial for action monitoring, regulation, and awareness, it also creates noise and may potentially lead to illusory perceptions of coherence, i.e., perceiving events to co-occur that have nothing to do with each other. During early childhood, the temporal binding window, and hence the noise, decreases (Lewkowicz & Flom, 2014), and these developmental changes persist into adolescence (Hillock-Dunn & Wallace, 2012). The narrowing of the temporal binding window over time may result from an increased precision in the prediction of action-outcomes. That is, as we grow up, we learn which signals are likely to follow our actions (e.g., clapping our hands is bound to produce a distinct sound, visual pattern, and a certain sensation in both hands, but is not always followed by the light turning on), and in what timeframe. As a consequence, the brain may need less time to process and integrate these anticipated multisensory signals (Kail, 1991).

Indeed, learned associations between action events have been shown to crucially affect whether action events are perceived to occur at the same time, a phenomenon also referred to as 'temporal binding' (Buehner & Humphreys, 2009; Cravo, Claessens, & Baldo, 2009; Haggard, Clark, & Kalogeras, 2002). Specifically, when having learned that a key press is always followed by a specific sound after a predictable delay (e.g., 100ms), the action and delayed outcome are perceived as occurring closer together in time (Eagleman & Holcombe, 2002; Haggard et al., 2002). These prediction effects are so pervasive that when the sound is presented earlier than predicted (e.g., immediately after the key press), this creates the intriguing illusion of the sound preceding the action (Stetson, Cui, Montague, & Eagleman, 2006). Furthermore, as people are better able to predict the outcomes of intentional compared to unintentional (e.g., externally triggered) actions, people generally perceive actions and outcomes as occurring closer together in time when performing intentional rather than unintentional actions (Haggard & Clark, 2003; Haggard et al., 2002). For this reason 'temporal binding' is also often referred to as 'intentional binding'. Thus, motor predictions regarding the co-occurence of events shape the perception of time and coherence (see Figure 4).

Temporal binding may be especially useful in social interactions where people perform actions and cause outcomes simultaneously or in close temporal proximity, such as when playing a duet on the piano (i.e., quatre-mains). Specifically, the precision with which we can generally predict the outcomes of our own actions narrows the window within which action-events are bound together in time. Hence, our own action-outcomes are more likely

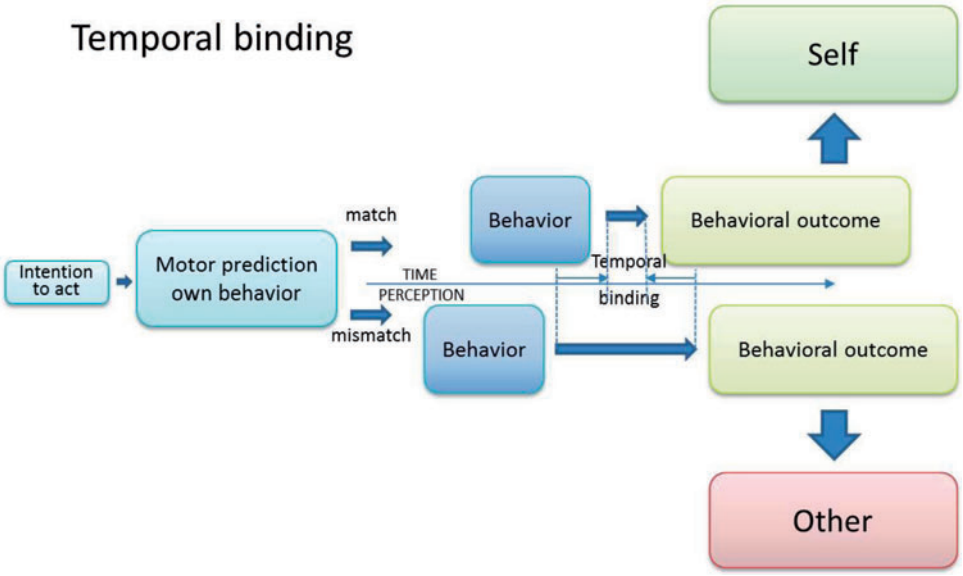


Figure 4. This figure depicts the temporal binding between behavior and behavioral outcomes as a consequence of internal motor predictions, and how this temporal binding may inform self-other distinction.

to match the precise internal predictions, and are thus more likely to fit the temporal binding window. Consequently, our own actions are more likely to be bound together in time with our own action-outcomes, rather than with action-outcomes of others that are less predictable. As such, the temporal perception of actions and resulting outcomes may crucially aid the distinction between our own and other's action-outcomes.

In addition, temporal binding may aid the integration, or understanding of other people's behavior. That is, because people generally have less precise predictions about the performance and consequences of other people's actions, the temporal window within which actions and outcomes of others' are bound together is wider. This enables people to perceive others' actions as coherent (Obhi & Hall, 2011a, 2011b; Wohlschlager, Haggard, Gesierich, & Prinz, 2003), without interfering with the monitoring and awareness of their own actions.

Temporal binding in schizophrenia. Only recently, studies addressed temporal binding of actions and outcomes in schizophrenia patients (Haggard, Martin, Taylor-Clarke, Jeannerod, & Franck, 2003; Voss et al., 2010). These studies suggest that, compared with controls, patients have a greater temporal binding window (i.e., more noise) during which (multi)sensory signals are integrated. Consequently, patients are more likely to perceive other-produced outcomes as following from their own actions and vice versa. As such, patients' increased temporal binding

window may crucially affect their temporal awareness of action, and as such their ability to integrate or distinguish self and other.

Additionally, a recent study indicated that, in contrast to controls, the temporal binding window of patients does not narrow as the probability of action-outcomes increases (Voss et al., 2010). This insensitivity to the increased likelihood that a certain sensory signal results from a certain action may promote the integration of irrelevant sensory signals that occur after intentional action performance. As a consequence, schizophrenia patients may perceive illusory relations between their own actions, resulting action-outcomes, and other events (e.g., the doorbell, a voice on the radio, lightning), which may promote the formation of delusions and hallucinations (Corlett, Honey, & Fletcher, 2007; Nathaniel-James & Frith, 2009).

Cognitive expectations and abnormalities in self-awareness in schizophrenia. There is recent evidence to suggest that both sensory attenuation and temporal binding do not only result from motor prediction processes, but can also arise from cognitive expectations about the source or outcome of an action (Desantis, Roussel, & Waszak, 2011; Desantis, Weiss, Schütz-Bosbach, & Waszak, 2012; Gentsch & Schütz-Bosbach, 2011; Moore et al., 2009). For example, when outcome expectations are induced by presenting the action-outcome before action performance (e.g., through priming), people show stronger sensory attenuation (Gentsch & Schütz-Bosbach, 2011), and stronger temporal binding between action and outcome (Moore et al., 2009; see Fig. 5).

The influence of such cognitive expectation processes on the self-awareness of action has not yet been studied in schizophrenia. However, as patients often have false expectations or delusional beliefs about the potential sources and outcomes of their actions, it is likely that cognitive processes further complicate self-awareness of action in schizophrenia. For example, patients suffering from delusions of control may expect the outcomes of their actions to be caused by others, which would decrease sensory attenuation and temporal binding. As a consequence, they are more likely to perceive their action-outcomes as unrelated to their own action-performance, which would then reinforce their delusions of control. An intriguing possibility is that cognitive expectation processes are especially influential in schizophrenia, as impairments in motor predictions do not allow patients to differentiate between their own and others' actions. Hence, it is important to gain more insight in how cognitive expectation processes interact with motor prediction processes in producing sensory attenuation and temporal binding in healthy controls and schizophrenia patients. After all, cognitive expectations might be potential targets for cognitive therapy.

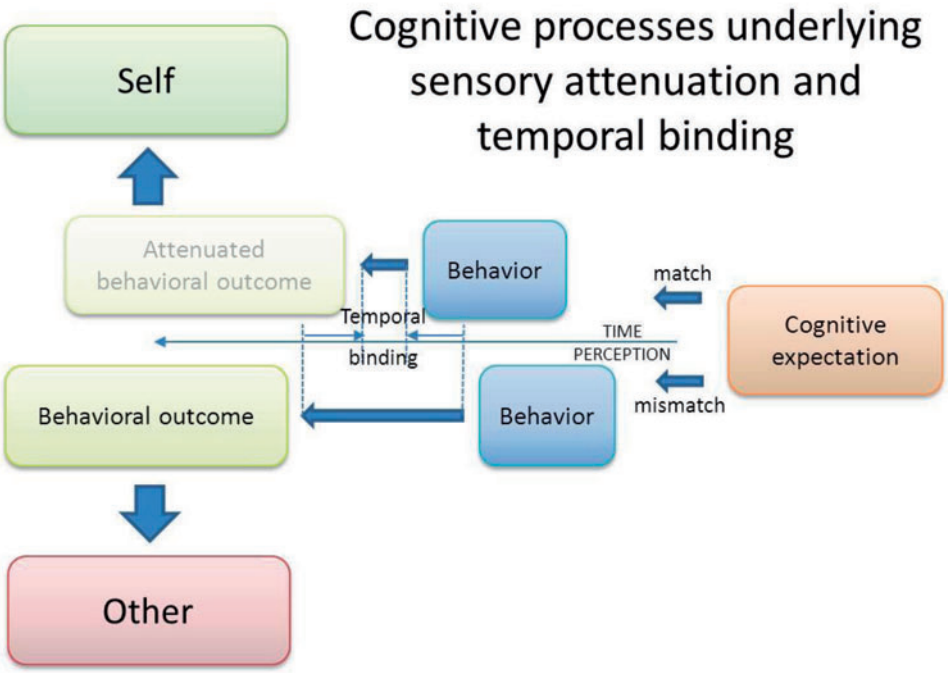


Figure 5. This figure shows how self-other distinction arises from the attenuation and temporal binding of cognitively expected behavioral outcomes.

2.2 Attributions of Agency

As suggested above, impaired self-awareness of actions may lead patients to attribute self-caused outcomes to the actions of other people, or to attribute outcomes caused by others to their own actions. Correct attribution of agency is essential to self-perception, social interaction, and our society in general (Daprati et al., 1997; Frith, 2013a; Hirstein & Sifferd, 2011; Lind, Kanfer, & Earley, 1990; Moretto, Walsh, & Haggard, 2011). In this section we will discuss more direct empirical evidence of aberrant agency attributions in schizophrenia. Again, we will disentangle the role and implications of motor prediction processes and cognitive expectation processes. Basically, we will argue that the involvement of cognitive processes increases when motor processes are uninformative or unreliable. Furthermore, how cognitive processes affect agency attribution might be dependent on the symptom profile of a patient.

Agency attribution from a motor perspective. As became apparent in the last section, the motor system may play an important role in the feeling of causing our own actions and resulting outcomes (i.e., feeling of agency). First, feelings of agency may be informed by the awareness of our own actions(e.g., sensory attenuation and temporal binding). However, when and how action awareness affects attributions of agency is still unclear (Dewey & Knoblich,

2014; Ebert & Wegner, 2010; Frith, 2013a; Synofzik et al., 2013; van der Weiden, Aarts, et al., 2013). For example, when one's conversation partner speaks in a soft voice (i.e., resembling sensory attenuation), one does not necessarily experience agency over her voice. Second, motor predictions may affect agency attributions in a more direct way. That is, because people can generally quite precisely predict the outcomes of their own actions, while they are less accurate in predicting the actions and outcomes of other people, people typically attribute agency to themselves when outcomes match their predictions and to others when outcomes mismatch their predictions (see left side of Figure 6).

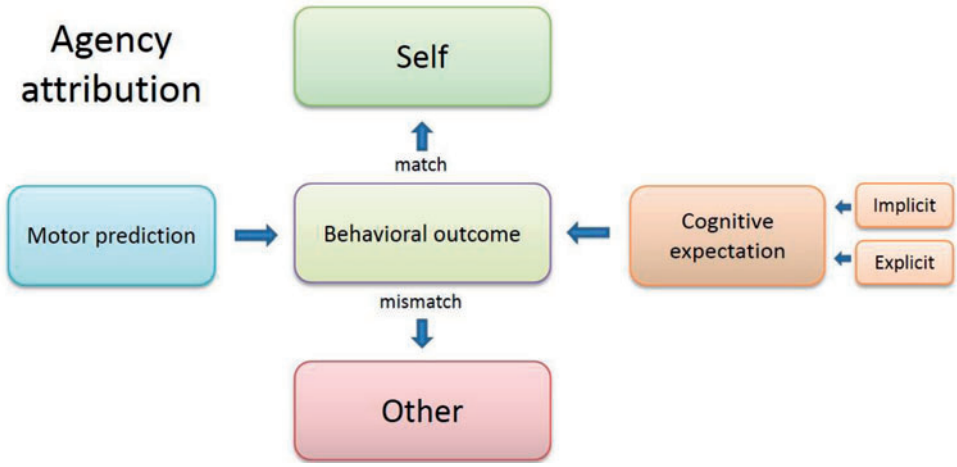


Figure 6. This figure depicts the contribution of motor prediction and implicit as well as explicit cognitive expectation processes to the attribution of agency.

Agency attribution from a motor perspective in schizophrenia. As referred to previously, there is evidence to suggest that in patients with schizophrenia motor prediction is distorted (Bender et al., 2012; Ford et al., 2013, 2008). As a result, it is more difficult to determine whether a sensory event matches the internal prediction, and hence, to attribute action-outcomes to either self or other. This impairment is reflected in several psychotic symptoms. That is, patients may be inclined to attribute agency over self-produced outcomes to others (under-attributing agency to self), such as auditory hallucinations (Gould, 1948; M. F. Green & Kinsbourne, 1990; van der Gaag, 2006), or delusions of alien control (Frith, 2005). Conversely, patients may attribute outcomes that were generated by others to themselves (over-attributing agency to self), such as manifested in grandiose delusions or delusions of reference (Maeda et al., 2012). Indeed, although there is still relatively little research on explicit agency attributions in schizophrenia, both types of misattributions have been observed in schizophrenia patients (Hur, Kwon, Lee, & Park, 2014; Johns et al., 2001; Park & Nasrallah, 2014; Schimansky, David, Wulf,

& Haker, 2010), and even in people at-risk to develop the disorder (Hauser et al., 2011; Johns et al., 2010; Thompson et al., 2013).

Over-attributions of agency in schizophrenia. In a recent study, participants' experiences of agency were measured while feedback of their cursor movements toward an asterisk in the left or right upper corner of the computer screen was manipulated. Participants either saw real feedback of their movement, or false feedback (i.e., cursor still moved toward the asterisk, but deviated slightly in onset, pace, and path from their current movement). Participants were led to believe that on several trials they would not see their own movement, but the movement of the experimenter who performed the task in another room. At the end of each trial, participants indicated whether they had seen their own or the experimenter's movement. Results showed that, compared with healthy controls, schizophrenia patients more often identified the false feedback movements as self-generated (Schimansky et al., 2010).

Over-attributions of agency are often explained to result from too much noise in motor predictions. That is, because of impairments in the internal prediction of action-outcomes, schizophrenia patients may perceive outcomes that are in fact slightly deviant (e.g., spatially or temporally) as matching their internal predictions (Metcalfe, Van Snellenberg, DeRosse, Balsam, & Malhotra, 2012). This perception may result from patients' increased temporal binding window, facilitating the multisensory integration of actions and relevant as well as irrelevant external events. As a consequence, patients may learn associations between their actions and outcomes that actually occur beyond their control (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010). This flexibility in schizophrenia patients' representation of their own behavior thus leaves room for over-attributions of agency.

Over-attributions of external events to the self as a result of an increased temporal binding window is not limited to over-attributions of agency over action-outcomes, but also extends to false attributions of body ownership in schizophrenia patients (Peled et al., 2000; Thakkar et al., 2011), but also in individuals with schizotypal experiences (Asai et al., 2011). That is, the integration of synchronous multisensory input, e.g., tactile perception of touch on one's own hand and visual perception of touch on a rubber hand is known to create the illusion that the rubber hand is one's own body (Botvinick & Cohen, 1998; Suzuki, Garfinkel, Critchley, & Seth, 2013). Compared with healthy controls, schizophrenia patients report stronger rubber hand illusions. This supports the notion that patients have a more flexible representation of their 'self', resulting in a reduced ability to distinguish self and other and a tendency to over-attribute external events or objects (such as a rubber hand) to themselves.

In line with clinical observations, there is empirical support that over-attributions of agency are specifically related to delusions of control (Hauser et al., 2011), but not with a wider spectrum of first-rank symptoms (i.e., passivity symptoms such as thought insertion, depersonalisation and delusions of alien control; Schimansky et al., 2010).

Under-attributions of agency in schizophrenia. In contrast to over-attributing agency to oneself, there is also convincing evidence that, compared with controls, schizophrenia patients tend to under-attribute agency over outcomes to themselves (Johns et al., 2001; Renes et al., 2013). In other words, schizophrenia patients typically fail to recognize their action-outcomes as their own. For instance, in one study participants had to read sentences aloud while they simultaneously heard the sentences in their own voice, their own voice distorted (i.e., increased by 3 semi-tones), or another person's voice. When asked to indicate whether they heard their own voice (normal or distorted) or another person's voice, they were more inclined to attribute their own voice to the other person as compared with healthy individuals (Johns et al., 2001).

A possible explanation for finding both over- and under-attribution of self-agency in patients is a crucial difference in the tasks used in the different studies. In studies where patients tend to under-attribute agency to themselves the deviations or distortions from their own or self-produced actions are clearly noticeable and can be consciously reflected upon. In contrast, studies providing evidence of over-attribution use subtle deviations from people's own, self-produced actions that may still be perceived to match patients' noisy internal predictions. Cognitive reflections resulting from action awareness thus seem to play a key role in the attribution of self-agency. Hence, in order to fully understand when patients over- versus under-attribute agency to themselves, it is important to also consider the cognitive processes underlying experiences of agency.

Agency attribution from a cognitive perspective. In situations where the prediction of the outcome of our action is uninformative or less reliable, cognitive inferences of agency are especially influential (Moore et al., 2009; Synofzik, Vosgerau, & Newen, 2008; Vosgerau & Synofzik, 2012). This is the case when our actions may produce a number of different consequences or when there are other agents who also perform actions that may produce multiple outcomes. For example, when you make a funny face and people start laughing, you may have predicted their laughter, but that does not mean you were the one that made them laugh. They may as well be laughing because someone is imitating you in a funny way. In such situations people have to rely on cognitive inferential processes to arrive at the experience that they (rather than someone else) were the cause of their own actions and resulting outcomes. Hence, patients who have impairments in motor prediction processes are probably chronically more dependent on such cognitive inferential processes (Horan et al., 2012; Metcalfe et al., 2012). As a result, they are more susceptible to cognitive biases and beliefs that may direct their agency experiences toward over- or under-attribution (Bentall, Kinderman, & Kaney, 1994; Martin & Penn, 2002; Thompson et al., 2013).

Explicit cognitive expectations. According to the cognitive inferential account to self-agency people typically infer that they caused a behavioral outcome when this outcome matches the outcome they had in mind (Wegner, 2002). For example, if you were craving pasta all day and

you come home to discover that your partner made pasta for dinner, you may feel that you somehow, magically, caused your partner to do so. In some situations people have a certain outcome in mind because they have an explicit goal to reach a certain outcome (e.g., eating pasta). Yet, most (especially social) behavior is not planned or intentional (Bargh & Morsella, 2008; Custers & Aarts, 2010; Fourneret & Jeannerod, 1998; Moskowitz, 2002; Soon, Brass, Heinze, & Haynes, 2008). Still, people can experience self-agency over this 'unintentional' behavior and its consequences. So, how do experiences of self-agency over behavioral outcomes unfold in ambiguous (social) situations characterized by the absence of an explicit goal and associated motor predictions?

Implicit cognitive expectations. Recent studies showed that the inferential process underlying experiences of self-agency is not only susceptible to goal-directed processes, but also to subtle environmental cues that carry information about the outcomes of our actions outside of conscious awareness. In experimental tasks, such subtle outcome information is presented with an intensity that is too low to reach the threshold of conscious awareness (i.e., subliminal priming). One commonly used experimental task aimed at assessing cognitive agency inferences is the so-called 'wheel of fortune task' (Aarts et al., 2005; Belayachi & Van der Linden, 2010; Dannenberg, Förster, & Jostmann, 2012; Renes, van der Weiden, et al., 2015; van der Weiden, Ruys, & Aarts, 2013). This task requires participants to move a gray square along a rectangular path consisting of eight white squares in counterclockwise direction. At the same time the computer moves another grey square at the same speed in the opposite direction. After some time, a stop cue appears, and participants have to stop the movement of the squares by pressing a stop button. The moment that they press the stop button ostensibly determines on what locations the grey squares will stop. In actuality, participants have no actual control (i.e., the computer always determines the squares' stop locations), rendering internal motor predictions unreliable and uninformative for attributing agency. Crucially, participants only get to see one of the square's stop locations, presented in black to make the cause of this outcome ambiguous. After each trial, participants rate the extent to which they feel that they caused their square to stop on the presented location, as a measure of experienced self-agency. To manipulate their experiences of self-agency, participants are either assigned the goal to stop their square on a specific location, or are briefly primed with the location instead. The presented stop location either matches or mismatches these goals or primes.

Indeed, experienced self-agency is generally increased when an action-outcome matches one's explicit goal, and decreased when an action-outcome mismatches one's explicit goal (Aarts et al., 2005; van der Weiden, Ruys, et al., 2013). Similarly, experienced self-agency is generally enhanced when an action-outcome has been primed in advance, even though people do not consciously detect the outcome primes (Aarts et al., 2005; Belayachi & Van der Linden, 2010; Sato, 2009; van der Weiden, Ruys, et al., 2013). Thus, cognitive expectations underlying agency experiences can be shaped by explicit goals as well as implicit primes,

albeit through different mechanisms and with different consequences (van der Weiden, Ruys, et al., 2013).

Cognitive agency processing in schizophrenia. Surprisingly, in patients with schizophrenia, these cognitive inferential processes have not yet received much attention. Only recently, we conducted a study on the influence of both implicit and explicit outcome cues (i.e., goals and primes) on experiences of self-agency in healthy controls and schizophrenia patients (Renes et al., 2013). In this study, participants performed the 'wheel of fortune task' as described above.

Results showed that both healthy controls and schizophrenia patients experienced more self-agency over outcomes that matched, rather than mismatched the goals (Voss et al., 2010), although patients overall experienced less self-agency (i.e., under-attribution of agency) . Moreover, in contrast to controls, the implicit outcome primes had no effect on experiences of self-agency in patients. Importantly, in line with the notion that fast bottom-up visual processing is intact in schizophrenia (Del Cul, Dehaene, & Leboyer, 2006), we recently replicated and extended this finding by showing that schizophrenia patients were unable to use implicit outcome information when inferring self-agency, regardless of their intact ability to visually process and attend to the implicit outcome primes (Renes, van der Weiden, et al., 2015).

Thus, in the presence of others and in the absence of an explicit goal to reach a specific outcome, patients grope in the dark and are likely to under-attribute agency to themselves. Patients' inability to use subtle, implicit cues that convey information on what outcome to expect when performing an action may be particularly problematic in social interaction where information is usually implicitly available (e.g., in non-verbal communication). These findings thus converge with patients' general inability to take the social context into account (M. J. Green et al., 2008; Hemsley, 2005a, 2005b; Penn et al., 2002).

The weighing of motor predictions and cognitive expectations in schizophrenia. In contrast to implicit agency processing, patients showed no impairments in experiencing self-agency over outcomes that matched their explicitly set goals in our study. However, explicit agency processing may under certain circumstances bias patients to over- or under-attribute agency to themselves (Maeda et al., 2012; Renes et al., 2013; Schimansky et al., 2010). That is, whereas errors in motor prediction (e.g., temporal or spatial deviations) usually weigh stronger than cognitive inferences (Moore et al., 2009; Synofzik, Vosgerau, & Lindner, 2009) and normally lead to the attribution of agency to others (see blue arrow in Figure 7), schizophrenia patients' insensitivity to motor prediction errors causes them to attribute agency based on their cognitive outcome expectations (e.g., based on goal achievement; orange arrow in Figure 7).

Thus, when outcomes are slightly deviant but still match their cognitive expectations (e.g., when hearing one's own voice a few milliseconds later), patients will over-attribute agency to themselves. Indeed, in the studies discussed earlier that showed over-attributions of agency in schizophrenia, outcomes may have been deviant (e.g., movement feedback of the cursor

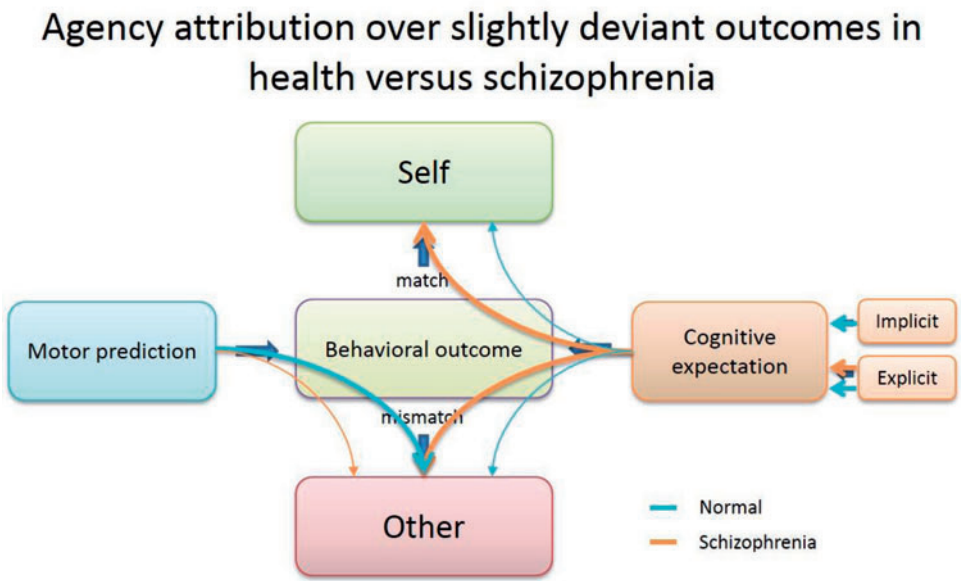


Figure 7. This figure illustrates how schizophrenia patients deviate from healthy controls when attributing agency over outcomes that are slightly deviant from internal motor predictions. The blue arrow shows how errors in motor prediction (e.g., temporal or spatial deviations) weigh stronger than cognitive inferences and normally lead to the attribution of agency to others. The orange arrow depicts how schizophrenia patients' insensitivity to motor prediction errors causes them to attribute agency based on cognitive expectations. Thus, when outcomes are slightly deviant but still match cognitive expectations (e.g., when hearing one's own voice a few milliseconds later), patients will over-attribute agency to themselves. However, when outcomes are not as expected (i.e., in the absence of an explicit expectation or when outcomes deviate to a large extent from one's expectation, e.g., when hearing a voice that is clearly and qualitatively different from one's own), patients tend to attribute agency to others, and as such under-attribute agency to themselves.

differed in onset, pace, or path), but were always congruent with the goal they were pursuing (e.g., the cursor reached the intended location). Yet, when outcomes are not as expected (i.e., in the absence of an explicit expectation or when outcomes deviate to a large extent from one's expectation, e.g., when hearing a voice that is clearly and qualitatively different from one's own), patients tend to attribute agency to others, and as such under-attribute agency to themselves.

Cognitive outcome expectations, and hence agency attributions, may be crucially modulated by cognitive biases and personal beliefs (Aarts & van den Bos, 2011; Desantis et al., 2011; Fitch, 1970). Since patients' excessively rely on cognitive inferences, they may be even more susceptible to such cognitive biases and beliefs. For instance, as a result of impaired motor predictions, patients may develop the belief that their actions bare no relation to the events they observe in their environment whatsoever (i.e., defeatist beliefs; see van der Weiden, Aarts,

& Ruys, 2011). Similarly, some patients may actually develop the belief that they can cause virtually any external event (i.e., grandiose beliefs). Such beliefs may bias agency attributions toward under and over attributions of agency respectively, thereby further reinforcing prior beliefs.

This way, patients' impairments in processing implicitly available information may not only underlie attributional biases, but may also reinforce their bias against disconfirmatory evidence (Garety & Freeman, 1999; Penn, Lawrence, Roberts, Sanna, & Roberts, 2008; Woodward, Moritz, Cuttler, & Whitman, 2006). In line with this notion, recent research showed that patients who predominantly had positive symptoms were more likely to *over-attribute* agency over deviant yet goal-congruent outcomes to themselves (Maeda et al., 2012, 2013), whereas patients who predominantly had negative symptoms were more likely to *under-attribute* agency over deviant yet goal-congruent outcomes to themselves (Maeda et al., 2013). Perhaps patients with predominantly positive symptoms have higher expectations of reaching their goals than do patients with predominantly negative symptoms. Such expectations may also bias patients with predominantly positive symptoms toward under-attributions of agency when outcomes are goal-incongruent (i.e., when hearing voices with negative content). Given the crucial role of beliefs in agency attributions in schizophrenia, it would be interesting for future research to test the effect of therapies aimed at reducing defeatist beliefs in patients with symptoms of under-attribution (i.e., delusions of control, thought broadcasting, thought insertion, thought withdrawal, or auditory (verbal) hallucinations).

In conclusion, when investigating agency attribution in schizophrenia patients, it is essential to take into account motor as well as cognitive processes, implicitly as well as explicitly available outcome information, and cognitive biases and beliefs that may or may not be expressed in schizophrenia symptoms. These factors may jointly or independently drive patients to either over- or under-attribute agency to themselves, and as such distinguish self from others.

Summary Part 2

To summarize (see also Table 2), in part 2 we showed how motor predictions and cognitive expectations aid the distinction of self and other as the cause of behavior, as reflected in self-awareness and attributions of agency. Specifically, as a consequence of reliable internal motor predictions, one's own behavioral outcomes are generally perceived as less intense (Blakemore et al., 1998; Roussel et al., 2013) and as temporally closer to the performance of action (Haggard et al., 2003; Moore & Haggard, 2008). As such, motor predictions aid self-other distinction, as is also supported by the role of motor predictions in attributions of agency (Sato, 2009; van der Weiden et al., 2011). Because schizophrenia patients have impaired motor predictions (Farrer & Franck, 2007), they typically struggle to distinguish self from other (Blakemore et al., 2000; Johns et al., 2001; Renes et al., 2013). Importantly, when motor predictions are less reliable, as is the case in schizophrenia, the distinction between self and other is crucially influenced by

cognitive expectations about the outcomes of our actions (Aarts et al., 2005; van der Weiden, Aarts, et al., 2013; van der Weiden, Ruys, et al., 2013). These cognitive expectations are biased by patients' symptoms and may lead to over- as well as under-attributions of agency (Maeda et al., 2012, 2013). As such, cognitive expectation processes are potentially interesting targets for cognitive therapy with the aim of improving self-other distinction and social functioning.

Table 2. Summary of motor and cognitive processes involved in schizophrenia patients' impairments in self-perception, and their implications for normal (in italic) versus abnormal (in bold) self-other integration and self-other distinction.

Model	Normal	Schizophrenia	Implications for self-other integration	Implications for self-other distinction
		MOTOR		
1. Action awareness				
Sensory attenuation	Attenuation of self-produced outcomes	No attenuation of self-produced outcomes		**Less self-other distinction**
Temporal binding	Integration of predicted multisensory signals that occur in close temporal proximity	Integration of a variety of multisensory signals that do not belong together due to increased binding window	**Too much integration of internal and external signals**	**Less self-other distinction**
2. Agency attribution				
Motor prediction	Mispredictions lead to less experienced self-agency	Mispredictions do not lower experienced self-agency		**Over-attribution of agency to self**
		COGNITIVE		
Implicit cues	Matching outcome representations enhance experienced self-agency	Matching outcome representations do not enhance experienced self-agency		**Under-attribution of agency to self**
Goal attainment	Enhances experienced self-agency	Enhances experienced self-agency		*Normal attribution of agency to self*

Concluding Remarks

As follows from the theoretical models and empirical studies reviewed above, self-other distinction is the product of motor prediction and cognitive processes that are involved in the understanding of other people's behaviors and emotions (other-perspective) as well as the understanding of one's own behaviors and emotions (self-perspective). Figure 8 shows an integrative model of the processes involved in self-other distinction.

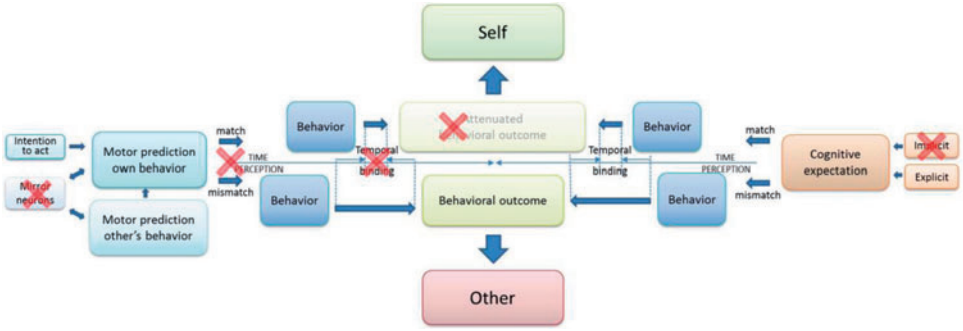


Figure 8. This integrative model illustrates how the distinction between self (upper part of model) and other (lower part of model) results from both motor prediction (left part of the model) and cognitive expectation (right part of the model) processes. The red crosses indicate impairments in schizophrenia.

So far, research on self-other processing in schizophrenia neglected the notion that self-other integration and self-other distinction are inextricably intertwined, and this has usually not been recognized in experimental set-ups. Yet, as we argued, both integration and distinction play a key role in the development of psychotic symptoms and impairments in social functioning. In the present review, we discussed how models that were developed to map either self-perception (self-perspective) or the perception of others (other-perspective) explain self-other integration as well as self-other distinction.

Self-Other Integration

Motor. Classic motor prediction models that took center stage in most research on self-other processing account for patients' *ability* to integrate self and other. Specifically, mirror neurons are active for both self-produced and other-produced actions. This enables patients to understand *basic* intentions of others. However, patients tend to integrate the behaviors and emotions of others too much, due to increased motor simulation (reflected in abnormal first order ToM) and an increased temporal binding window (reflected in abnormal action awareness).

Cognitive. Importantly, we further showed how cognitive biases and demands (e.g., processing speed) cause patients to incorrectly integrate and hence misunderstand more *complex* and dynamic intentions and emotions (reflected in abnormal second order ToM). As such, we have provided a framework for understanding schizophrenia patients' impairments in theory of mind, which have been a topic of debate in the literature. In addition, we showed that patients' incorrect integration causes them to inappropriately respond to and bond with others (reflected in abnormal mimicry).

Self-Other Distinction

Motor. Although patients show mirror neuron activation for their own as well as others' actions, the amount of activation does not differentiate between their own and others' actions, resulting in a lack of distinction between their own and others' behaviors and emotions. This is reflected in patients' abnormal action awareness (i.e., decreased sensory attenuation and an increased temporal binding window) and over-attributions of agency.

Cognitive. We also introduced a new perspective on abnormal agency attribution, by explaining how impairments in both motor prediction (i.e., reduced awareness of subtle distortions) and cognitive processes (i.e., biased expectations) may lead to over versus under-attribution of agency, as apparent in specific psychotic symptoms.

In some areas integration and distinction are more difficult to disentangle based on the existing literature. For example, patients' abnormalities in theory of mind (e.g., emotion contagion) may result from increased neural activation in response to others' intentions or emotions, or from decreased down-regulation of others' intentions or emotions relative to their own intentions or emotions (Decety & Meyer, 2008). Similarly, in temporal binding, increased integration of self and other (and hence a reduced ability to differentiate between one's own and others' actions) may follow from impaired motor prediction (reduced distinction) as well as from too much simulation of others' actions (increased integration). Also with regard to mimicry, it remains an open question whether patients' reduced mimicry reflects an absence of mimicry (i.e., reduced integration or increased distinction), or merely incorrect mimicry (and thus incorrect integration). Future research may shed more light on how integration and distinction processes interact to shape people's perception and understanding of their own and others' behaviors and emotions.

To conclude, there is more to self-other processing than meets the eye. Hence, in order to enhance our understanding of self-other processing and impairments herein in schizophrenia, future research should take into account the complexity of social perception and behavior. Specifically, we argue that disentangling self-other integration and distinction, as well as motor prediction and cognitive expectation processes, will crucially advance current research on social cognition and social functioning in both healthy controls and schizophrenia patients, and may serve to improve patients' understanding, coordination, and attribution of behavior, and ultimately, their quality of social life.

Multisensory integration underlying body ownership in schizophrenia and offspring of patients: a study using the rubber hand illusion paradigm

Merel Prikken
Anouk van der Weiden
Heleen Baalbergen
Manon H.J. Hillegers
René S. Kahn
H. Aarts
Neeltje E.M. van Haren

3

In preparation

Abstract

Background: Recent views on schizophrenia describe self-disturbances as being central to the disease. Indeed, empirical evidence suggests that patients have aberrant experiences of body ownership, i.e., they have the feeling that they are not the subject of their own bodily experiences. However, empirical evidence is scarce and little is known about the development of these disturbances.

Methods: With a Rubber Hand Illusion (RHI) paradigm, body ownership was assessed in patients with schizophrenia (n=54), healthy controls (n=56), children/adolescents with increased familial risk for developing schizophrenia (n=24) or mood disorders (n=33), and children/adolescents without this risk (n=18). In this paradigm, a visible rubber hand and the invisible real hand were stroked synchronously and asynchronously and subsequently, subjective illusory experiences and proprioceptive drift were measured.

Results: First, all groups showed the expected effect of the RHI, i.e., stronger proprioceptive drift and increased subjective illusory experiences after synchronous compared with asynchronous stroking. Second, the effect of synchronicity on subjective experiences was significantly weaker in patients as compared with healthy individuals and subjective ratings correlated positively with delusions in patients. Last, no significant differences were found between children/adolescents with and without increased familial risk.

Conclusion: We found subtle disturbances in body ownership experiences in patients with schizophrenia and a relation with delusions. No evidence was found for impairments in individuals with increased familial to develop schizophrenia or mood disorders. Longitudinal data might reveal whether impairments in body ownership are predictive of psychosis onset.

Introduction

Distinguishing between self and others may seem an automatic and fluent process to most of us. However, schizophrenia is seen as a disorder of basic self-disturbance in which the relation between the self and the world is instable and complex (Sass & Parnas, 2003; van der Weiden et al., 2015). These disturbances are evident in both self-agency experiences, i.e., the feeling that we cause our own actions and consequences, and body ownership experiences, i.e., the feeling that we are the subject of our own bodily experiences (Frith, Blakemore, & Wolpert, 2000b; Gallagher, 2000; Tsakiris, Schütz-Bosbach, & Gallagher, 2007). Although abnormal experiences of body ownership are well-described psychotic symptoms, we still know surprisingly little about their etiology and development.

Body ownership experiences result from a multisensory integration process, in which visual, tactile, and proprioceptive information is integrated (Botvinick, 2004; Ehrsson, Spence, & Passingham, 2004). Matching sensory information from different modalities creates a sense of ownership over bodily parts (Botvinick & Cohen, 1998), e.g., when we see and feel the touch of someone's hand on our arm, we simply know it is our own arm that is touched. However, a mismatch can induce the illusion of *not* being the owner of a body part. During development, some flexibility in this process of multisensory integration is necessary, as our maturing body changes in terms of size and shape. When the body reaches a more adult, and thus more constant size, this process becomes more efficient (Cowie, Sterling, & Bremner, 2016; Gori, Del Viva, Sandini, & Burr, 2008). Multisensory integration might be disturbed in schizophrenia, such that patients are more likely to integrate multisensory signals, even if they do not logically belong together. Consequently, patients with schizophrenia are more susceptible to body ownership illusions than healthy controls (Lev-Ari et al., 2015; Peled et al., 2000; Thakkar et al., 2011).

Impairments in body ownership have been assessed with a variety of Rubber Hand Illusion (RHI) paradigms (Ferri et al., 2014; Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014; Lev-Ari et al., 2015; Peled et al., 2003, 2000; Thakkar et al., 2011). In the originial RHI experiment, the subject's own invisible hand and a visible rubber hand (positioned near the hidden hand) are stroked synchronously or asynchronously (Botvinick & Cohen, 1998). As the illusion mainly materializes when stroking is applied synchronously, periods of asynchronous stroking can be used as a control condition (Botvinick & Cohen, 1998; Kammers, de Vignemont, Verhagen, & Dijkerman, 2009). During the experiment, the body's internal model is constantly adjusted to match *seeing* the touched rubber hand and *feeling* the touch on one's own hand (Tsakiris, 2010), leading to ownership illusions over the rubber hand. This illusion is thought to depend on the temporal binding window in which stimuli from different modalities are perceived as occurring together (Costantini et al., 2016). More specifically, a larger time window allows for integration of more incoming stimuli, which might lead to a stronger rubber hand illusion.

Most studies on the RHI in schizophrenia measured the subjective experience of the illusion and showed that patients, compared with healthy controls, rated the illusion as more intense, possibly indicating a more flexible sense of ownership (Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014; Peled et al., 2000; Thakkar et al., 2011). Although the evidence is sparse, it has been found that the strength of these illusory experiences is positively related to the severity of positive psychotic symptoms, such as hallucinations or delusions of reference (Peled et al., 2000; Thakkar et al., 2011). Therefore, these studies suggested that multisensory integration deficits might underlie specific psychotic symptoms. Besides measuring subjective RHI experiences, the illusion can be quantified by assessing proprioceptive drift, i.e., the perceived shift of the location of one's own hand towards the rubber hand after stroking. Previously, it was found that the effect of synchronous relative to asynchronous stroking on proprioceptive drift was larger in patients with schizophrenia compared with healthy individuals (Thakkar et al., 2011). Although this finding confirms body ownership disturbances, it is the only study reporting proprioceptive drift in these patients thus far. Therefore, the current study aims to replicate these findings.

Interestingly, it has been suggested that basic self-disturbances, including self-awareness and presence, can predict the transition to psychosis in individuals at ultra-high risk (Nelson et al., 2012). Regarding body-ownership specifically, there is evidence that altered RHI-measures are present in non-clinical adults with schizotypal personality traits or psychotic-like experiences, suggesting that they might be related to a vulnerability for psychosis (Asai et al., 2011; Germine, Benson, Cohen, & Hooker, 2013; Graham, Martin-Iverson, Holmes, & Waters, 2014; Thakkar et al., 2011). In the search for markers that predict future conversion to psychosis and to extend our knowledge about the development of disturbances of body-ownership, we examine the RHI in children and adolescents at increased familial risk to develop schizophrenia.

In the current study the RHI was administered in two cohorts. The first cohort consisted of patients with schizophrenia and healthy adults. Our aim was to replicate previous findings in patients (i.e., a more flexible sense of body ownership), using a well-controlled experimental procedure. That is, synchronous as well as asynchronous stroking conditions were applied within participants. Also, subjective experiences *and* proprioceptive drift in the stimulated as well as in the unstimulated hand were measured. Based on previous studies, we expect a positive relation between RHI measures and psychotic symptoms. Second, to our knowledge, no studies have been performed on the relevance of the RHI as a marker in those with increased risk to develop schizophrenia in the future. Therefore, we examine whether increased familial risk to develop schizophrenia (i.e., offspring of patients with schizophrenia), relative to increased familial risk for mood disorders and controls, is related to alterations in RHI measures.

Methods

Subjects

Two cohorts were included. The first cohort consisted of 54 patients with a DSM-IV diagnosis of schizophrenia (SZ) and 56 healthy controls (HC), aged between 18 and 50. Diagnoses were confirmed with the Comprehensive Assessment of Symptoms and History (Andreasen, Flaum, & Arndt, 1992). Patients were recruited from the psychiatry department of the University Medical Center Utrecht (UMCU), other psychiatric institutions in the Utrecht area, and patient associations. Healthy controls were recruited from notice boards and an online recruiting company for scientific research (www.proefpersonen.nl). Exclusion criteria were an IQ<80 and drug or alcohol abuse over the past six months. Furthermore, exclusion criteria for patients were the presence of a psychotic episode at the time of testing and use of chronic medication other than psychiatric medication. Healthy controls had no history of psychiatric illness, no first-degree relatives with a psychotic illness, and did not use chronic medication.

The second cohort was part of the second measurement of an ongoing longitudinal offspring study and consisted of 24 offspring of patients with a schizophrenia spectrum disorder (SZO), 33 offspring of patients with a bipolar disorder (BPO), and 18 controls (CO). At baseline, SZO and BPO had at least one first-degree or two second-degree family members with a schizophrenia spectrum or bipolar disorder diagnosis respectively (confirmed by the Structured Clinical Interview for DSM IV (First, Spitzer, Gibbon, & Williams, 2002)). CO did not have a history of psychiatric illness, did not have a first-degree family member with a psychotic or affective disorder, and did not use psychotropic medication. Participants were aged between 11 and 22 and had an IQ>70. Recruitment of SZO and BPO was done at the psychiatry department of the UMCU, other psychiatric institutions in the Netherlands, and patient associations. CO were recruited from primary and secondary schools in the Utrecht area.

All participants were Dutch speaking. Informed consent was given by participants themselves and by parents of participants younger than 18. The Human Ethics Committee of the University Medical Center Utrecht approved both studies. All participants were financially compensated for study participation.

Measurements

The Rubber Hand Illusion (RHI). Body ownership was measured with the RHI (Botvinick & Cohen, 1998). Participants placed their hands in a box and a cape was used to cover the arms and wrists (Figure 1). The right hand and the rubber hand were at equal distances from the middle of the body (Kammers et al., 2009). To prevent the left and right hands of young participants to be too far apart, baseline positions of the hands were corrected for arm length.

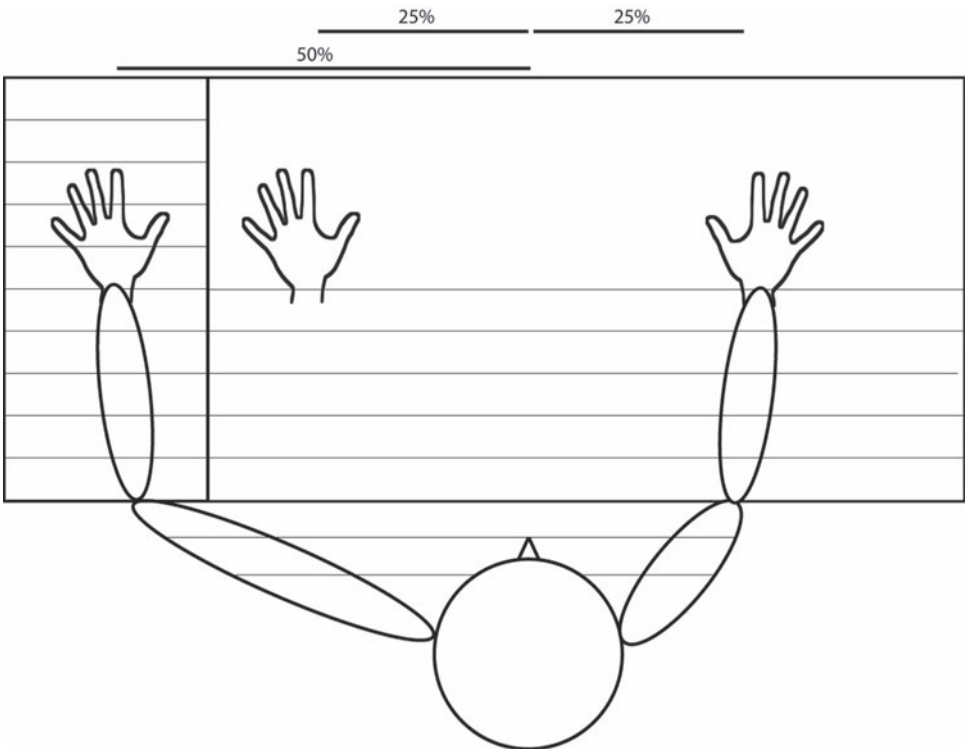


Figure 1. Experimental set-up RHI. Thin lines represent parts of the set-up that is invisible to the participant during stroking of the left and rubber hand. Percentages indicate the proportion of arm length.

At the start of the experiment, the box was covered by a wooden panel. Prior to seeing the rubber hand *and* any tactile manipulation by the experimenter, participants had to estimate the position of their own hands as a baseline measure. To obtain this estimation, the experimenter slowly moved the own index finger along the top of the experimental setting (twice: once from each side of the box) and participants were instructed to say 'stop' when they had the feeling that the index finger of the experimenter was aligned with their own index finger (Kammers et al., 2009). A ruler was attached at the bottom of the experimental setup to measure participants' estimations.

Then, participants closed their eyes and the wooden panel was placed vertically between the left hand and the rubber hand. Consequently, only the right hand and the rubber left hand were visible to the participant. The rubber hand and the participant's left hand were stroked with a soft brush, which could occur synchronously (same timing and location on own and rubber hand) or asynchronously (different timing and location). Participants watched the rubber hand during stroking. In both conditions, participants estimated the position of

their own left and right index finger after four periods of stroking: after 2 minutes and three times after 20 seconds (Cowie, Makin, & Bremner, 2013). The side from which the experimenter started moving the index finger along the top of the experimental setting to measure the estimated position of the hands was counterbalanced within participants (i.e., twice from the left and twice from the right). The order in which the synchronous and asynchronous condition were administered was counterbalanced between participants.

Proprioceptive drift was measured by calculating the difference between the mean of the four post-manipulation measures and the mean baseline measure; a positive value indicated drift *towards* the rubber hand. For each participant, drift was calculated four times: after the synchronous and asynchronous condition in both the stimulated and unstimulated hand. As the position of the hands was based on arm length of the participant, drift was calculated as a percentage of this length.

Subjective RHI experiences after the synchronous and asynchronous condition were measured with two questions: 'When I was stroking with the paintbrush, did it sometimes feel as if you could feel the touch of the brush where the fake hand was?' and 'When I was stroking with the paintbrush, did it sometimes feel like the fake hand was your hand, or belonged to you?'(Cowie et al., 2013). These questions were rated on a 7-point scale, ranging from 0 (no, not at all) to 6 (yes, very). In most studies a more extensive questionnaire is used (Botvinick & Cohen, 1998), but to make sure that young individuals could understand the questions correctly and could differentiate between them, this two-item questionnaire was used.

Symptomatology. In SZ, the Self-Experience Lifetime Frequency Scale (SELF) was used to assess disturbances in self-experiences (Heering et al., 2016). This self-report questionnaire measures the presence and frequency of lifetime disturbances of self-awareness and experiences of depersonalization (e.g., 'Have you felt unreal or like a stranger to yourself?'). Scores were rated on a scale from 0 (never/not distressed) to 4 (all the time/severely distressed). All SELF-items (scores for presence and for frequency) were added to obtain a total score (Heering et al., 2016). Also, current level of psychotic symptoms in SZ was assessed by the Positive And Negative Syndrome Scale (PANSS (Kay, Fiszbein, & Opler, 1987)).

In SZO, BPO, and CO the presence of psychotic symptoms was assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL (Kaufman et al., 1997)). Symptoms were scored as absent, subthreshold, or threshold.

Statistical analyses

To determine group differences in age, (parental) years of education, and gender, independent samples t-tests (HC/SZ), ANOVA's (CO/BPO/SZO), and Chi-square tests were performed.

In both samples, ratings on the two questionnaire items were highly correlated in both the synchronous and asynchronous condition (r_s between .52 and .65, all p's<.001) and had

good internal consistency (Cronbach's α between .72 and .78). Therefore, the two items were combined by calculating the mean to represent the strength of subjective RHI experiences.

As asynchronous stroking was used as a control condition, the effect of synchronicity (synchronous relative to asynchronous stroking) on subjective RHI experiences and proprioceptive drift was the main outcome measures.

Cohort 1: Case-control. First, to check for effects of group, synchronicity, and laterality on proprioceptive drift, a repeated-measures ANOVA was performed with group (SZ/HC) as between-subjects factor and synchronicity (synchronous/asynchronous stroking) and laterality (stimulated/unstimulated hand) as within-subject factors. The same (without laterality) was done for subjective RHI experiences. Second, counterbalancing effects, estimated baseline positions, and the relation between proprioceptive drift and subjective RHI experiences were analyzed (Supplemental materials). Then, the relation between RHI measures and SELF-score was assessed in patients. As the total SELF-score was not normally distributed, Spearman's correlation was used to assess the relationship of SELF-score with drift in the synchronous and asynchronous condition, subjective RHI experience in the synchronous and asynchronous condition, and synchronicity effects (i.e., difference between synchronous and asynchronous condition). Last, the relation between these RHI measures and PANSS positive subscale, PANSS item 1-delusions, and PANSS item 3-hallucinations was assessed. Bonferroni correction for multiple comparisons was used (α=0.05/4 symptom scores=0.0125).

Cohort 2: Offspring. First, similar analyses were performed to compare RHI measures between SZO, BPO, and CO. Next, the relation between psychotic symptoms and RHI measures was assessed in SZO and BPO only, as in CO no psychotic symptoms were present. Two groups were created based on the lifetime presence of psychotic symptoms (yes/no). Presence was scored when at least one of the symptoms from the K-SADS-PL hallucinations or delusions supplement was scored as 'threshold', as this might indicate an elevated risk to develop psychosis later in life (Yung, Phillips, Yuen, & McGorry, 2004). Using Mann-Whitney-U tests, in SZO, BPO, and SZO+BPO combined, the two symptom groups were compared on proprioceptive drift and subjective RHI experience in the synchronous and asynchronous condition, and synchronicity effects.

RHI and age (exploratory). Sample 1 and 2 were combined in order to assess the effect of age on RHI measures. Then, age was added as a covariate in a repeated measures ANCOVA with synchronicity as a within-subjects factor.

Results

Demographic and clinical characteristics

Table 1 shows demographic and clinical information of both cohorts. Patients had fewer years of education than controls. In offspring, significantly more males and fewer females were present in CO as compared with SZO. After the experiment, six participants (2 HC, 2 SZ, 1 CO, and 1 SZO) indicated that they used spatial reference points when proprioceptive drift was measured. Therefore, they were removed from all proprioceptive drift analyses. One patient was excluded from subjective RHI-analyses due to insufficient understanding of the questions.

Cohort 1: Case-control

As expected, the effect of synchronicity on proprioceptive drift was more pronounced in the stimulated than in the unstimulated hand ($F(1,104)=21.73$, $p<.001$, $\eta_p^2=.17$; synchronicity*laterality). Follow-up analyses on both hands separately confirmed that in the stimulated hand only, proprioceptive drift was larger after synchronous compared to asynchronous stroking, in controls and patients (Table 2, Figure 2). Also, subjective RHI ratings were higher after synchronous than after asynchronous stroking. The effect of synchronicity on subjective RHI ratings was significantly smaller in patients than controls (Table 2, Figure 2). Follow-up analyses showed that only in the asynchronous condition subjective RHI ratings were marginally higher in patients as compared with healthy controls ($t(107)=-1.81$, $p=.07$, Cohen's $d=.35$).

There were no counterbalancing effects and baseline estimation errors did not differ between the groups (Supplemental materials). Furthermore, in both groups a significant relationship between proprioceptive drift and subjective RHI experiences was found (Supplemental materials).

A significant positive correlation (after multiple comparison correction) was found between the PANSS delusions and the strength of subjective RHI experiences in the synchronous condition ($r_s=0.36$, $p=.01$; see supplemental table 4). Also, at trend level, subjective ratings were positively related to the SELF (synchronous condition), PANSS-positive (synchronous and asynchronous condition), and PANSS-delusions (asynchronous condition).

Table 1. Demographics and clinical characteristics in healthy controls, patients, control offspring, and offspring of schizophrenia or bipolar disorder patients.

	Healthy controls	Schizophrenia	Group differences	Control offspring	Offspring schizophrenia	Offspring bipolar disorder	Group differences
N	56	54		18	24	33	
Age (years)	33.84 (8.04)	34.08 (7.98)	$t(108)=-0.16$, $p=.88$	16.06 (2.62)	16.92 (2.36)	17.69 (2.46)	$F(2,72)=2.57$, $p=.08$
Gender (M/F)	52/4	46/8	$\chi^2(1)= 1.66$, $p=.20$	13/5	6/18	15/18	$X^2(2)=9.26$, $p=.01$
Years of education[a]	13.80 (1.80)	12.93 (2.07)	$t(108)=2.37$, $p=.02$	N/A	N/A	N/A	
Parental years of education	13.60 (2.75)	14.56 (3.56)	$t(101)=-1.53$, $p=.13$	15.67 (1.78)	14.74 (2.22)	14.73 (2.13)	$F(2,71)=1.38$, $p=.26$
Antipsychotic medication							
Typical/atypical/both	0	6/45/1		0	2/0/0	1/0/0	
None	46	1		18	22	32	
PANSS[b]							
Positive		12.60 (3.70)					
Negative		13.42 (5.10)					
General		24.90 (4.98)					
Total		50.92 (10.10)					

[a]Information was not available for all participants (missing: HC=3, PT=4): [b]for 2 patients PANSS was not available due to drop-out from the study

Table 2: ANOVA results regarding effects of synchronous and asynchronous stroking on RHI measures.[+]

	Effect	Cohort 1: case-control	Cohort 2: offpsring
Proprioceptive drift			
Unstimulated hand	Group	*F*(1,104)=.31, *p*= .58, *ηp2*=.003	*F*(2,70)=.09, *p*=.92, *ηp2*=.003
	Synchronicity	*F*(1,104)=.07, *p* = .80, *ηp2*= .001	*F*(1,70)=.05, *p*=.82, *ηp2*=.001
	Synchronicity *Group	*F*(1,104)=.01, *p*=.93, *ηp2*<.001	*F*(2,70)=.04, *p*=.96, *ηp2*=.001
Stimulated hand	Group	*F*(1,104)=.04, *p*= .85, *ηp2*<.001	*F*(2,70)=1.23, *p*=.30., *ηp2*=.03
	Synchronicity	**$F(1,104)=26.86, p<.001, \eta_p^2=.21$**	**$F(1,70)=21.94, p<0.001, \eta_p^2=.24$**
	Synchronicity *Group	*F*(1,104)=.08, *p*= .78, *ηp2*=.001	*F*(2,70)=.25, *p*=.78, *ηp2*=.01
Subjective RHI	Group	*F*(1,107)=.79, *p*= .38, *ηp2*=.007	*F*(2,72)=.15, *p*=.86, *ηp2*=.004
	Synchronicity	**$F(1,107)=107.92, p<.001, \eta_p^2=.50$**	**$F(1,72)=140.75, p<.001, \eta_p^2=.66$**
	Synchronicity *Group	**$F(1,107)=5.04, p=.03, \eta_p^2=.05$**	*F*(2,72)=1.07, *p*=.35, *ηp2*=.03

[+] For raw means and sd's of RHI measures, see Supplemental table 1. As the data did not meet all assumptions for parametric testing, non-parametric tests were also performed, which yielded similar conclusions. **Bold =** significant at α=.05.

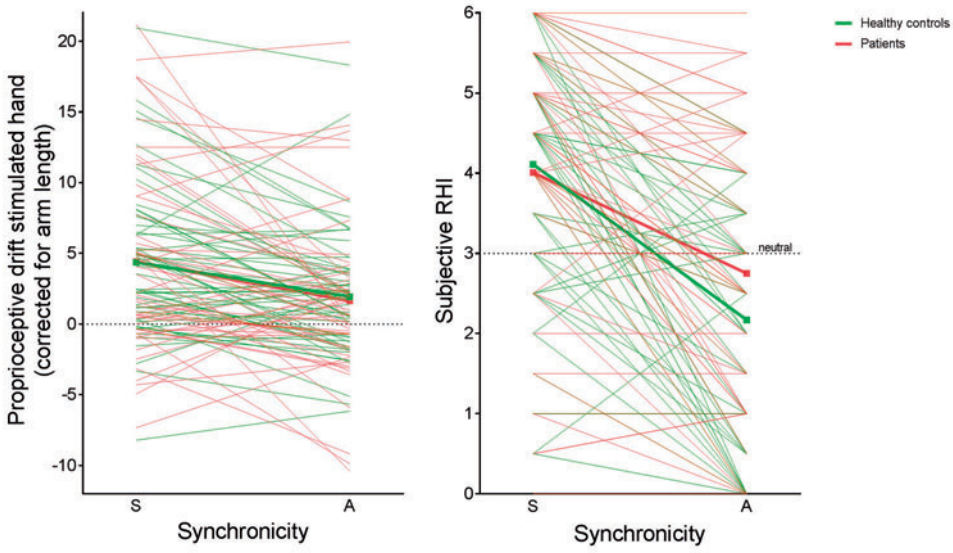


Figure 2. Individual (thin lines) and mean (bold lines) RHI measures for healthy controls and patients with schizophrenia after synchronous(S) and asynchronous(A) stroking. Lines represent synchronicity effects. Subjective RHI: scores range from 'no, not at all'(0) to 'yes, very'(6)

Cohort 2: Offspring

Similar to cohort 1, the synchronicity effect was larger in the stimulated than in the unstimulated hand ($F(1,70)=13.17$, $p=.001$, $\eta_p^2=.16$). Follow-up analyses on proprioceptive drift showed significance in the stimulated hand only (Table 2 and Figure 3). Also, a significant synchronicity effect was found on subjective RHI ratings. No significant group differences were found between SZO, BPO, and CO. Results regarding counterbalancing, baseline estimation errors, and the relation between proprioceptive drift and subjective RHI experiences are reported in the Supplemental materials. Baseline estimation errors did not differ between the groups. Furthermore, the effect of synchronicity on proprioceptive drift was significantly stronger when the synchronous condition was applied first. A significant relation between proprioceptive drift and subjective RHI experiences was found in the asynchronous condition only.

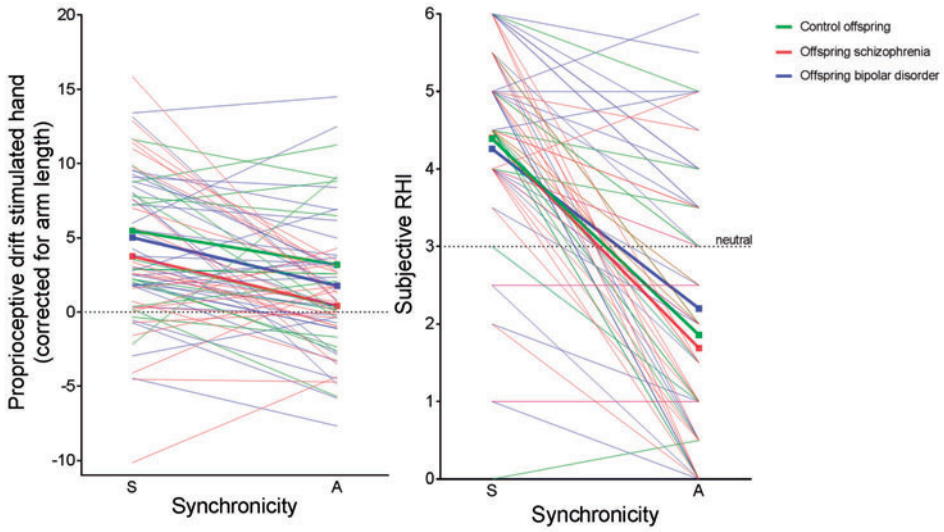


Figure 3. Individual (thin lines) and mean (bold lines) RHI measures for control offspring and offspring of patients with schizophrenia spectrum or bipolar disorder after synchronous(S) and asynchronous(A) stroking. Lines represent synchronicity effects. Subjective RHI: scores range from 'no, not at all'(0) to 'yes, very'(6).

38% (9/24) of SZO and 12% (4/33) of BPO experienced at least one psychotic symptom (lifetime). RHI measures did not differ between participants with and without these symptoms in SZO, BPO, or both groups combined (all p's>.31; Supplemental table 5). Additional analyses using subthreshold (instead of threshold) presence of psychotic symptoms as a cut-off yielded similar conclusions.

RHI and age (exploratory)

No main effects of age on proprioceptive drift or subjective RHI were found ($F(1,177)=.004$, $p=.95$, $\eta_p^2<.001$ and $F(1,182)=.63$, $p=.43$, $\eta_p^2=.003$, respectively). However, a significant interaction was found between age and the effect of synchronicity on subjective RHI ratings ($F(1,182)=9.09$, $p=.003$, $\eta_p^2=.05$), which was marginally significant for proprioceptive drift ($F(1,177)=3.15$, $p=.08$, $\eta_p^2=.02$; see Supplemental figure 1).

Discussion

The current study investigated susceptibility to body ownership illusions in healthy individuals, patients with schizophrenia, and children/adolescents with and without an increased familial risk to develop schizophrenia or mood disorders. First, as expected, we found that synchronous stroking of the own and the rubber hand increased both proprioceptive drift of the stimulated hand and subjective ratings in all groups. Interestingly, the synchronicity effect on subjective RHI experiences was significantly less pronounced in patients compared with controls, which was explained by increased illusory experiences after asynchronous stroking. Furthermore, subjective RHI ratings were positively related to severity of delusions in patients. Last, no body ownership abnormalities were found in children/adolescents at increased familial risk to develop schizophrenia or mood disorders.

Despite a low effect size, our finding that the synchronicity effect on subjective ratings of body ownership was significantly smaller in patients than in controls is consistent with the hypothesis that patients have an increased temporal binding window (Foucher, Lacambre, Pham, Giersch, & Elliott, 2007; Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014). That is, their time window to perceive two stimuli as similar might be larger (Foucher et al., 2007). Consequently, asynchronous stroking might have felt more synchronous to patients, which possibly leads to a more flexible sense of body ownership (Costantini et al., 2016; Thakkar et al., 2011). This is supported by our finding that specifically in the *asynchronous* condition patients rated the strength of the illusion marginally stronger than controls. Although in contrast to most other studies we used only a two-item questionnaire, our findings are in line with previous suggestions that patients are more susceptible to the illusion (Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014; Lev-Ari et al., 2015; Peled et al., 2000; Thakkar et al., 2011). Importantly, this group difference on subjective ratings could not be explained by group differences on the extent to which subjective ratings depended on proprioceptive drift or to differences in the estimation of baseline positions.

Although alterations in subjective body ownership illusions have been reported before in schizophrenia, to our knowledge, the current study is only the second to also provide insight into potential proprioceptive drift abnormalities. Here, we did not find group differences in proprioceptive drift. These findings are partly in line with an earlier study (using an experimental

set-up similar to ours (Thakkar et al., 2011)). That is, similar to our findings, Thakkar and colleagues found a significant synchronicity effect in patients. However, in contrast with our findings, they found that the effect in patients was significantly larger than in healthy controls. Importantly, their results could be explained by the absence of an effect of synchronicity on proprioceptive drift in controls. The absence of such an effect was surprising given the consistent evidence for its presence in studies with healthy individuals (Botvinick & Cohen, 1998; Shimada, Fukuda, & Hiraki, 2009; Tsakiris & Haggard, 2005). Another explanation for the differential findings in our study and the study of Thakkar and colleagues might be that the sample size in our study was almost twice as large.

That group differences were found in multisensory integration processes related to the subjective illusion, but not proprioceptive drift, suggests different underlying mechanisms. This has been suggested before, but the exact differences remain unclear (Abdulkarim & Ehrsson, 2016; Aimola Davies, White, & Davies, 2013; Rohde, Luca, & Ernst, 2011). A possible explanation might come from the distinction between bottom-up (i.e., sensory input) and top-down (i.e., cognitive representation of body schema) mechanisms that influence multisensory integration (IJsselsteijn, de Kort, & Haans, 2006; Tsakiris & Haggard, 2005). Top-down mechanisms have been suggested to influence subjective ratings of the illusion, but not proprioceptive drift (Dempsey-Jones & Kritikos, 2014). Consequently, alterations in cognitive representations might be underlying to the specific impairments found in our study. Thus, to confirm the conclusion that proprioceptive drift alterations are not present in schizophrenia patients, and to investigate the distinction between bottom-up and top-down mechanisms of multisensory integration, additional studies are needed.

RHI measures did not differ between children/adolescents with and without increased familial risk to develop psychosis. This implicates that we found no evidence that familial risk for developing schizophrenia (nor mood disorder) might not be a vulnerability marker for the development of schizophrenia. As the sample sizes were small in our offspring groups, these findings must be interpreted with caution. It should be noted that the offspring group included individuals that will not experience any mental disorder later in life and that the alterations in patients in our case-control sample were only subtle. This led to low statistical power to detect alterations during a *possible* premorbid stage. In order to further examine whether impairments in body ownership as measured by the RHI are predictive of developing schizophrenia, longitudinal studies are necessary. Such studies would add to previous findings of self-disturbances as a marker for psychosis onset, such as the finding that altered bodily sensations and anomalous self-experiences might predict conversion to psychosis (Nelson et al., 2012).

Although the number of studies on the rubber hand illusion are sparse in children and adolescents, it has been shown that multisensory integration and the flexible weighting process underlying body ownership is constantly developing across age (Cowie et al., 2013, 2016;

Graham, Martin-Iverson, Holmes, & Waters, 2014). This is in line with our exploratory analysis, which showed that the effect of synchronicity changes with age. Also, it is confirmed by our findings regarding differential counterbalancing effects and a differential relation between proprioceptive drift and subjective RHI experiences in children/adolescents (i.e. no significant association in the asynchronous condition, while this is present in adults). Previously, it has been suggested that the ability to localize one's own hand in the RHI paradigm is developed around the age of 10-11, as younger individuals showed an overall larger proprioceptive drift as compared with adults (Cowie et al., 2013, 2016). Additionally, others suggest that proprioceptive drift again increases in late adulthood (Graham, Martin-Iverson, Holmes, & Waters, 2014). Although these studies used slightly different experimental set-ups and age groups, together they suggest a U-shaped development of multisensory integration, which becomes more efficient in adolescence but loses its efficiency in late adulthood. However, one large study in healthy individuals with age groups ranging from childhood until late adulthood is necessary to confirm the proposed U-shape.

Taken together, our findings suggest subtle alterations in embodiment experiences in patients with schizophrenia. Interestingly, the severity of delusions in the past week (measured by the PANSS) was positively related with the strength of subjective RHI experiences in the synchronous condition. These findings are in line with previous studies that showed significant associations between strength of the subjective illusory RHI-experiences and severity of hallucinations, delusions of reference, delusions of control, and somatic delusions (Peled et al., 2000; Thakkar et al., 2011). Moreover, evidence suggests that in healthy individuals, psychotic-like symptoms (e.g., schizotypy) are associated with body ownership illusions (Asai et al., 2011; Germine et al., 2013; Graham, Martin-Iverson, Holmes, & Waters, 2014; Thakkar et al., 2011). Thus, these findings confirm the hypothesis that there is a relation between multisensory integration impairments and positive symptoms of schizophrenia, which may suggest that they share similar underlying mechanisms. We did not find evidence for a relationship between multisensory integration and disturbed self-experiences in patients or lifetime presence of any delusion or hallucination in our high-risk sample. The fact that these symptoms were measured *lifetime*, whereas PANSS measures *current* symptoms, might explain this.

Limitations

Some limitations should be considered when interpreting the findings. First, as symptom severity in patients was very low at time of measurement, it should be mentioned that results might be different in more severely ill patients. Second, an important note is that large individual differences in RHI responses were present in all groups, as displayed in Figures 2 and 3. It can be expected that individuals differ in sensitivity to the RHI and some will not

show the effect of synchronicity at all, but it is not clear why in some individuals the effect of synchronicity is reversed. Important questions for future research emerge from these findings: What causes these individual differences and do they influence our current way of looking into sensory integration processes underlying RHI experiences? For example, it has been suggested that temperament affects proprioceptive drift (Kállai et al., 2015). Also, individual differences might be caused by methodological factors, such as the potential influence of non-systematic variation in tactile stimulation or the social context in which the illusion was administrated.

Conclusion

In summary, our findings suggest that patients with schizophrenia have subtle impairments in multisensory integration processes underlying body ownership. Specifically, they show impairments in subjective body ownership illusions, which are related to the severity of delusions in particular. Furthermore, we found no evidence for disturbances of body ownership in those at increased familial risk to develop schizophrenia. The current study contributes to the understanding of body ownership impairments in psychosis and its development and provides suggestions for further research on this topic.

Supplemental material

Supplemental table 1. Raw means and sd's of RHI-measures per group

	Proprioceptive drift in stimulated hand		Subjective RHI	
	synchronous	asynchronous	synchronous	asynchronous
cohort 1: case-control				
HC	4.36 (5.31)	1.83 (4.40)	4.11 (1.51)	2.17 (1.60)
SZ	4.40 (6.64)	1.64 (5.83)	4.01 (1.72)	2.75 (1.83)
cohort 2: offspring				
CO	5.47 (6.62)	3.18 (5.65)	4.39 (1.27)	1.86 (1.41)
SZO	3.75 (6.37)	0.41 (2.50)	4.40 (1.24)	1.69 (1.42)
BPO	5.07 (5.30)	1.77 (4.96)	4.26 (1.57)	2.20 (1.87)

HC=healthy control; SZ=patients with schizophrenia; CO=control offspring; SZO=offspring schizophrenia; BPO=offspring bipolar disorder

Analysis of control aspects – counterbalancing and baseline estimation errors

To check for counterbalancing effects regarding the order in which the conditions were administered, this variable (synchronous-asynchronous and asynchronous-synchronous) was added as a between-subjects factor in the repeated measures ANOVA's. Furthermore, group differences in initial estimation errors at baseline measurement, calculated by subtracting the actual baseline position of the stimulated hand from the estimated baseline position, were assessed using Mann-Whitney U and Kruskall-Wallis tests.

In sample 1 (patients and healthy controls), adding counterbalancing to the repeated measure ANOVA's revealed that the order in which the synchronous and asynchronous conditions were administered did not influence the strength of the synchronicity effects, i.e., no synchronicity*counterbalancing interaction was found (Supplemental table 2, part A). Also, baseline estimation errors did not differ between patients and healthy controls (Supplemental table 3, part A).

In sample 2 (offspring with and without familial risk for psychosis) a significant synchronicity*counterbalancing interaction in the proprioceptive drift analysis indicated that counterbalancing order influenced the strength of the synchronicity effect (Supplemental table 2, part B). Follow-up analyses showed that a significant effect of synchronicity was found when synchronous stroking was applied first ($F(1,36)=28.62$, $p<.001$, $\eta_p^2=.44$), which was only marginally significant when asynchronous stroking was applied first ($F(1,35)=3.59$, $p=.07$, $\eta_p^2=.09$). Furthermore, Kruskall-Wallis tests showed that baseline estimation errors did not differ between the groups (Supplemental table 3, part B)

Supplemental table 2: Repeated measures ANOVA results on the effect of counterbalancing on synchronicity effects in sample 1 (part A) and sample 2 (part B).

	Effect	Test statistics
A. cohort 1: case-control		
Proprioceptive drift	Counterbalancing	$F(1,102)=..01$, $p=.94$, $\eta_p^2<.001$
in stimulated hand	Group x Counterbalancing	$F(2,102)=.07$, $p=.94$, $\eta_p^2=.001$
	Synchronicity x Counterbalancing	$F(1,102)=2.39$, $p=.13$, $\eta_p^2=.02$
	Synchronicity x Group x Counterbalancing	$F(2,102)=.21$, $p=.81$, $\eta_p^2=.004$
Subjective RHI	Counterbalancing	$F(1,105)=1.79$, $p=.18$, $\eta_p^2=.02$
	Group x Counterbalancing	$F(2,105)=.87$, $p=.42$, $\eta_p^2=.02$
	Synchronicity x Counterbalancing	$F(1,105)=.93$, $p=.34$, $\eta_p^2=.01$
	Synchronicity x Group x Counterbalancing	$F(2,105)=3.13$, $p<.05$, $\eta_p^2=.06$*[a]
B. cohort 2: offspring		
Proprioceptive drift	Counterbalancing	$F(1,69)=1.06$, $p=.31$, $\eta_p^2=.02$
in stimulated hand	Group x Counterbalancing	$F(2,69)=1.18$, $p=.32$, $\eta_p^2=.03$
	Synchronicity x Counterbalancing	$F(1,69)=7.67$, $p=.01$, $\eta_p^2=.10$*
	Synchronicity x Group x Counterbalancing	$F(2,69)=.26$, $p=.77$, $\eta_p^2=.01$
Subjective RHI	Counterbalancing	$F(1,71)=.82$, $p=.37$, $\eta_p^2=.01$
	Group x Counterbalancing	$F(2,71)=.26$, $p=.78$, $\eta_p^2=.01$
	Synchronicity x Counterbalancing	$F(1,71)=.52$, $p=.47$, $\eta_p^2=.01$
	Synchronicity x Group x Counterbalancing	$F(2,71)=.42$, $p=.66$, $\eta_p^2=.01$

*Significant at α=.05. [a] Follow-up analyses showed that in both patients and healthy controls, counterbalancing order had no significant effect on the synchronicity effect ($p=.19$ and $p=.93$, respectively).

Relation between proprioceptive drift and subjective RHI experiences

The relationship between the strength of the proprioceptive drift and subjective RHI experiences was examined. In both the synchronous and synchronous condition bootstrapped linear regression analyses were performed using the entry method. In these analyses, proprioceptive drift in the stimulated hand was used as dependent variable and group, subjective RHI (transformed to z-scores), and the interaction between the two as independent variables.

In sample 1 (healthy controls and patients) the strength of the subjective RHI was a significant predictor of proprioceptive drift in the stimulated hand in both the synchronous (B=1.62, $p=.003$, CI=.49-2.72) and asynchronous condition (B=1.29, $p=.03$, CI=.17-2.72). This relation did not differ between patients and healthy controls, as the group*subjective RHI interactions were no significant predictors in the regression models (p's>.07).

In sample 2 (offspring with and without familial risk for psychosis), regression analyses revealed a significant relationship between proprioceptive drift and subjective RHI experiences in the synchronous condition (B=3.94, $p=.001$, CI=2.07-6.56), while this was only marginally

Supplemental table 3: Mean (standard deviation) baseline estimation errors in sample 1 (part A) and sample 2 (part B)

A. cohort 1: case-control	HC (n=54)	SZ (n=52)	Group differences
Unstimulated hand			
synchronous condition	1.67 (2.69)	2.25 (2.81)	U=1205.00, p=.21
asynchronous condition	1.63 (2.57)	2.37 (2.66)	U=1198.00, p=.19
Stimulated hand			
synchronous condition	-1.68 (3.19)	-1.68 (3.03)	U=1358.50, p=.77
asynchronous condition	-1.49 (3.47)	-2.87 (4.58)	U=1138.00, p=.09

B. cohort 2: offspring	CO (n=17)	SZO (n=23)	BPO (n=33)	Group differences
Unstimulated hand				
synchronous condition	1.93 (3.82)	2.29 (2.60)	2.05 (2.49)	$\chi^2(2)$=.13, p=.94
asynchronous condition	1.90 (2.84)	2.22 (2.57)	2.02 (3.29)	$\chi^2(2)$=.30, p=.86
Stimulated hand				
synchronous condition	-2.87 (4.00)	-3.72 (2.75)	-3.92 (3.82)	$\chi^2(2)$=1.42, p=.49
asynchronous condition	-2.82 (3.54)	-4.17 (3.18)	-3.89 (4.01)	$\chi^2(2)$=1.82, p=.40

HC=healthy control; SZ=patients with schizophrenia; CO=control offspring; SZO=offspring schizophrenia; BPO=offspring bipolar disorder

significant in the asynchronous condition (B=1.72, p=.09, CI=-5.99-4.88). Additionally, the relationship in the asynchronous condition differed between SZO and CO (B=-3.56, p=.01, CI=-6.48 - -1.20). Follow-up analyses indicated a correlation between subjective experiences and proprioceptive drift (asynchronous) in CO (r_s=0.59, p=.01), but not in SZO (r_s=0.11, p=.61).

RHI measures and symptoms

Supplemental table 4: Spearman's correlation between symptoms and RHI measures in patients with schizophrenia

	SELF	PANSS positive	PANSS P1 delusions	PANSS P3 hallucinations
Subjective rating - synchronous	.29*	.29*	.36**	.20
Subjective rating - asynchronous	.11	.28*	.30*	.18
Synchronicity effect – subjective RHI	.11	-.15	-.10	-.07
Drift - synchronous	-.10	.12	.11	.20
Drift - asynchronous	.01	.24	.18	.11
Synchronicity effect - proprioceptive drift	-.03	-.02	.00	.02

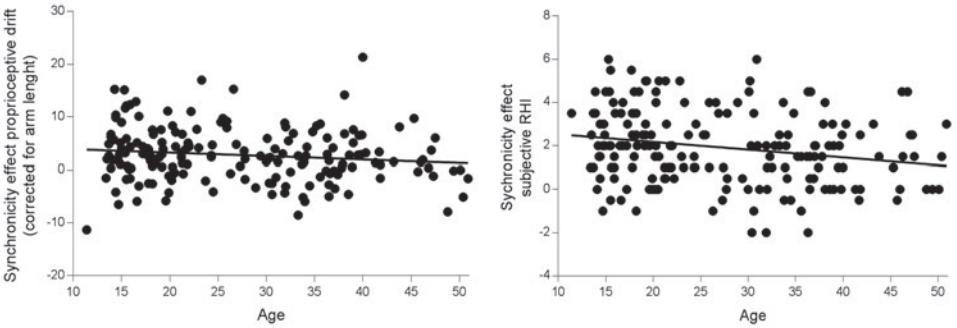
*significant at α=.05; **significant after Bonferroni correction at α=.0125; SELF=Self-Experiences Lifetime and Frequency; PANSS=Positive and Negative Syndrome Scale

Supplemental table 5: Comparison of RHI measures between offspring of patients with schizophrenia or bipolar disorder with and without lifetime psychotic symptoms.

	Group differences		
	SZO	BPO	SZO + BPO
Subjective rating - synchronous	*U*=54.00, *p*=.41	*U*=57.00, *p*=.96	*U*=255.50, *p*=.56
Subjective rating - asynchronous	*U*=62.00, *p*=.74	*U*=50.50, *p*=.68	*U*=247.00, *p*=.46
Synchronicity effect – subjective	*U*=55.00, *p*=.47	*U*=57.50, *p*=.98	*U*=233.00, *p*=.31
Drift - synchronous	*U*=56.00, *p*=.80	*U*=57.00, *p*=.96	*U*=245.00, *p*=.70
Drift - asynchronous	*U*=54.00, *p*=.70	*U*=48.00, *p*=.58	*U*=222.00, *p*=.40
Synchronicity effect - proprioceptive drift	*U*=60.00, *p*=1.00	*U*=48.00, *p*=.58	*U*=247.00, *p*=.73

SZO=Offspring schizophrenia; BPO=Offspring bipolar disorder

RHI and age



Supplemental figure 1. Correlation between age and sychronicity effects.

Impaired self-agency inferences in schizophrenia: the role of cognitive capacity and causal reasoning style

Merel Prikken
Anouk van der Weiden
René S. Kahn
Henk Aarts
Neeltje E.M. van Haren

4

Reference:
Prikken, M., van der Weiden, A., Kahn, R. S., Aarts, H., & van Haren, N. E. M. (2018). Impaired self-agency inferences in schizophrenia: The role of cognitive capacity and causal reasoning style. European Psychiatry, 47, 27-34.

Abstract

Background. The sense of self-agency, i.e., experiencing oneself as the cause of one's own actions, is impaired in patients with schizophrenia. Normally, inferences of self-agency are enhanced when actual outcomes match with pre-activated outcome information, where this pre-activation can result from explicitly set goals (i.e., goal-based route) or implicitly primed outcome information (i.e., prime-based route). Previous research suggests that patients show specific impairments in the prime-based route, implicating that they do not rely on matches between implicitly available outcome information and actual action-outcomes when inferring self-agency. The question remains: Why? Here, we examine whether neurocognitive functioning and self-serving bias (SSB) may explain abnormalities in patients' agency inferences.
Methods. 36 patients and 36 healthy controls performed a commonly used agency inference task to measure goal- and prime-based self-agency inferences. Neurocognitive functioning was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) and the SSB was assessed with the Internal Personal and Situational Attributions Questionnaire.
Results. Results showed a substantial smaller effect of primed outcome information on agency experiences in patients compared with healthy controls. Whereas patients and controls differed on BACS and marginally on SSB scores, these differences were not related to patients' impairments in prime-based agency inferences.
Conclusions. Patients showed impairments in prime-based agency inferences, thereby replicating previous studies. This finding could not be explained by cognitive dysfunction or SSB. Results are discussed in the context of the recent surge to understand and examine deficits in agency experiences in schizophrenia.

Introduction

The complex syndrome of schizophrenia has often been described as a disturbance of the minimal self, in which patients have a decreased sense of self-presence (Nelson et al., 2014; Sass, 2014; Sass & Parnas, 2003). The concepts that are key to this fundamental sense of self are body ownership and self-agency (Hur et al., 2014). Disturbances in self-agency experiences, in which patients have problems identifying the cause of their own bodily movements or thoughts, are reflected in Schneiderian first rank symptoms such as delusions of control and auditory verbal hallucinations (Waters & Badcock, 2010). In experimental settings, these aberrant experiences have been consistently found (Daprati et al., 1997; Franck et al., 2001; Maeda et al., 2013; Schimansky et al., 2010; Synofzik et al., 2010), but the underlying mechanisms responsible for these impairments are still under investigation.

Understanding ourselves is a prerequisite for understanding the thoughts and intentions of others, which implicates that self-disturbances underlie social cognitive, and thus social functioning deficits in patients with schizophrenia (Fett et al., 2011; Nelson et al., 2009). To better understand human interaction and patients' impairments herein, we distinguish between two routes that explain inferences of self-agency (Aarts et al., 2005; van der Weiden, Aarts, et al., 2013). First, in goal-directed behavior, self-agency is generally inferred when an action-outcome matches an explicitly set goal. For example, when someone intentionally raises her voice to get attention from someone else, and that person turns around, a feeling of self-agency arises. However, human interaction does not always occur in such an explicit and deliberate way. A substantial part of our social behavior advances implicitly, without an explicit goal or prior intention. In these situations agency inferences can result from implicitly associated cues or situations that can unconsciously pre-activate or prime an outcome representation in the agent's mind. For example, an implicitly pre-activated emotional expression can influence a feeling of self-agency over emotional expressions in others (Ruys & Aarts, 2012). That is, although to a lesser extent than is the case in goal-directed behavior, a match between this primed outcome representation and the actual action-outcome also enhances agency experiences (van der Weiden, Ruys, et al., 2013). Whereas the process of action selection, action execution, and processing of the actual outcome of one's action *may* require cognitive control, the prime-based agency inference itself seems to materialize without much attention. Together, this illustrates that feelings of authorship in social situations can be affected unconsciously.

Interestingly, patients with schizophrenia show specific impairments in agency inferences of behavior that is not explicitly instigated by goal-directed thought (Prikken et al., 2017; Renes, van der Weiden, et al., 2015; Renes et al., 2013). Specifically, by employing a reliable and widely used agency task allowing to examine goal-based and prime-based agency inferences, patients (in contrast to healthy controls) showed less (or even no) enhanced experiences of self-agency over action outcomes that match primed outcome information. The impaired

prime-based agency inferences in patients could not be explained by motivational problems to conduct the task (Renes et al., 2013), problems in visual processing of primed information (Renes, van der Weiden, et al., 2015), or symptom severity (Prikken et al., 2017). Consequently, the question remains: What then causes these impaired inferences of self-agency that are thought to be involved in social interaction? This question might be answered by considering whether patients and healthy controls differ in the way they process agency cues on a cognitive, affective, and sensorimotor level (Synofzik et al., 2013). In the current study, we focus on the cognitive level and examine two potential candidates that have been suggested to play a role in schizophrenia patients' decreased functioning, i.e., neurocognitive functioning and causal reasoning style.

First, overall cognitive decline is one of the core deficits of schizophrenia (Heinrichs & Zakzanis, 1998; Kuperberg & Heckers, 2000; Velligan et al., 1997; Vöhringer et al., 2013), which might be a potential cause for impairments in prime-based agency inferences. That is, cognitive resources are required to mobilize the selection, execution, and perception of the actions over which we infer agency. The neurocognitive deficits in schizophrenia include a broad range of domains, including executive functioning and attentional problems (Heinrichs & Zakzanis, 1998). Although our previous research showed that individual differences in self-reported attention during task performance could not explain patients' impairments in prime-based agency inferences (Renes et al., 2013), decreased insight into their own neurocognitive functioning asks for a more objective measure (Medalia & Thysen, 2010). Therefore, here we use a short version of a cognitive test battery to explore whether patients' impairments in prime-based agency processing are attributable to decreased neurocognitive functioning or whether they are independent constructs.

A second (social) cognitive feature that is related to self-agency pertains to the way that people attribute the cause of events to internal (e.g., ability or personality) or external factors (e.g., other people or circumstances) (Rotter, 1966). A well-known causal reasoning bias is the self-serving bias (or externalizing bias), which is the tendency to attribute positive events to the self and negative events to external sources (Kinderman & Bentall, 1996; Miller & Ross, 1975). Importantly, in patients with schizophrenia an aberrant self-serving bias has been observed compared with healthy controls. Although most studies showed a stronger self-serving bias in psychotic patients (Janssen et al., 2006; Kaney & Bentall, 1992; Langdon, Ward, & Coltheart, 2010; Mehta, Thirthalli, Bhagyavathi, et al., 2014), some studies found the opposite (Lincoln, Mehl, Kesting, & Rief, 2011; Mehl et al., 2014), and others found no evidence for group differences at all (Berry, Bucci, Kinderman, Emsley, & Corcoran, 2015; Donohoe et al., 2008; Martin & Penn, 2002). These inconsistent findings might be explained by different methodologies or psychopathology. Therefore, in the current study we will assess group differences in self-serving bias by employing a widely used measure of self-attributions.

Furthermore, although prime-based agency inferences are found to be relevant in social

interaction (Ruys & Aarts, 2012), uncertainty exists about its relation with (impaired) social cognitive functioning. Interestingly, the social cognitive principle of the self-serving bias overlaps with the process underlying agency inferences. Specifically, when inferring self-agency over an action-outcome, matching goals or primes may give rise to a feeling of success and are more likely to be attributed to the self (i.e., a positive event leads to self-attribution) (Aarts, 2007; van der Weiden, Ruys, et al., 2013). Conversely, a mismatch between a goal or prime and action-outcome may give rise to a feeling of failure and is more often attributed to external sources (i.e., a negative event leads to external attribution). Building on this theoretical relation between the self-serving bias and the principles underlying agency experiences, we explore whether an aberrant self-serving bias are related to patients' impairments in prime-based agency processing.

Methods

Subjects

36 patients with a DSM-IV diagnosis of schizophrenia and 36 healthy controls (gender and age matched) participated in this study. Diagnoses were checked with the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992). Patients were recruited from the psychiatry department of the University Medical Center Utrecht (UMCU), from previous studies performed at this department, and from other psychiatric institutions in the Utrecht area. Healthy controls were recruited through advertisements on notice boards and an online recruiting company for scientific research (www.proefpersonen.nl).

Participants were aged between 18 and 50, Dutch speaking, able to give informed consent, and had a (premorbid) IQ of at least 80 (Schmand, Bakker, Saan, & Louman, 1991). Also, they had no history of closed-head injury, neurological or endocrinological disorders, and did not meet DSM-IV criteria for drug or alcohol abuse in the past six months. Participants did not chronically use medication (for patients: other than psychiatric medication). Patients were not experiencing a psychotic episode at the time of testing. Healthy controls did not have a history of psychiatric illness and did not have a first or second degree family member with a psychotic disorder. All participants were financially compensated and the study was approved by the UMCU Human Ethics Committee.

Procedures and measures

Agency inference task. An agency inference task was used to measure goal-based and prime-based agency inferences (Aarts et al., 2005; Renes et al., 2013). In this task participants believed they were in control of a rotating square that traversed along a path, see Figure 1 (for task details, see Aarts et al., 2005; Prikken et al., 2017; Renes et al., 2013). When the s-key was pressed during the start cue, two squares (one of the participant and one of the computer)

started moving in opposite directions. Participants were told that when 'stop' appeared in the middle of the screen, both squares continue to move *invisibly* at the same speed. When they pressed the enter-key to stop this invisible rotation, one of the tiles turned black. They were told that the location of this tile randomly represented the final position of their own or the computer's square. After each trial, participants indicated on a 9-point scale (not at all(1) – strongly(9)) to what extent they felt they were the one that caused the square to stop at that specific location (i.e., experienced self-agency).

In the prime-based condition an outcome location was subtly primed just before the stop-cue (see Figure 1a; for checks regarding unawareness of the prime, see (Aarts, Custers, & Marien, 2009; Aarts et al., 2005; van der Weiden, Aarts, & Ruys, 2010; van der Weiden et al., 2011; van der Weiden, Ruys, et al., 2013)). Conversely, in the goal-based condition participants explicitly received the goal to stop their square at a certain location (Figure 1b). Importantly, in reality the presented outcome location was always predetermined by the program and thus occurred independent of the participant's key press. This predetermined outcome could either match or mismatch the goals and primes. The difference between agency ratings on matching and mismatching trials (i.e., matching effect) reflects the strength of inferring agency on the basis of goal-based or prime-based agency cues.

Figure 1. Agency inference task. Both conditions comprised 32 trials. Each tile was used as a goal or prime twice in each block: once as a match and once as a mismatch. The prime-based condition was administered before the goal-based condition.

Neurocognitive functioning. Neurocognitive functioning was assessed by the Brief Assessment of Cognition in Schizophrenia (BACS), which covers those cognitive domains that are most disturbed in schizophrenia (Keefe et al., 2004). The BACS consists of six tasks covering verbal memory, working memory, motor speed, verbal fluency, attention, speed of

information processing, and executive functioning, which are intercorrelated and have good internal consistency (Cronbach's α = 0.74 in our dataset) (Keefe et al., 2004). Therefore, the mean of all standardized subscale scores was used as a measure of cognitive capacity.

Attributional style. The Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) was used to measure attributional style (Kinderman & Bentall, 1996). This 32-item questionnaire was verbally administered by a trained experimenter. Participants had to come up with a most likely cause of a situation (e.g., 'a friend betrayed the trust you had in her'). Then, they had to indicate whether this cause was most likely due to self (internal attribution), another person (external personal attribution), or circumstances (external situational attribution). The questionnaire consists of 16 positive and 16 negative situations.

Self-serving bias (SSB), representing the tendency to attribute more positive than negative events to the self, was calculated by subtracting the number of internal attributions for negative events from the number of internal attributions for positive events (Kinderman & Bentall, 1996).

Additionally, by adding all items that are attributed to the self, the IPSAQ allows us to estimate a general tendency to make internal attributions, irrespective of the valence of the event. To correct for missing items, we measured a general attribution to the self by taking the proportion of completed items in which the proposed situation was attributed to the self. In order to calculate the reliability of this measure, IPSAQ scores were dichotomized ('internally attributed' and 'externally attributed') and only the participants that fully completed the IPSAQ were included (n=63). Cronbach's α of 0.78 indicated good internal consistency for this measure of a general tendency to attribute events to the self.

Statistical analyses

First, group differences in age, gender, own and parental years of education, BACS, and IPSAQ scores were analyzed using independent sample t-tests and a chi-square test.

Second, to test potential differences between healthy controls and patients with respect to goal-based and prime-based inferences, two separate repeated measures ANOVA's were performed according to the experimental design: Matching (matching vs. mismatching trials) x Group with the first factor as within-subjects variable and the latter one as between-subjects variable. Also, matching effects per group were evaluated by performing the same repeated measures ANOVA in both groups separately. Additionally, a potential relation between internal predictions based on the reaction time to press 'stop' and the strength of agency experiences was examined. For detailed methods of this analysis, see supplement 1.

Third, the relationship between goal- and prime-based agency inferences and neurocognitive functioning on the one hand, and self-serving bias on the other, we conducted two separate ANOVA's including the BACS or the SSB measure as covariate to test the specific main effects of BACS or SSB and their interaction effects with Group and Matching, respectively. SSB scores were centered.

Last, we explored the relationship between a generally biased attribution to the self and overall agency ratings to assess whether agency experiences in our task are in concordance with feelings of personal causation in daily situations. Therefore, linear regression analyses were performed with Group, the proportion of self-attributions in the IPSAQ, and its interaction as independent variables. Mean agency rating (ratings irrespective of the manipulation of matching) was used as dependent variable. This was done for prime-based and goal-based agency ratings separately.

Results

Demographics and clinical characteristics are displayed in table 1. Age, gender distribution, and parental level of education did not differ between patients and healthy controls. As expected, healthy controls had significantly more years of education, a higher (premorbid) IQ,

Table 1: Demographics, clinical characteristics, and BACS and IPSAQ descriptives.

	Schizophrenia patients (n=36)	Healthy controls (n=36)	Group differences
Age	32.33 (6.97)	31.01 (6.32)	$t(70)=-0.84$, $p=0.40$, Cohen's $d=0.20$
Gender (m/f)	31/5	32/4	$X^2(1)=0.13$, $p=0.72$, $r=0.04$
Years of education	13.11 (2.01)	14.06 (1.88) [a]	$t(69)=2.05$, $p=0.04$, Cohen's $d=0.49$
Parental years of education	14.67 (3.30)[b]	14.34 (2.40)[c]	$t(63)=-0.45$, $p=0.66$, Cohen's $d=0.12$
(Premorbid) IQ [+]	100.28 (6.21)[c]	105.58 (6.45)[b]	$t(63)=3.36$, $p=0.001$, Cohen's $d=0.84$
Years of illness duration	13.01 (7.34)[c]	N/A	
Antipsychotic medication typical/atypical/both/none	4/30/1/1	N/A	
PANSS			
positive	12.39 (3.50)	N/A	
negative	12.81 (5.29)	N/A	
general	24.58 (4.33)	N/A	
total	49.78 (8.56)	N/A	
BACS total score [++]			
raw score	237.06 (34.04)	278.38 (36.76)[d]	$t(68)=4.88$, $p<0.001$, Cohen's $d=1.18$
IPSAQ [+++]			
Self-serving bias	0.79 (2.91)[d]	2.03 (2.98)	$t(68)=1.75$, $p=0.09$, Cohen's $d=0.42$
General attribution to self	0.45 (0.15)[d]	0.36 (0.15)	$t(68)=-2.59$, $p=0.01$, Cohen's $d=0.60$

[a] n=35 [b] n =33 [c] n=32 [d] n=34 [+] measured with the Dutch Adult Reading Test (Schmand et al., 1991): Participants with a non-Dutch native language or dyslexia were removed from IQ analysis [++] due to missing data BACS total score could not be calculated for 2 participants [+++] 2 patients with >3 missing items were removed from IPSAQ analysis

and a higher BACS total score. Patients had a significantly greater general tendency to attribute situations to the self, while the self-serving bias was marginally larger in healthy controls.

Self-agency experiences in schizophrenia patients and healthy controls

Table 2 shows results regarding self-agency experiences. In both the goal-based and prime-based condition a main effect of matching was found in both groups, indicating higher agency ratings on matching compared with mismatching trials. In the prime-based condition, the matching effect (i.e., the strength of the effect of primes on agency experiences) was significantly larger in healthy controls than in patients (Matching x Group). In the goal-based condition, this difference was only marginally significant. Additional analyses showed that agency experiences were independent of potential internal predictions (see supplement 1).

Table 2: Repeated measures ANOVA results regarding self-agency experiences.[+]

Mean self-agency ratings (sd)	Schizophrenia patients (n=36)		Healthy Controls (n=36)		Group differences			
Prime-based: match trials	5.20 (1.43)		5.84 (1.17)		$t(70)=2.08$, $p=0.04$, Cohen's $d=0.49$			
Prime-based: mismatch trials	4.24 (1.23)		3.75 (1.36)		$t(70)=-1.60$, $p=0.11$, Cohen's $d=0.38$			
Goal-based: match trials	6.78 (1.58) [a]		7.07 (1.22)		$t(69)=0.88$, $p=0.38$, Cohen's $d=0.20$			
Goal-based: mismatch trials	3.61 (1.38) [a]		3.00 (1.25)		$t(69)=-1.94$, $p=0.06$, Cohen's $d=0.46$			
Repeated measures ANOVA	**Prime-based agency experiences**				**Goal-based agency experiences**			
	df	*F*	Sig.	η_p^2	*df*	*F*	Sig.	η_p^2
Group	1,70	0.15	0.70	0.002	1,69	0.68	0.41	0.01
Matching	1,70	41.61	<0.001	0.37	1,69	191.18	<0.001	0.74
Matching x Group	1,70	5.66	0.02	0.08	1,69	2.95	0.09	0.04
Simple main effects	**Matching effect: prime-based**				**Matching effect: goal-based**			
	df	*F*	Sig.	η_p^2	*df*	*F*	Sig.	η_p^2
Schizophrenia patients	1,35	10.53	0.003	0.23	1,34	59.30	<0.001	0.64
Healthy controls	1,35	32.13	<0.001	0.48	1,35	155.65	<0.001	0.82

[+] As seven patients also participated in our previous study with the same task (Prikken et al., 2017), which might have influenced their responses to the present task, we repeated these analyses without these participants. These results yielded the same conclusions. [a]n=35:one patient refused to continue with the task and only completed the prime-based condition.

The role of neurocognitive functioning in goal-based and prime-based agency inferences

ANCOVA results (Table 3) revealed a significant Matching x BACS interaction in the goal-based, but not in the prime-based agency inference task. This implies a positive relation between neurocognitive functioning and the matching effect in the goal-based condition, i.e., the extent to which goals inform agency inferences (Figure 2). Non-significant Matching

x Group x BACS interactions indicate that the relation between neurocognitive functioning and agency inferences did not differ between patients and healthy controls. For correlation coefficients between BACS subtests and agency inferences, see Supplement 2.

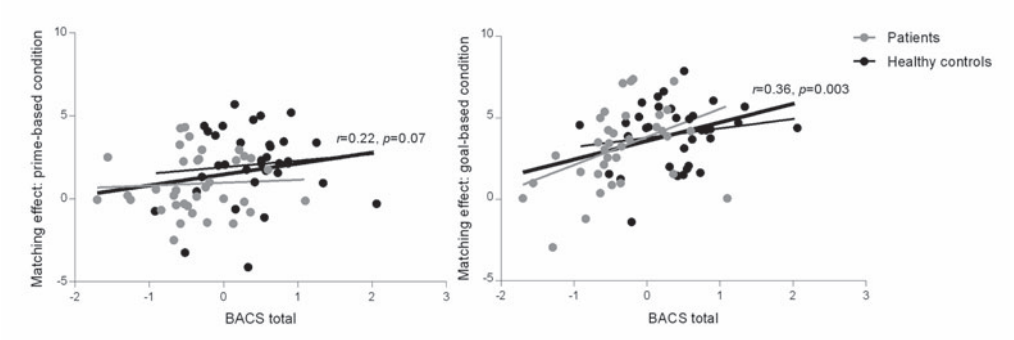


Figure 2: The relationship between cognitive capacity and matching effect in the prime-based and goal-based condition. Thin lines represent the regression line in healthy controls (n=34) and patients (n=36 in the prime-based condition and n=35 in the goal-based condition). Bold line represents the regression line in the total sample.

Table 3: Repeated measures ANCOVA results regarding the effect of cognitive capacity and causal reasoning style on self-agency experiences.

Neurocognitive functioning	Prime-based agency experiences (*df*=1,67)			Goal-based agency experiences (*df*=1,66)		
	F	**Sig.**	η_p^2	***F***	**Sig.**	η_p^2
BACS	0.29	0.59	0.96	0.01	0.93	<0.001
Group x BACS	0.80	0.38	0.01	3.16	0.08	0.05
Matching x BACS	3.38	0.07	0.05	9.73	0.003	0.13
Matching x Group x BACS	0.05	0.83	0.001	1.75	0.19	0.03
Causal reasoning style	Prime-based agency experiences (*df*=1,67)			Goal-based agency experiences (*df*=1,66)		
	F	**Sig.**	η_p^2	***F***	**Sig.**	η_p^2
SSB	2.36	0.13	0.03	0.06	0.81	0.001
Group x SSB	<0.001	1.00	<0.001	0.04	0.83	0.001
Matching x SSB	0.23	0.64	0.00	<0.001	0.99	<0.001
Matching x Group x SSB	1.00	0.32	0.02	0.03	0.87	<0.001

BACS= Behavioral Assessment of Cognition in Schizophrenia; SSB=Self-Serving Bias

The role of causal reasoning style in goal-based and prime-based agency inferences

Although the self-serving bias was marginally larger in healthy controls (Table 1), ANCOVA results showed that it was not related to the matching effect in the goal-based and prime-based condition (no Matching x SSB and Matching x Group x SSB interactions: Table 3).

Additionally, regression analyses to assess the relation between the tendency to attribute to the self in our task and in the IPSAQ revealed no significant predictors. That is, the general tendency to attribute to the self, group, and the interaction between the two were no significant predictors of mean agency ratings in our task.

Discussion

Building on previous findings revealing that patients with schizophrenia show abnormalities in prime-based agency processing, this study examined two possible cognitive correlates of this impairment, namely neurocognitive functioning and self-serving bias. First, in the current sample a significant effect of goals and primes on agency inferences was found in both healthy controls and patients. Importantly, compared with healthy controls, patients were less informed by primes when inferring self-agency, which is in line with findings from two previous studies that used the exact same task (Renes, van der Weiden, et al., 2015; Renes et al., 2013). To increase statistical power, we combined data of these previous studies with the present study (see supplement 3). These analyses confirmed that the effect of primes on agency inferences was significantly smaller in patients compared with healthy controls in a combined sample of 180 participants (90 in each group). Importantly, combined data from the study of Renes et al. (2013) and the current study showed that group differences in matching effect in the prime-based condition were marginally larger than group differences in matching effect in the goal-based condition (see supplement 3). It should be noted that the strength of the group effects was different between the studies. A possible explanation for these findings might be differences in study protocols or it may be simply due to sampling differences, but the exact reason remains unclear. To summarize, all studies individually suggest specific impairments in prime-based agency inferences in patients and most importantly, findings of the three studies combined confirm these specific impairments.

In the present study, we tested and excluded the possibility that decreased neurocognitive functioning drives patients' deficits in prime-based agency inferences. Although at trend level a relation between BACS and prime-based inferences is found, the effect size is small and the trend can be explained by the finding that patients score significantly lower on both variables (Figure 2). Interestingly, goal-based agency inferences were significantly related to individual differences in neurocognitive functioning in the total sample (N = 69). Although this relation appears stronger in patients than in healthy controls, it did not differ statistically between the groups. This suggests that the relation between goal-based agency inferences and cognitive processing is also present in patients with schizophrenia, i.e., a sample with reduced neurocognitive functioning. The current sample might be too small to detect such an interaction with group, and hence, the absence of the interaction should be treated with caution. Of importance, the findings of the current study relate to agency inferences research

in healthy individuals (Hon, Poh, & Soon, 2013; Renes, van Haren, & Aarts, 2015). Specifically, increasing cognitive load (e.g., by a working memory task) seemed to negatively affect *goal*-based, but not *prime*-based agency inferences.

These findings suggest two important implications. First, the goal-based route to self-agency experiences relies on attentional processes that aid goal attainment (e.g., monitoring and feedback processing). Hence, taxing these attentional processes impairs goal-based agency inferences, and, as the present findings suggest, this might be similar for healthy individuals and patients suffering from schizophrenia. Second, *prime*-based agency inferences can occur rather automatically and seem to materialize without much attention. As these implicit inferences are essential to social cognitive behavior (Nosek, Hawkins, & Frazier, 2011), our findings support the hypothesis that patients' difficulties with relying on subtle agency cues might be related to their problems in social functioning (Daprati et al., 1997; Frith, 2013b; Moretto et al., 2011; van der Weiden et al., 2015). However, empirical evidence for this hypothesis is lacking.

Furthermore, we explored the relationship between the self-serving bias and agency inferences. First, patients showed weaker self-serving biases compared to control subjects, but this difference did not reach the conventional level of significance. Accordingly, the present study adds another piece of data to earlier research suggesting that schizophrenia is not related to the self-serving bias (Berry et al., 2015; Donohoe et al., 2008; Martin & Penn, 2002). Furthermore, the effect of primes on agency inferences was unrelated to differences in self-serving bias, indicating that, at least in the current study, patients' impairments in prime-based agency processing cannot be explained by an aberrant self-serving bias. Finally, a generally biased attribution to the self, as estimated from the IPSAQ, was not related to the level of overall agency experiences in our task. These results are in line with previous research that showed no significant relation between locus of control (i.e., related to our measure of a generally biased attribution of the self) and indirect measures of self-agency (i.e., temporal binding and sensory attenuation) (Dewey & Knoblich, 2014). We extend this finding to a more explicit measure of self-agency, confirming that ratings of self-agency in a specific task setting (as we examined here) might tap into different processes underlying the sense of agency than a measure of general experiences of control (as represented in general measures of self-attributions or locus of control). More specifically, our results suggest that attributions in social situations are influenced by additional factors, which might overrule cognitive inferences. We wish to stress here that we do not know yet whether the underlying mechanisms of agency experiences, as we studied in the goal-based vs. primed-based agency inference task, directly pertain to actual agency experiences that people have in everyday situations, or whether there are important moderators that may shed light on the link between basic mechanisms and more complex real life social situations. This discrepancy is also apparent in the absence of

clinical correlates of patients-impaired prime-based agency processing (Prikken et al., 2017 and Supplement 4). Nevertheless, our results indicate that the agency inference task clearly taps into disturbed processes that are relevant to schizophrenia. To better understand the possible clinical implications of these problems, future studies should focus on designing an agency inference task with more ecological validity in order to better assess the behavioral and clinical consequences of impaired prime-based agency processing.

Conclusions

In the present study we observed aberrant prime-based agency inferences in patients with schizophrenia. This replicates previous studies and suggests robustness of the finding. Also, the current study showed that decreased neurocognitive functioning negatively influences goal-based agency inferences. However, patients' impairments in prime-based agency inferences could neither be explained by decreased neurocognitive functioning nor by an aberrant self-serving bias. The confirmation that prime-based inferences can occur rather automatically underscores its potential relevance for behavior in social situations. The integration and distinction between self and other as a cause of behavior are essential to social functioning, but it remains a challenge to take the complexity of social processes into account in experimental settings (van der Weiden et al., 2015). In order to study the behavioral relevance of patients' deficits in prime-based inferences, future studies should focus on developing an agency inference task that taps into everyday situations.

Supplement 1: Response time analyses

Methods

The agency inference task was designed to render participants' predictions of outcome locations unreliable. That is, participants could not follow their square from the moment they had to press the stop key. However, the square could be followed in mind. Based on the timing of pressing the STOP cue, a prediction of their square's stop location could have been made. Participants might have based their agency rating on this possible internal prediction. If that is true, the closer the participant landed their square to the presented outcome location, the higher agency ratings would be.

In order to examine this possibility, the response time to push the Enter button in reaction to the STOP cue was analyzed (for detailed methods, see also (Aarts et al., 2005; van der Weiden, Ruys, et al., 2013). In the experiment, the last presentation of the participant's square was always four locations farther than the goal or prime location. Therefore, in matching trials the time from the onset of the last location of the square and onset of the outcome location was 400 ms (1 lap of 800 ms / 2). For mismatching trials, the goal or prime was randomly presented half a lap from the outcome location or one tile before or after this location. Hence, the time from the onset of the last location of the participant' square to the onset of the stop location in mismatching trials was either 800 ms (1 lap) or 700 ms (-1 tile) or 900 ms (+1 tile).

Then, the time between the STOP cue and the *onset* of the presented stop location was 283 ms for matches and 583, 683, or 783 for mismatches (i.e., 400 ms, and 700, 800, or 900 ms, minus 50 ms from the last presentation of the participant's square, and minus 67 ms for the priming event). The response time to stop exactly on the outcome location *at half its presentation time* was 308, 608, 708, or 808 ms (283, 583, 683, or 783 plus 25 ms).

Pearson's correlation between this response time and self-agency experiences was then calculated to assess their relationship.

Results

No significant correlations were found (goal-based match, r=.21, p=.09; goal-based mismatch, r= -.11, p=.36; prime-based match, r= -.08, p=.50; prime-based mismatch, r=.05, p=.65). To check whether the reported group differences in prime-based agency inferences might be related to this issue, we also assessed correlation coefficients within each group. In both the matching and mismatching trials, results remained non-significant (prime-based match health controls, r= -.09, p=.59; prime-based mismatch healthy controls, r= .32, p=.06; prime-based match patients, r=.06, p=.73; prime-based mismatch patients, r= -.09, p=.62).

These results were similar to previous findings in our group (van der Weiden, Ruys, et al., 2013). That is, we confirmed that agency experiences in our task are independent of potential internal predictions.

Supplement 2: BACS subscales and agency inferences

Supplemental table 1: BACS subtasks and corresponding cognitive domains.

BACS subtest	Cognitive domain
List learning	Verbal memory
Digit symbol sequencing	Working memory
Token motor task	Motor speed
Verbal Fluency	Processing speed
Symbol coding	Attention/processing speed
Tower test	Executive functioning

Supplemental table 2: Spearman's correlation between BACS subscales and agency inferences.

	Prime-based matching effect (n=70)	Goal-based matching effect (n=69)
List learning	*rs*=.16, *p*=.20	*rs*=.22, *p*=.07
Digit symbol sequencing	*rs*=.27, *p*=.02	*rs*=.20, *p*=.10
Token motor task	*rs*=-.05, *p*=.71	*rs*=.19, *p*=.12
Verbal fluency	*rs*=.09, *p*=.48	*rs*=.34, *p*=.004
Symbol coding	*rs*=.10, *p*=.43	*rs*=.28, *p*=.02
Tower test	*rs*=.32, *p*=.01	*rs*=.25, *p*=.04

Supplement 3: Comparison of agency inferences in three different studies

Method

To gain statistical power, we combined data from the current study with data from previous studies performed in our group.

First, to assess group differences in prime-based agency inferences specifically, we could combine our sample with that of Renes and colleagues (Renes, van der Weiden, et al., 2015; Renes et al., 2013), thereby increasing the sample size to 90 patients and 90 healthy controls. To examine prime-based agency inferences in these studies, a repeated measures ANOVA was performed with Matching (match and mismatch) as within-subjects variable and Group (HC and SZ) as between-subjects factor. Then, the variable Study (3 studies) was added as a between-subjects variable to specifically test its effect on Matching, Group, and the Matching x Group interaction.

Second, data from the current study and the study by (Renes et al., 2013) were combined (59 healthy controls and 58 patients) to assess (group)differences between goal-based and prime-based agency inferences. A repeated measures ANOVA with Matching (match and mismatch) and Condition (prime-based and goal-based) as a within subjects variables and Group (HC and SZ) as between-subjects factor was performed. Again, the variable Study (2 studies) was added as between-subjects factor to specifically test potential differences in the Matching x Condition x Group interaction between studies.

Results

Group differences in prime-based agency inferences. In the combined sample a significant effect of matching was found, which was different between healthy controls and patients (Supplemental table 3). Additionally, the matching effect did not differ between the studies (Supplemental table 4).

Supplemental table 3: Group differences in prime-based agency inferences

Effect	Test results
Group	$F(1,178)=0.04$, $p=0.84$, $\eta_p^2<0.001$
Matching	$F(1,178)=46.29$, $p<0.001$, $\eta_p^2=0.21$
Matching x Group	$F(1,178)=11.64$, $p=0.001$, $\eta_p^2=0.06$

Supplemental table 4: Study comparison of prime-based agency inferences

Effect	Test results
Study	$F(2,174)=2.69$, $p=0.07$, $\eta_p^2=0.03$
Group x Study	$F(3,174)=0.82$, $p=0.49$, $\eta_p^2=0.01$
Matching x Study	$F(2,174)=2.22$, $p=0.11$, $\eta_p^2=0.03$
Matching x Group x Study	$F(3,174)=3.97$, $p=0.01$, $\eta_p^2=0.06$

Differences between prime-based and goal-based agency inferences. Upplemental table 5 shows that the matching effect was significantly different between the goal-based and prime-based condition. Also, group differences in matching effect differ marginally between goal-based and prime-based condition (3-way interaction), indicating possible larger group differences in prime-based compared with goal-based agency inferences. A marginal difference between studies was found regarding this 3-way interaction, $F(2,113)=3.02$, $p=0.05$, $\eta_p^2=0.05$.

Supplemental table 5: Group and condition differences in agency inferences

Effect	Test results
Group	$F(1,115)=2.44$, $p=0.12$, $\eta_p^2=0.02$
Matching	$F(1,115)=14.34$, $p<0.001$, $\eta_p^2=0.11$
Condition	$F(1,115)=249.61$, $p<0.001$, $\eta_p^2=0.69$
Matching x Group	$F(1,115)=0.008$ $p=0.93$, $\eta_p^2<0.001$
Condition x Group	$F(1,115)=7.55$, $p=0.007$, $\eta_p^2=0.06$
Matching x Condition	$F(1,115)=97.59$, $p<0.001$, $\eta_p^2=0.46$
Matching x Group x Condition	$F(1,115)=3.51$, $p=0.06$, $\eta_p^2=0.03$

Supplement 4: Symptoms related to agency inferences and self-serving bias

Both self-agency and the self-serving bias have been found to be related to psychopathology (especially hallucinations, paranoid delusion, passivity symptoms and depression) in patients (Diez-Alegría, Vázquez, Nieto-Moreno, Valiente, & Fuentenebro, 2006; Graham-Schmidt, Martin-Iverson, & Waters, 2017; Maeda et al., 2013; Wittorf et al., 2012). Therefore, we explored these associations in our sample using Spearman's correlation coefficient. Due to the low frequency of current presence of delusions of control (n=0), thought broadcasting (n=3), thought insertion (n=4), and thought withdrawal (n=0), correlational analysis could not be performed for these symptoms.

Results in Supplemental table 6 showed that only a significant correlation was found between the prime-based matching effect and PANSS general psychopathology. However, this correlation did not survive Bonferroni correction for multiple testing (α=.05/7=.007).

Supplemental table 6: Spearman's correlation between psychopathology in patients and study outcome measures (agency inferences and self-serving bias)

PANSS	Prime-based matching effect (n=36)	Goal-based matching effect (n=35)	Self-serving bias (n=34)
positive subscale	r_s=.13, p=.46	r_s=.10, p=.59	r_s=-.26, p=.14
negative subscale	r_s=-.01, p=.96	r_s=-.25, p=.15	r_s=.11, p=.53
general subscale	r_s=.35, p=.04	r_s=-.11, p=.53	r_s=-.32, p=.06
total	r_s=.19, p=.26	r_s=-.11, p=.51	r_s=-.26, p=.14
suspiciousness/persecution	r_s=.21, p=.22	r_s=.23, p=.18	r_s=-.26, p=.14
hallucinations	r_s=.05, p=.79	r_s=-.19, p=.29	r_s=-.24, p=.17
depression	r_s=.12, p=.50	r_s=-.13, p=.45	r_s=-.10, p=.57

Abnormal agency experiences in schizophrenia patients: examining the role of psychotic symptoms and familial risk.

Merel Prikken
Anouk van der Weiden
Robert A. Renes
Martijn G.J.C. Koevoets
Henriette D. Heering
René S. Kahn
Henk Aarts
Neeltje E.M. van Haren

5

Reference:
Prikken, M., van der Weiden, A., Renes, R. A., Koevoets, M. G. J. C., Heering, H. D., Kahn, R. S., Aarts, H. & van Haren, N. E. M. (2017). Abnormal agency experiences in schizophrenia patients: Examining the role of psychotic symptoms and familial risk. Psychiatry Research, 250, 270-276.

Abstract

Background. Experiencing self-agency over one's own action outcomes is essential for social functioning. Recent research revealed that patients with schizophrenia do not use implicitly available information about their action-outcomes (i.e., prime-based agency inference) to arrive at self-agency experiences. Here, we examined whether this is related to symptoms and/or familial risk to develop the disease.

Methods. Fifty-four patients, 54 controls, and 19 unaffected (and unrelated) siblings performed an agency inference task, in which experienced agency was measured over action-outcomes that matched or mismatched outcome-primes that were presented before action performance. The Positive and Negative Syndrome Scale (PANSS) and Comprehensive Assessment of Symptoms and History (CASH) were administered to assess psychopathology.

Results. Impairments in prime-based inferences did not differ between patients with symptoms of over- and underattribution. However, patients with agency underattribution symptoms reported significantly lower overall self-agency experiences. Siblings displayed stronger prime-based agency inferences than patients, but weaker prime-based inferences than healthy controls. However, these differences were not statistically significant.

Conclusions. Findings suggest that impairments in prime-based agency inferences may be a trait characteristic of schizophrenia. Moreover, this study may stimulate further research on the familial basis and the clinical relevance of impairments in implicit agency inferences.

Introduction

Patients with schizophrenia often feel that they are not causing their own thoughts and actions (e.g., delusions of control or thought insertion). Such experiences may be explained by impairments in self-agency, i.e., the experience that we cause our own actions and the consequences of those actions. For example, when you press the button of an ice machine, you automatically feel that it was you who made the ice cubes fall out. Also, in more complex (social) situations this experience is crucial. For example, when you make a joke it matters whether you feel that you made the people around you laugh, or whether you think they are laughing for some other reason. By focusing on impairments in these self-agency processes and genetic vulnerability to these impairments, this study aims to contribute to a better understanding of the origin of psychotic symptoms.

Two models have been described to explain the underlying mechanisms of the experience of self-agency: motor prediction and cognitive inference. During action performance, the motor system constantly makes predictions about consequences of actions. The motor prediction model assumes that outcomes are perceived as self-produced when a prediction matches the sensory feedback (e.g., the sound of ice cubes falling out). In case of a mismatch between the prediction and the actual outcome, people are likely to attribute agency to someone or something else (Frith et al., 2000b; Wolpert & Flanagan, 2001). Several studies on schizophrenia, using various experimental paradigms based on the motor prediction model (e.g., corollary discharge or temporal binding), demonstrated impairments in agency attribution in different stages of the disease. (Daprati et al., 1997; Franck et al., 2001; Hauser et al., 2011; Hur et al., 2014; Johns et al., 2001; Maeda et al., 2012, 2013; Schimansky et al., 2010; Synofzik et al., 2010).

In situations with multiple possible outcomes and multiple possible agents, motor predictions regarding the actual outcome can no longer reliably guide feelings of self-agency and consequently, retrospective cognitive inferences of agency become important (Aarts et al., 2005; van der Weiden, Aarts, et al., 2013; Wegner, 2002). The cognitive inference model assumes that people *infer* self-agency based on knowledge and beliefs regarding the effects (e.g., laughter) of their actions (e.g., making a joke) before they perform them, and regarding the influence of other factors (e.g., someone who is imitating you in a funny way). Similar to the matching/mismatching process within motor prediction, when an event matches (rather than mismatches) one's prior beliefs and expectations, one is likely to infer self-agency. It has been suggested that schizophrenia patients may rely more on this cognitive route towards agency due to deficits in motor prediction processes (Synofzik et al., 2013; Voss et al., 2010).

Studies on cognitive agency inferences distinguish two different routes: a goal-based (explicit) and a prime-based (implicit) route (Aarts et al., 2005; van der Weiden, Ruys, et al., 2013). Goal-based agency inferences are involved in planned behavior, whereas prime-based agency inferences are involved in behavior that is instigated by environmental cues. Previous studies from our group revealed that schizophrenia patients show specific deficits in this second

route, showing that they are unable to use implicitly available cues in the environment when making agency inferences (Renes, van der Weiden, et al., 2015; Renes et al., 2013). However, it is not known whether these impairments in making prime-based inferences relate to specific psychotic symptoms or familial risk. By combining two independent samples (Renes, van der Weiden, et al., 2015; Renes et al., 2013) we now have the statistical power to perform sub-group analyses in order to address these questions. In the current paper, we investigate two possible implications of schizophrenia patients' impairments in making prime-based inferences.

First, impairments in prime-based inferences may specifically explain symptoms of over- and underattribution of self-agency. One could argue that over-attributing self-agency is reflected in, for example, grandiose delusions or delusions of reference, i.e., patients feel they are capable of causing events that are actually outside of their control (Synofzik et al., 2013). To our knowledge, such symptoms of overattribution have not been studied in relation to self-agency processing yet. In contrast, delusions of control (i.e., patients experience no control over their thoughts and actions) or auditory hallucinations, (i.e., patients perceive inner speech as originating from an external source (Balconi, 2010)) may imply underattribution of self-agency (or attribution to the outside world). These symptoms are also referred to as first-rank symptoms (Carpenter, Strauss, & Muleh, 1973; Heering, van Haren, & Derks, 2013) or passivity symptoms and have previously been associated with impaired agency processing (Daprati et al., 1997; Franck et al., 2001; Synofzik et al., 2010; Waters & Badcock, 2010). However, to our knowledge separate clusters consisting exclusively of symptoms of overattribution or underattribution of agency have not been studied in experimental settings. Therefore, we examine whether prime-based agency inferences, as well as overall level of experienced self-agency are related to these clusters of symptoms. Specifically, we expect patients with symptoms of under-attribution to experience less self-agency overall, and that this may be related to a decreased sensitivity to implicit outcome-primes. Conversely, we expect patients with symptoms of over-attribution to experience more self-agency overall, and that this may be related to an increased sensitivity to implicit outcome-primes.

Second, we aim to investigate whether the disturbance in prime-based agency inferences is related to familial risk to develop schizophrenia and could serve as a vulnerability marker for the disease. Schizophrenia is highly heritable (Cardno et al., 1999; Kendler, Pedersen, Neale, & Mathé, 1995), and there is ample evidence that neural or cognitive features of the illness are related to the familial or genetic risk to develop the illness. Previously, it has been suggested that impairments in self-monitoring may be a vulnerability marker for psychosis (Versmissen et al., 2007). Indeed, studies in unaffected siblings of patients have shown that they perform at an intermediate level between patients and healthy controls on self-processing tasks, such as action monitoring (Hommes et al., 2012) and verbal source monitoring tasks (Brunelin et al., 2007). Here, we examine impairments in prime-based inferences as a possible vulnerability

marker for schizophrenia by exploring whether unaffected siblings of schizophrenia patients perform at an intermediate level on a prime-based agency inference task, which would suggest that the familial risk to develop the illness is reflected in abnormal self-processing.

Methods

Subjects

A total of 54 patients with a DSM-IV diagnosis of schizophrenia, 19 unaffected (unrelated) siblings of patients with a non-affective psychotic disorder (of which 16 patients were diagnosed with schizophrenia, 1 with schizophreniform disorder, and 2 with psychotic disorder NOS), and 54 control subjects participated in the study. Patients and controls were included from two independent samples that have been described previously (sample 1 (Renes et al., 2013) and sample 2 (Renes, van der Weiden, et al., 2015)). In these patient samples, similar inclusion and exclusion criteria were used.

Exclusion criteria were an IQ below 70, drug or alcohol abuse in the past six months, a history of head trauma, neurological illness or endocrine dysfunction. Controls and siblings had no history of psychiatric illness. Additionally, controls had no first-degree relatives with a psychotic illness and did not use chronic medication. Within the patient group, all but three participants were receiving antipsychotic medication at time of testing.

Patients were recruited from the psychiatry department of the University Medical Center Utrecht (UMCU) and Amsterdam Medical Centre (AMC). Siblings were recruited from the Genetic Risk and Outcome of Psychosis project (Korver et al., 2012) and healthy controls were recruited via advertisements. After explaining the study procedures, participants gave written consent. They were financially compensated for study participation. The study was approved by the Human Ethics Committee of the UMCU.

Procedures and measures

Diagnosis and symptom levels. Lifetime and current presence and severity of symptoms and diagnosis were measured by the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). This instrument assesses diagnoses in the affective and psychotic spectrum. Additionally, current symptom levels were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

Prime-based agency inference task. Participants learned that the study was designed to examine experiences of personal causation and how they come and go. For this purpose, we used the Wheel of Fortune task (Aarts et al., 2005; Renes et al., 2013). In this computer task, when participants pressed the s-key, two squares started moving in opposite direction along a rectangular path, consisting of eight white squares (see Figure 1). A dark grey square,

representing the participant's square, rapidly (50 ms. per tile) moved in a counter-clockwise direction. Simultaneously, a light grey square, representing the computer's square, moved in the opposite direction at the same speed. When after 4 to 5 laps "stop" appeared in the center of the screen, the moving squares became invisible to the participant and they had to press the enter-key immediately, thereby stopping the movement of their own square. This action turned one of the eight white tiles black, which represented the final position of either their own square or the computer's. After each stop, participants indicated the extent to which they felt they had caused their square to stop at that particular position [9-point scale: not at all (1)–strongly (9)].

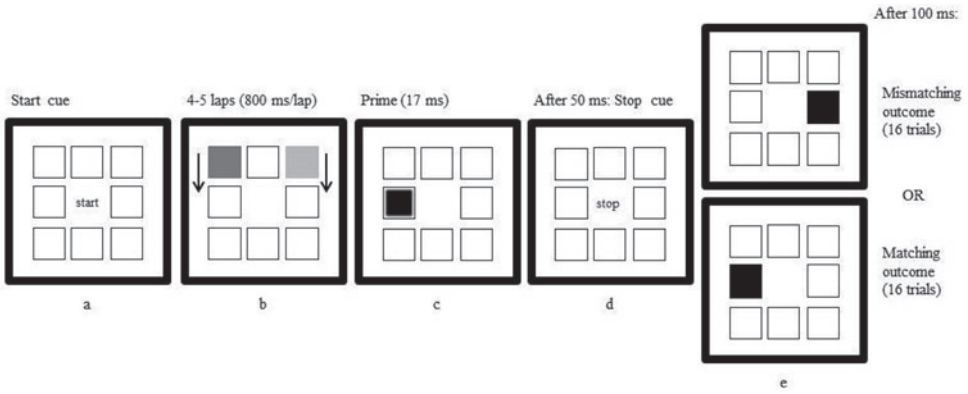


Figure 1. Wheel of fortune task. a) Start cue appears and participants press start-key. b) Participant's (dark grey) and computer's square (light grey) move in opposite directions. c) Just before the stop cue appears, outcome information is primed. d) At the presentation of the stop cue, squares disappear and continue to move invisibly. Participants press stop-key. e) A predetermined outcome is presented that either matches or mismatches the prime.

Importantly, in reality the program always determined the outcome position and thus, actual stops occurred independently of participants' key press. In each trial, one location was subtly primed just before participants pressed the stop-key and saw the outcome location. These primes lasted for 17 ms., equal to one frame on a 60hz. monitor. They either matched (i.e., same location) or mismatched (i.e., three or four positions away) the outcome and were used to activate a representation of the outcome during ongoing action, without requiring a predetermined intention. The difference between agency experiences on matching and mismatching trials (i.e., matching effect) indicates patients' susceptibility to implicit agency cues. A stronger matching effect represents more use of subtly activated outcome representations when inferring self-agency.

The task comprised 32 trials that were divided in 2 blocks of 16 trials. In each block, the black square was used as an implicit prime twice on each of the eight tiles of the path, once as a match and once as a mismatch. The trials were randomly presented within each block

and there was a short break (30 s) between the blocks. Participants practiced to assure they understood the task.

Statistical analyses

Patients, unaffected siblings, and controls were compared on age, gender, and level of own and parental education using ANOVA and a χ^2 test. For methods concerning the comparison between the two patient samples, see supplemental materials.

Aim 1: Self-agency and psychotic symptoms.

Prime-based inferences in relation to symptom severity. In patients, the relationship between matching effect (i.e., the difference in agency scores on matching and mismatching trials) and current symptom severity (PANSS positive, negative, general, and total score) was assessed using Spearman Rank correlations. Our sample of 54 patients should allow us to detect a significant moderate effect. We used Bonferroni correction for significance tests: α=0.05/4 symptom scores=0.0125.

Prime-based inferences in relation to symptoms of over- and underattribution. To examine the symptoms of underattribution (UA) or overattribution (OA) in relation to agency, patients were divided in groups based on present-state symptom levels as assessed by the CASH. OA included experiences in which agency is inaccurately attributed to the self: delusions of guilt, grandiose delusions, religious delusions, and delusions of reference. UA included symptoms in which agency is inaccurately attributed to an external source: delusions of control, thought broadcasting, thought insertion, thought withdrawal, and auditory (verbal) hallucinations. By defining the clusters on a mechanistic and not on a content level (e.g., paranoid/non-paranoid), we aim to understand the mechanisms underlying self-processing.

Participants were classified as UA/OA when a score of at least 1(questionable) was present on at least one of the UA/OA symptoms. Four groups were created based on these symptoms: 1) patients with OA only (OA+; *n*=7), 2) those with UA only (UA+; *n*=12), 3) patients with OA and UA (UAOA+; *n*=18), and 4) those without OA and UA (UAOA-; *n*=17). One outlier from the UAOA+ group was excluded for further analyses, as the overall agency score exceeded more than three times the standard deviation of that group.

Groups were tested for differences in age, gender, years of education, and years of illness using independent samples t-tests and a χ^2 test. To test group differences regarding the ability to make implicit agency inferences, a repeated-measures ANOVA with Group (OA+, UA+, UAOA+, and UAOA-) as between-subjects variable and Matching (matching and mismatching outcomes) as within-subjects variable was used. Assumptions for parametric testing were not violated (all *p*'s > 0.52).

Overall self-agency experiences in relation to symptoms of over- and underattribution. Overall agency was calculated by taking the mean of all trials, irrespective of the priming manipulation. As the assumption of normality was violated for this variable, a Mann-Whitney U and Kruskall-Wallis test were used to compare overall agency scores between patients and healthy controls and between the four groups regarding over- and underattribution (UA+, OA+, UAOA-, and UAOA+), respectively. Post-hoc, Mann-Whitney U tests were used (Bonferroni correction: α=0.05/6=0.008). In these analyses, OA+ and UA+ were of particular interest in examining our hypotheses.

Aim 2: Prime-based inferences in patients, siblings, and healthy controls. Group differences in agency experiences were assessed using a repeated-measures ANOVA with Group (patients, siblings, and healthy controls) as between-subjects variable and Matching (matching and mismatching outcomes) as within-subjects variable. Assumptions for parametric testing were not violated (all *p*'s > 0.19). Simple effects of Matching (i.e., matching effect) within each group were also assessed by using a repeated-measures ANOVA. MANOVA was used to perform follow-up analyses in order to further assess group differences. As our sibling sample was relatively small, these analyses are exploratory.

Results

Demographics and clinical characteristics

No differences were found between the two patients samples regarding task performance, see supplemental materials. Demographic and clinical characteristics of patients, unrelated and unaffected siblings, and controls are displayed in Table 1. Significantly more female participants were included in the sibling group as compared with healthy controls and patients and group differences in age were marginally significant. As expected, patients had fewer years of education than healthy controls and siblings, whereas parental years of education did not differ between groups.

Aim 1: Self-agency and psychotic symptoms

Prime-based inferences in relation to symptom severity. In patients, no significant correlations were found between matching effect and scores on the PANSS total, positive, negative, and general scale (respectively: *r*= -0.01, *p*=0.93; *r*= 0.12, *p*=0.40; *r*= 0.08, *p*=0.59; *r*= -0.003, *p*=0.98).

Table 1. Demographic and clinical characteristics of patients (PT), unaffected (and unrelated) siblings (SIB), and healthy control subjects (HC). Means (SD) are displayed.

	Patients (*n*=54)	Siblings (*n*=19)	Controls (*n*=54)	Group differences
Gender (*n*(male/female))	48/6	12/7	47/7	$X^2(2)=7{,}56$, $p=0.02$*, $\varphi=0.24$ HC & PT > SIB
Age	30.8 (7.24)	34.7 (5.67)	30.1 (7.53)	$F(2,124)=3.00$, $p=0.053$, $\eta_p^2=0.05$
Illness duration	10.54 (7.52)[a]	N/A	N/A	
Years of education	13.04 (1.98)	14.32 (1.95)	14.04 (2.34)	$F(2,124)=4.03$,$p=0.02$*, $\eta_p^2=0.06$ HC & SIB > PT
Parental years of education	13.98 (3.18)[b]	13.74 (2.62)	14.04 (2.62)[c]	$F(2,124)=0.08$, $p=0.93$, $\eta_p^2=0.001$
Antipsychotic medication	2	N/A	N/A	
Typical	49			
Atypical	3			
None				
PANSS		N/A	N/A	
Positive	12.06 (4.20)			
Negative	13.80 (6.00)			
General	26.15 (7.92)			
Total	52.00 (15.25)			

* significant at $p<0.05$; [a] $n=52$; [b] $n=47$, [c] $n=51$

Prime-based inferences in relation to symptoms of over- and underattribution. The four groups based on symptoms of over- and underattribution differed significantly on age and years of illness, but not on gender and years of education. However, as age and years of illness were not related to mean agency scores ($r_s=-0.10$, $p=0.48$, and $r_s=0.07$, $p=0.64$), it was not accounted for in further analyses.

A repeated measures analysis showed no main effect of Matching, $F(1,50)=0.56$, $p=0.46$, $\eta_p^2=0.01$, indicating no difference between agency experiences on matching and mismatching trials (i.e., matching effect). Also, no group differences between UA+, OA+, UAOA+, and UAOA- were found on matching effect, $F(3,50)=0.11$, $p=0.96$, $\eta_p^2=0.006$.

Overall self-agency experiences in relation to symptoms of over- and under-attribution. Overall agency ratings did not differ between patients and healthy controls, $U=1382$, $z=-0.305$, $p=0.76$, $r=-0.03$. The mean agency scores within patients follow-up the expected pattern, with the lowest agency scores for UA+, followed by UAOA+, and finally OA+ and UAOA-. A Kruskall Wallis test was used to compare overall agency scores in the four subgroups based on symptoms of over- and underattribution. The four groups differed significantly, $\chi2(3)=10.59$, $p=0.01$. Figure 2 and Table 2 display distributions and means of agency scores in patients.

Post-hoc Mann-Whitney U tests showed that after Bonferroni correction only UA+ scored significantly lower than UAOA-. In addition, a trend level difference was found between UA+ and OA+, reflecting lower scores in UA+, and between UAOA- and UAOA+, reflecting lower scores in UAOA+.

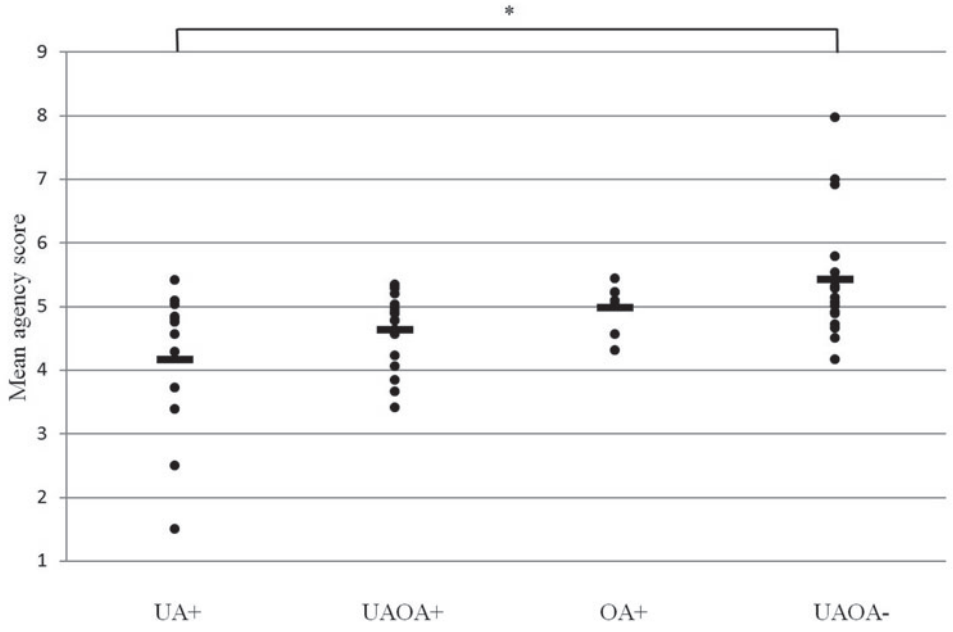


Figure 2. Level of experienced agency in groups based on symptoms of over- and underattribution. UA+=underattribution only, UAOA+=under- and overattribution, OA+=overattribution only, UAOA-=no under- or overattribution. *significant at $p<0.05$ after bonferroni correction.

Table 2. Means and post-hoc Mann-Whitney U test results regarding level of experienced agency in groups based on symptoms of over- and underattribution.

		Group differences		
Groups	**Means**	**UA+**	**UAOA+**	**OA+**
UA+ (n=12)	4.16 (1.18)	-	-	-
UAOA+ (n=17)	4.63 (1.01)	*U*=80.00,*p*=0.33, *r*=-0.22	-	-
OA+ (n=7)	4.98 (0.40)	*U*=19.50,*p*=0.01*,*r*=-0.44	*U*=38.00,*p*=0.17, *r*=-0.22	-
UAOA- (n=17)	5.42 (1.00)	*U*=41.00,*p*=0.007**, *r*=-0.50	*U* =76.00,*p*=0.02*, *r*=-0.33	*U*=47.50,*p*=0.45, *r*=-0.16

*significant at $p<0.05$; **significant after Bonferroni correction; OA+=overattribution only, UAOA+=over- and underattribution UA+=underattribution only, , UAOA-=no over- or underattribution.

Aim 2: Prime-based inferences in patients, siblings, and healthy controls

Gender, age, and years of education differed significantly between the three groups, but were not related to matching effect. Therefore, they are not controlled for in the repeated measures ANOVA. Figure 3 and Table 3 show a visual display and summary statistics regarding the group differences in self-agency experiences and matching effects. Overall, a main effect of Matching was found, showing that agency experiences were higher in matching trials, compared with mismatching trials. There was no main effect of Group, implying that there are no differences in overall agency scores between patients, siblings and controls, irrespective of the task manipulation.

Most importantly, the analysis yielded a significant Matching by Group interaction, implicating group differences in the matching effect. Simple effects analyses, depicted in Table 3, showed that healthy controls experienced more agency on matching trials compared with mismatching trials, while it reached trend level significance in siblings and was not present

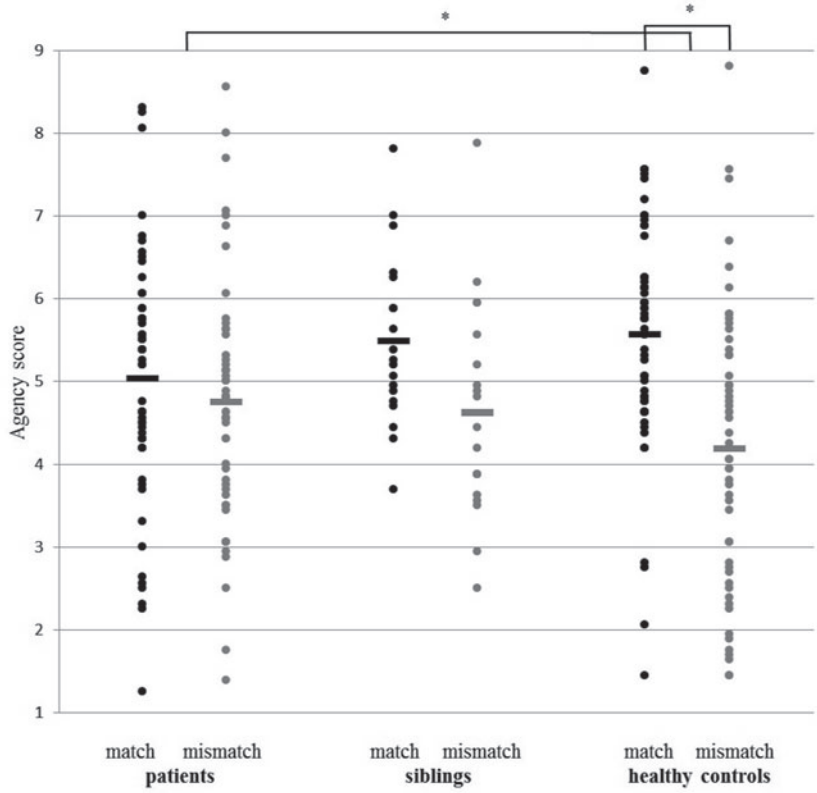


Figure 3. Self-agency scores in patients, siblings, and healthy controls. Mean scores on match and mismatch trials are depicted. *significant at $p<0.05$.

in patients. The means and effect sizes of the matching effect within groups indicated that siblings (M=0.87, η_p^2=0.17) scored in between patients (M=0.280, η_p^2=0.02) and healthy controls (M=1.38, η_p^2=0.24). However, MANOVA's showed that siblings did not differ significantly from either patients or healthy controls.

In line with our previous findings on the two independent patient samples separately (Renes, van der Weiden, et al., 2015; Renes et al., 2013), a MANOVA revealed a significant difference between patients and healthy controls, reflecting a significant matching effect in controls, which was absent in patients.

Table 3. Statistical analyses of self-agency scores and matching effects in patients, unaffected (and unrelated) siblings and healthy controls.

Mean agency scores				**Main analysis: Repeated measures ANOVA (*df*=2,124)**			
	Patients(*n*=54)	Siblings (*n*=19)	Controls (*n*=54)		F	Sig.	η_p^2
Match	5.03 (1.51)	5.49 (1.03)	5.58 (1.38)	Group	0.24	0.79	0.00
Mismatch	4.75 (1.45)	4.61 (1.30)	4.19 (1.67)	Matching	14.30	<0.001*	0.10
Matching effect	0.28 (2.04)	0.87 (1.98)	1.38 (2.49)	Matching x Group	3.30	0.04*	0.05

Simple effects analyses: Repeated measures ANOVA

	Patients (*df*=1,53)			**Siblings (*df*=1,18)**			**Healthy controls (*df*=1,53)**		
	F	**Sig.**	**η_p^2**	***F***	**Sig.**	**η_p^2**	***F***	**Sig.**	**η_p^2**
Matching	1.02	0.32	0.02	3.68	0.07	0.17	16.61	<.001*	0.24

Follow-up analyses: MANOVA (*df* = 2,124)

	Healthy controls-Patients			**Healthy controls-Siblings**			**Patients-Siblings**		
	t	**Sig.**	**Cohen's d_s**	***t***	**Sig.**	**Cohen's d_s**	***t***	**Sig.**	**Cohen's d_s**
Matching x Group	2.56	0.01*	0.49	0.86	0.39	0.28	0.99	0.32	0.26

*significant at p<0.05 level

Discussion

In the present study we found that patients with symptoms of underattribution of agency (i.e., delusions of control, thought broadcasting, thought insertion, thought withdrawal, or auditory (verbal) hallucinations) experienced less agency than patients without any symptoms of over- or underattribution. Second, the disturbances in prime-based agency inferences did not differ between patients with either symptoms of over- or underattribution and were not related to severity of psychotic symptoms. Finally, the matching effect in siblings was intermediate between that of patients and healthy controls, although this did not reach significance.

Symptoms of over- and underattribution: the role of prime-based inferences

In the current study we differentiated between patients who did or did not experience symptoms of overattribution or underattribution. The level of experienced agency did not differ between patients who only showed symptoms of overattribution and the other three groups. This may indicate that these patients did not necessarily overattribute in the presence of other agents (e.g., a computer) and in the absence of an explicit goal to reach a specific outcome (van der Weiden et al., 2015). However, more research on this subgroup of patients is needed, as a sampling issue (i.e., the low number of patients with overattribution symptoms only) might have influenced the results.

Interestingly, confirming our hypothesis, patients with exclusively symptoms of underattribution experienced less self-agency relative to patients without symptoms of over- and underattribution and, at trend level, to patients with symptoms of overattribution only. These results suggest that patients who experience symptoms of underattribution indeed tend to under-attribute agency in situations where other possible agents are present (e.g., a computer) and where behavior is not goal-directed. Other studies that investigated impairments in agency attribution in patients with symptoms of underattribution reported contradictory results regarding the direction of the attribution bias in their experimental paradigms (Franck et al., 2001; Hauser et al., 2011; Johns et al., 2001; Schimansky et al., 2010). A possible explanation for the inconsistent findings may be the way of defining symptoms of underattribution. In our study 31% of the patients showed both overattribution and underattribution symptoms at the time of testing. Thus, in previous studies, patients selected on symptoms of underattribution may have also had symptoms of overattribution. This makes it difficult to interpret the deficits in agency processing in terms of specificity for symptoms related to agency attribution. In this context it is important to note that although symptoms of over- and underattribution can easily be distinguished on theoretical grounds, clinically it is a challenge to study these symptom clusters separately.

In our paradigm, we used a subtle manipulation (matching vs. mismatching outcome primes) to examine agency experiences that do not rely on motor prediction. This enabled us to assess the relationship between (abnormalities in) implicit agency inferences and specific symptoms, independent of the previously reported impairments in motor prediction (Daprati et al., 1997; Franck et al., 2001; Hauser et al., 2011; Hur et al., 2014; Johns et al., 2001; Maeda et al., 2012, 2013; Schimansky et al., 2010; Synofzik et al., 2010). Our findings indicate that the presence or absence of symptoms of over- and underattribution did not influence patients' ability to use implicit cues when guiding feelings of self-agency. Thus, although symptoms of underattribution were related to agency-underattribution in our task, these symptoms cannot be explained by patients' impairments in using primes when inferring self-agency.

Symptoms of over- and underattribution: alternative explanations

Why then, do these patients with symptoms of underattribution experience less agency? It is unlikely that goal-based agency inferences are related to underattribution symptoms, as we previously showed that patients with schizophrenia do not have problems in using goal-based inferences to guide agency experiences (Renes, van der Weiden, et al., 2015; Renes et al., 2013). However, as mentioned in the introduction, people do not only consider action-outcome information when inferring self-agency, but also take into account other (e.g., agent-related) information when answering the question 'Am I the most likely cause of this event?' (see also: Wegner and Wheatley, 1999). Here, we address a few possible explanations for decreased agency experiences in patients with symptoms of underattribution.

Other explanations from a cognitive level. Agency attribution is affected by several factors, for example by the presence of background beliefs (Desantis et al., 2011; Synofzik et al., 2013). In fact, a patient's strongly held belief about having no influence on causality might overrule implicit agency cues, such as the primes used in our experiment.

Also, increased attention to other (delusional) agents might decrease self-agency experiences and induce or maintain symptoms of underattribution. The amount of attention towards other agents or towards the self might fluctuate from time to time, which might also explain why symptoms of over- and underattribution can coexist. So far, the role of agent-related information in agency inferences has received little empirical attention. However, given patients' impairments in social context processing, this may be a promising direction for future research (Penn et al., 2002; White, Borgan, Ralley, & Shergill, 2016).

Motor prediction. Another way to explain symptoms of over- and underattribution is by impairments in motor prediction. Specifically, when motor predictions are less precise, a mismatching outcome may be perceived as matching one's prediction, resulting in overattribution of self-agency (van der Weiden et al., 2015). Yet, when one is completely surprised by the outcome of one's action because it was not predicted at all, this may result in underattribution (cf., Blakemore et al., 2000). Although there is evidence for a relation between impairments in motor prediction and symptoms of underattribution (Franck et al., 2001; Hauser et al., 2011; Johns et al., 2001), these results are inconsistent and it is still unclear when and how motor prediction impairments lead to underattribution (or overattribution). Future studies may shed light on this issue by distinguishing between patients with exclusively symptoms of over- or underattribution. Also, to explore whether impairments in motor-prediction or in cognitive inferences are more crucial, both processes should be tested in a single experiment.

Ownership. The sense of agency is closely related to body ownership (Klaver & Dijkerman, 2016; Ma & Hommel, 2015). In fact, a sense of body ownership is necessary to experience agency, but ownership does not necessarily require a sense of agency (Tsakiris, Schütz-Bosbach, et al., 2007). Importantly, more severe passivity symptoms (a concept that largely overlaps with our under-attribution symptoms) were associated with impairments in assessing

body schema (Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014). Therefore, a possible cause of decreased agency experiences in patients with symptoms of underattribution might be mediated by problems in experiencing body ownership.

Impairments in prime-based inferences as a trait characteristic

In our study, the absence of a relationship between the ability to make prime-based agency inferences on one hand and symptom type and severity on the other hand suggests that a reduced ability to arrive at prime-based agency inferences may be a trait characteristic of schizophrenia. In line with this notion, agency disturbances have also been found in populations at high clinical risk for psychosis (Hauser et al., 2011), indicating that these disturbances are present well before the first florid psychotic episode. Whether abnormal self-agency processing in high-risk populations is specific for those who will later develop schizophrenia has not been investigated. If the inability to make prime-based agency inferences is a trait factor, studies on self-agency processing in young high-risk individuals appear relevant to develop causal models of psychotic symptoms. So far, there is suggestive evidence that phenomenological experiences of self-disturbances might indeed be a specific predictor for psychosis later in life (Nelson et al., 2012; Parnas et al., 2014).

Impairments in prime-based agency inferences as a vulnerability marker?

As a second aim of the current study, we assessed whether problems in agency inferences have a familial (and thus possibly genetic) component. Previous studies showed that unaffected siblings of patients show poorer performance on (social) cognitive tasks and neurophysiological measures (Brunelin et al., 2007; Cella, Hamid, Butt, & Wykes, 2015; Lavoie et al., 2013; Seidman et al., 2015) compared to healthy controls. Brunelin et al. (2007) showed that unaffected siblings performed at an intermediate level between healthy controls and schizophrenia patients on a source monitoring task, suggesting that poor source monitoring is a vulnerability marker of schizophrenia. Hommes et al. (2012) found similar results using an error-correction action-monitoring task. In our study, siblings also scored in between healthy controls and patients, although these differences were not statistically significant. The results of this exploratory analysis suggest that siblings do not show the same impairments in arriving at prime-based agency inferences as patients, while we can also not exclude the possibility that individuals at familial risk for schizophrenia are vulnerable to subtle impairments. Future studies should further examine this topic, for example by studying the development of agency impairments in genetic high risk populations.

Future research

When investigating self-agency, we cannot disregard the role of neurocognitive impairments seen in patients with schizophrenia. Previously, it was shown that prime-based inferences do not rely on attentional control, self-reported motivation and attention, or reaction times during the task (Renes et al., 2013), and that patients are able to detect briefly presented primes (Del Cul et al., 2006; Renes, van der Weiden, et al., 2015). These studies suggest that certain aspects of cognition do not relate to prime-based agency inferences. However, impaired neurocognition is one of the core deficits in schizophrenia. Hence, to exclude the possibility that impairments in prime-based inferences are due to neurocognitive impairments, we will include measures of, for instance, executive functioning and working memory performance in future studies.

Conclusions

In conclusion, this study revealed that patients with symptoms of underattribution experience an overall lower level of self-agency over action-outcomes that were or were not implicitly primed. However, the ability to unconsciously use primes when inferring self-agency could not explain the decreased agency experiences in these patients. Future research on, for example, the combined influence of motor prediction and inferences might shed light on the question regarding the origin of a decreased agency experience in patients with symptoms of underattribution. Second, we found that patients show a reduced ability to use implicitly available environmental cues to inform inferences of self- agency, irrespective of severity of symptoms, suggesting that this impairment is a trait characteristic that is present in different stages of the disease. Also, we provide preliminary and suggestive evidence that individuals at increased familial risk for psychosis might perform suboptimal when making prime-based agency inferences. Siblings performed in between patients and healthy controls, suggesting that future research should further examine implicit agency inferences in individuals at increased familial risk. These first steps in unraveling impairments in making agency inferences indicate that such impairments may be an important topic in future research.

Supplemental materials: Comparison between patient sample 1 and 2

Methods

Differences in age and years of education were compared using independent sample t-tests. Furthermore, in order to test potential differences between the two patient samples, they were compared on level of current symptom levels (PANSS scores) by using a Mann-Whitney U test. Furthermore, we investigated whether experiences of agency were comparable in both samples by using a repeated-measures ANOVA with Sample (sample 1 and 2) and Group (patients and healthy controls) as between-subjects factors and Matching (matching and mismatching outcomes) as within-subjects variable.

Results

See supplementary table 1 for results regarding group differences. The samples did not differ on age or years of education. PANSS total score was significantly higher in patient sample 1 compared with those of sample 2. This difference was reflected in all three subscales of the PANSS and can be explained by a higher percentage of inpatients in sample 1 compared with sample 2. Importantly, there was no significant interaction of Matching and Sample *(F*(1,104)=0.208, *p*=0.649), nor a three-way interaction with Group (*F*(1,104)=0.015, *p*=0.902). This indicates that there is no difference between samples in the case-control difference on the matching effect and consequently, both samples were combined for further analyses.

Supplementary table 1. Comparison of age, years of illness, and PANSS scores (mean (SD)) in patient sample 1 and patient sample 2.

	Sample 1 (n=23)	Sample 2 (n=31)	Group differences
Age	32.65 (7.08)	29.39 (7.15)	*t*=1.67, *p*=0.10
Years of education	13.22 (2.02)	12.90 (1.97)	*t*=0.57, *p*=0.57
PANSS total	63.43 (15.99)	43.52 (7.00)	*U*=56.0, *z*=-5.262, *p*<0.001*
PANSS positive	14.74 (4.43)	10.06 (2.68)	*U*=126.0, *z*=-4.068, *p*<0.001*
PANSS negative	16.52 (6.99)	11.77 (4.23)	*U*=176.5, *z*=-3.170, *p*=0.002*
PANSS general	32.17 (8.31)	21.68 (3.42)	*U*=60.0, *z*=-5.201, *p*<0.001*

*significant at *p*=0.05 level

The role of the self-reflection network in cognitive and affective empathy in schizophrenia and healthy individuals

Merel Prikken
Lisette van der Meer
Martijn G.J.C. Koevoets
Natascha M. den Bleijker
Matthijs Vink
Anouk van der Weiden
René S. Kahn
H. Aarts
Neeltje E.M. van Haren

6

In preparation

Abstract

Background. Patients with schizophrenia often show decreased empathic abilities. That is, they experience difficulties in understanding and integrating other people's emotions, thoughts, or perspectives. These problems might be related to alterations in self-reflective processing, as information about the self is necessary to understand others. The aim of the current study is to assess whether deficits in empathy are related to brain activity during self-reflective processing in patients with schizophrenia and healthy individuals.

Methods. A total of 57 patients and 52 controls underwent functional magnetic resonance imaging. Brain activity associated with self- and other-reflection was measured. Participants had to indicate whether trait adjectives described their personality, the prime-minister's personality, or were positive. Furthermore, measures of cognitive and affective empathy were obtained.

Results. Patients experienced significantly more affective empathy and showed less activity in the medial prefrontal cortex during self-reflective processing, compared with healthy controls. In patients, but not in healthy controls, affective empathy was negatively related with activation in the temporoparietal junction(TPJ)/angular gyrus during self-reflection. Furthermore, in the total sample cognitive empathy was positively related to insula activation during self-reflection, while affective empathy was negatively related to activation in the postcentral gyrus.

Conclusions. We demonstrated a relationship between self-reflective processing and empathy, and that this relation differs between cognitive and affective empathy. Most importantly, as the TPJ/angular gyrus are involved in making a distinction between self and other, our findings suggest that neural underpinnings of decreased self-other distinction might explain increased affective empathy in patients.

Introduction

Besides the well-known positive and negative psychotic symptoms, patients with schizophrenia often experience difficulties in social interaction and maintaining social relationships (Fett et al., 2011; Gardner et al., 2017). These problems are partly explained by deficits in social cognition, i.e., 'the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior' (Adolphs, 2001, p. 231). As these social cognitive deficits decrease patients' quality of life (Maat, Fett, Derks, & Investigators, 2012) and functional outcome (Fett et al., 2011), it is important to understand its etiology.

A subdomain of social cognition that has gained a lot of interest in the schizophrenia literature is empathy (also referred to as mentalizing or theory of mind). A recent meta-analysis demonstrated that within the domain of social cognition, it is particularly empathy that has been related to deficits in functional outcome (Fett et al., 2011). Studies showed that patients experience difficulties in understanding and integrating *emotional* experiences (i.e., affective empathy), as well as *thoughts or perspectives* (i.e., cognitive empathy) of others (Shamay-Tsoory, Tomer, Goldsher, Berger, & Aharon-Peretz, 2004). Meta-analyses and literature reviews concluded that patients with schizophrenia show less affective (Bonfils, Lysaker, Minor, & Salyers, 2016), as well as less cognitive empathy (Bora et al., 2009c; Brüne, 2005b; Savla, Vella, Armstrong, Penn, & Twamley, 2013; Sprong et al., 2007). However, they also tend to experience more personal distress, which is a subdomain of affective empathy (Bonfils, Lysaker, Minor, & Salyers, 2017).

Several hypotheses about the etiology of these deficits in empathy exist. For example, part of its variance can be explained by neurocognitive functioning, e.g., executive functioning or working memory (M. Bell, Tsang, Greig, & Bryson, 2009). There is also evidence that genetic factors are associated with empathic abilities (Bora, Yucel, & Pantelis, 2009b; Janssen, Krabbendam, Jolles, & van Os, 2003; Montag et al., 2012). Furthermore, it has been proposed that a disturbed sense of self might be underlying to the impairments in understanding others (Dimaggio, Lysaker, Carcione, Nicolò, & Semerari, 2008; van der Weiden et al., 2015). This proposition is supported by the Simulation Theory (ST) that states that knowledge about the self provides a framework for how we understand others (Gallese & Goldman, 1998). Importantly, self-disturbances are described as one of the core deficits in patients with schizophrenia and are reflected in psychotic symptoms, for example in delusions of control or thought insertion (Sass & Parnas, 2003).

Other evidence for a relationship between self- and other-processing comes from functional Magnetic Resonance Imaging (fMRI) studies. A meta-analysis showed that there is overlap between brain areas that are activated during reflection on one's own traits and on traits of others, including the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex (mPFC), temporal-parietal junction (TPJ), and angular gyrus. Importantly, alterations in brain activation in cortical midline structures (i.e., anterior cingulate cortex (ACC), mPFC,

and PCC) during self-reflective processing have been consistently found in patients with schizophrenia (Blackwood et al., 2004; J. S. Lee et al., 2016; Liu et al., 2014; Pankow et al., 2016; Pauly, Kircher, Schneider, & Habel, 2014; Tan et al., 2015; van der Meer, de Vos, et al., 2013).

Furthermore, although it has been suggested that the ACC is important in assessing *self-specificity* of stimuli (Murray, Schaer, & Debbané, 2012; van der Meer, Costafreda, Aleman, & David, 2010), this area is also involved in affective empathy (Shamay-Tsoory, 2011). Moreover, several brain areas, such as the mPFC, TPJ, inferior frontal gyrus (IFG), and angular gyrus are found to be involved in self-reflection *and* during tasks targeting cognitive or affective empathy among others (K. H. Lee, Farrow, Spence, & Woodruff, 2004; Murray et al., 2012; Northoff et al., 2006; Shamay-Tsoory, 2011; van der Meer et al., 2010). This again confirms the importance of self-processing in understanding other people's emotional states, in line with the ST.

Together, patients' impairments in self-reflective processing and in empathy, as well as the neural and conceptual overlap between self- and other-processing raise an interesting question (see also Saxe, Moran, Scholz, & Gabrieli, 2006). That is, are poor empathic abilities in patients related to (abnormal) brain activation during self-reflective processing? We investigated this relation for cognitive and affective empathy separately, given their different underlying neural pathways (Shamay-Tsoory, 2011). The current study aims to answer these questions by measuring brain activity during self-reflective processing and both cognitive and affective empathy in patients with schizophrenia and healthy individuals.

Methods

Subjects

A total of 57 patients with a DSM-IV diagnosis of schizophrenia and 52 controls completed the MRI-procedure of this study. Patients were recruited from the psychiatry department of the University Medical Center Utrecht (UMCU) and controls were recruited via online advertisement (www.proefpersonen.nl). All subjects were Dutch speaking, aged between 18-50, had a premorbid IQ above 80, did not suffer from alcohol or drug abuse in the past six months, did not have a history of closed-head injury or neurological/endocrinological dysfunction, did not use chronic medication (other than psychiatric medication in patients), and had no MRI-contraindications. Additionally, patients did not have an acute psychotic episode at the time of testing and controls did not have a psychiatric illness or a first or second degree relative with a psychotic illness. Subjects received monetary compensation for participating in the study and all subjects gave written informed consent. The ethics committee of the UMCU approved this study.

Measures

Cognitive empathy. The ability to make inferences about other's intentions and beliefs was

assessed with a theory of mind task, called the Hinting Task (HT) (Corcoran et al., 1995). The HT consists of ten short stories reflecting a conversation between two characters that ends with an obvious hint. The participant has to indicate what one character really meant when he gave this hint. Two points are awarded after an appropriate response. In case of an inappropriate response, the subject received an additional hint. An appropriate response after this second hint is awarded with one point.

Affective empathy. To measure affective empathy, individuals performed a computer task in which they viewed 22 film clips of ten seconds without sound (derived from Tettamanti et al., 2012). Each film clip consisted of a person portraying a neutral, happy, sad, or fearful emotion. After watching the film clip subjects were asked to what extend they experienced a set of emotions on a seven point Likert-scale ranging from one (not at all) to seven (very strongly). These emotions included positive (warm, compassionate, soft-hearted, tender, moved) and negative (worried, distressed, disturbed, upset, troubled, agitated) emotions. As Cronbach's alfa indicated internal consistency between these emotions (Cronbach's α = 0.96 in both groups), the mean of all items was used as a measure of affective empathy.

Self-reflection task (fMRI). During the self-reflection task (see Figure 1) positive and negative trait adjectives were judged by the participant (Van Buuren et al., 2010). They had to indicate whether these trait adjectives (e.g. 'lazy' or 'smart') were applicable to their own personality ('self' condition), the Dutch prime minister's ('other' condition), or whether this trait was positive ('control' condition). All trait adjectives were retrieved from a list of words that was previously validated for likeability (Anderson, 1968). Half of the traits included in the task had a positive valence and the other half had a negative valence. The task consisted of five blocks per condition, with eight trials per block, alternated with resting periods of 30 seconds. For all participants, the presentation order was equal.

MRI

MRI Image acquisition. MRI scanning was done with a 3.0 T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands). Images were collected using an eight-channel sensitivity-encoding (SENSE) parallel-imaging head coil. Whole-brain T2*-weighted echo planar images with blood-oxygen level-dependent (BOLD) contrast (395 volumes; 30 slices per volume; interleaved acquisition; repetition time= 1600 ms; echo time= 23.5 ms; field of view: 208 mm × 119.6 mm × 256 mm, sloped 20 degrees downward on the anterior-posterior axis; flip angle = 72.5°; 64 × 51 acquisition matrix; 4 × 4 mm in-plane resolution; 3.6 mm slice thickness; SENSE factor= 2.4). The first six images were dummy scans to allow for T1 equilibration effects. A whole-brain three-dimensional fast field echo T1-weighted scan (220 slices no-gap; repetition time = 10.03 ms; echo time = 4.6 ms; flip angle = 8°; field of view, 240 mm × 240 mm × 176 mm; voxel size= 0.75 x 0.75 x 0.80mm isotropic, parallel imaging SENSE-factor=2.5) was acquired for within-subject registration.

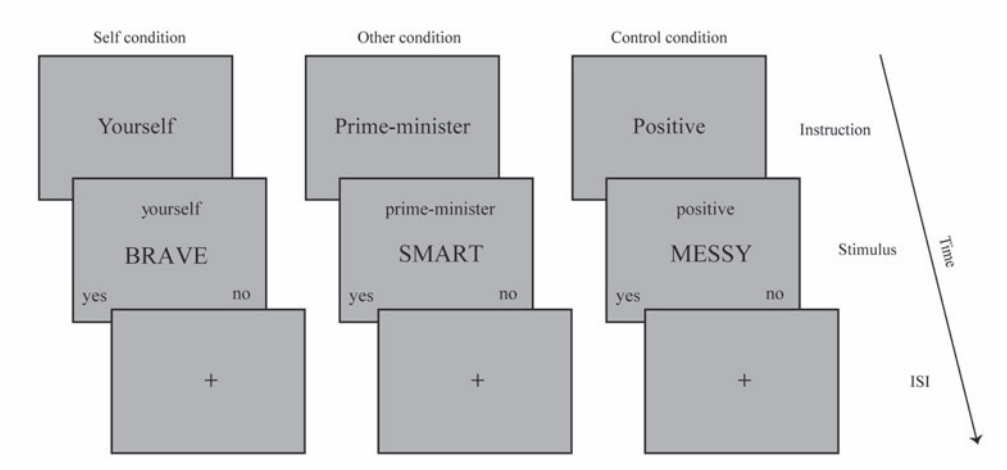


Figure 1. Self-reflection task. The duration of the instruction was 2000 ms. The duration of the interstimulus interval (ISI), i.e., the cross, depended on the reaction time and was 3500 ms maximum.

fMRI preprocessing. Image preprocessing and data analysis of the functional images of the self-reflection task was performed with Statistical Parametric Mapping (SPM) 12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). First, the orientation of the functional scans was registered to the anatomical image. Then, the scans were slice time corrected, realigned to the reference image to remove movement artefacts, and co-registered to the mean functional image. Furthermore, the functional images were spatially normalized on an anatomical MNI T1 template and smoothed using a 3D Gaussian filter (8 mm FWHM) which attenuates inter-individual differences in neuro-anatomy.

Data analyses

Behavioral data analyses. Group differences in demographic variables and behavioral measures were analyzed with an independent sample t-test, a chi-square test, or a Mann Whitney-U test (in case of skewed distributions). In all analyses, outliers were defined as deviating more than three standard deviations from the group mean.

fMRI analyses. FMRI data from two healthy controls and three patients could not be used due to scanner artefacts. Furthermore, one patient was excluded from fMRI analyses due to excessive head movement (>4mm). Six realignment parameters were included in the design as regressors of no interest. Furthermore, a high pass filter was applied with a cut-off of 0.0078 Hz to remove low-frequency noise. To assess self-reflection task effects in each participant, three contrasts were created: 'self>control', 'self >other', and 'other>control'. To assess group differences in task-related brain activation, whole-brain task activation was examined using a cluster-defining threshold (p<0.001; critical cluster size: 39, 41, and 44 voxels respectively, with a cluster probability of p<0.05, family-wise error corrected for multiple comparisons). To obtain

the cluster thresholds, an SPM script was used (CorrClusTh.m, https://www2.warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/scripts/spm). Then, cluster thresholded group differences in each contrast were assessed at whole brain level.

ROI analyses. ROI's were created by drawing a sphere (radius = 10 mm) around cluster centers that were retrieved from a meta-analysis (Murray et al., 2012), see Supplement 1 for a visual display. When an individual was an outlier in more than one ROI within one contrast, that individual was removed from both whole-brain and ROI-analyses on that contrast (outliers per contrast: self>control: one patient, self>other: two patients and one control, other>control: two patients). Independent sample t-tests were performed on mean activation in each ROI in each contrast.

In addition, Bayesian statistics (JASP Team, 2017; JASP Version 0.8.3.1) were applied to assess the likelihood of the data under the null-hypothesis (i.e., no group differences - effect size of 0.0) compared to a default alternative hypothesis (i.e., H1: delta ~ Cauchy (width = 0.707)). Importantly, when a frequentist approach (e.g., t-test) indicates the absence of an effect (e.g., $p>0.05$), the Bayesian approach can give additional information by assessing the likelihood of this absence. A Bayes factor (BF_{01}) higher than 1 indicates that the data is more likely under the null-hypothesis than under the alternative hypothesis. For example, a BF_{01} of 1.5 means that the data are 1.5 times more likely to occur under the null hypothesis compared to the alternative hypothesis. A high BF_{01} (>3), favors the hypothesis that there is no effect, while a low BF_{01} (<0.33, which is equal to BF_{10} (i.e., $1/BF_{01}$) > 3) favors the hypothesis that there is an effect. A BF_{01} between 0.33 and 3 indicates that the evidence is inconclusive.

Finally, Kendall's Tau B (T_b) was used to assess the relation between activation in the ROI's of each contrast on the one hand and cognitive and affective empathy on the other hand. Again, Bayesian statistics were applied to assess the likelihood of all effects. To check for group differences in this relationship, the interaction term of group*ROI-activity was assessed in bootstrapped regression analyses with cognitive or affective empathy as dependent variable.

Results

Demographic and behavioral group differences

Demographics, clinical information, and behavioral results are displayed in table 1. Age, gender distribution, and parental years of education did not differ between patients and controls. As expected, healthy controls had significantly more years of education and a higher premorbid IQ than patients. Furthermore, affective empathy was more pronounced in patients than in healthy controls (Figure 2). In the self-reflection task, patients attributed less positive and more negative words to themselves compared with healthy controls. Also, they rated more negative words as 'positive' in the control condition.

Table 1. Demographics, clinical information, and behavioral results.

		Schizophrenia patients (n=57)	Healthy controls (n=52)	Group differences
Age		35.33 (8.02)	34.28 (7.94)	$t(107)=.69$, $p=.50$
Gender (male/female)		49/8	47/5	$X^2(1)=.50$, $p=.48$
Yrs. of education		13.07 (2.15)	14.19 (1.77)	$U=930.00$, $p=.001$*
Parental yrs. of education[a]		14.24 (3.56)	13.90 (2.55)	$U=1104.00$, $p=.18$
Premorbid IQ[b]		99.72 (8.25)	103.81 (7.54)	$U=846.00$, $p=0.02$*
Illness duration (yrs.)		14.06 (7.79)		
Antipsychotic	Typical	4		
medication	Atypical	50		
	Both	1		
	None	2		
PANSS[c]	Positive	13.21 (3.78)		
	Negative	12.98 (4.97)		
	General	24.96 (4.89)		
	Total	51.16 (10.09)		
Cognitive empathy[c]		16.39 (2.81)	17.19 (1.62)	$U=1285.00$, $p=.29$
Affective empathy[d]		2.42 (0.88)	1.90 (0.65)	$U=881.00$, $p=.002$*
Percentage of endorsed trials and reaction time (ms) in the self-reflection task				
Self condition	Positive	80.96 (14.34)	89.04 (9.65)	$U=951.00$, $p=.001$*
	Negative	42.75 (17.82)	31.35 (12.05)	$U=960.00$, $p=.001$*
	RT	1465.02 (257.71)	1291.10 (243.19)	$t(107)=-3.62$, $p<.001$*
Other condition	Positive	71.26 (15.87)	67.64 (18.82)	$U=1345.00$, $p=.404$
	Negative	64.89 (18.73)	64.33 (18.26)	$U=1469.00$, $p=.937$
	RT	1569.18 (280.65)	1478.72 (278.22)	$t(107)=-1.69$, $p=.09$
Control condition	Positive	91.05 (10.84)	94.23 (6.29)	$U=130.00$, $p=.251$
	Negative	17.37 (10.81)	12.79 (10.54)	$U=1001.50$, $p=.003$*
	RT	1469.15 (271.76)	1307.35 (237.02)	$t(107)=-3.30$, $p=.001$*

PANSS = Positive and Negative Syndrome Scale (Kay et al., 1987)

[a] data from 3 patients and 4 healthy controls was missing due to drop-out or inability to recall and retrieve information

[b] measured with the Dutch Adult Reading Test (Schmand et al., 1991); 6 patients (+1 drop-out) and 5 healthy controls with a non-Dutch native language or dyslexia were removed from this analysis

[c] data from 1 patient was missing due to drop-out

[d] data from 4 patients and 1 healthy control were missing due to drop out (1 patient) and technical issues

*significant at p=0.05

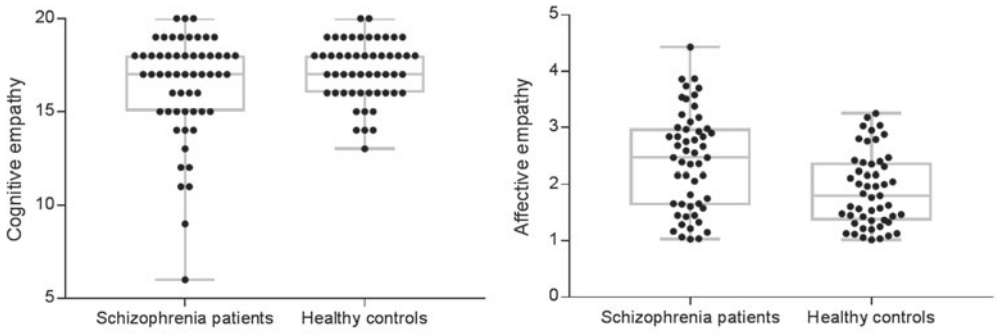


Figure 2. Distribution of cognitive and affective empathy scores per group.

fMRI results

Task effect. In Supplement 2, significant whole brain task activation is depicted for the total sample. The self>control contrast revealed peak activation in the precuneus, posterior and middle cingulate cortex (PCC, MCC), dorso- and ventromedial prefrontal cortex (dmPFC, vmPFC; dividing line at Talairach z-coordinate of 20 (van der Meer et al., 2010; Van Overwalle, 2009)), superior frontal cortex (SFC), angular gyrus, middle temporal gyrus (MTG), insula, inferior orbitofrontal cortex (OFC), and temporal pole (see supplemental table 1 for MNI-coordinates). Peak activation in the other>control contrast was located in similar areas: MTG, inferior OFC, precuneus, PCC, middle temporal pole, angular gyrus, and dmPFC. The self>other contrast revealed activation in the calcarine cortex, ACC, precuneus, and MCC.

Group differences. At whole brain level, no significant group differences were found in any of the contrasts. In Table 2 group differences per ROI are described. In the self>other contrast healthy controls showed more activation than patients in the right vMPFC and Bayesian statistics indicated that this difference was likely. For all other contrasts, evidence was inconclusive (10 ROI's with $3.00>BF_{01}>0.33$) or absent (7 ROI's with $BF_{01}>3$). When outliers were included in the analyses, no group differences were found, i.e., there were no BF_{01}'s smaller than 0.33 (Supplement 3).

Relation between self-reflective processing and empathy

Table 2 shows statistical significance and Bayesian factors regarding the relation between self- and other-reflective processing on one hand and cognitive and affective empathy on the other hand. In the self> control contrast, a significant positive correlation was found between activation in the right anterior insula and cognitive empathy (Figure 3A) and a significant negative correlation was found between activity in the right postcentral gyrus and affective empathy (Figure 3B) in both patients and controls (all *p*'s<0.05). The likelihood of these effects

was confirmed by BF_{01}<0.33. Furthermore, although a relationship between activity in the right TPJ/angular gyrus and affective empathy during the self>other contrast was not present in the total sample, it differed significantly between groups (Table 2). Follow-up analyses indicated that this relationship was significant and likely in patients (T_b=-0.34, p=0.001, BF_{01}=0.22), but not in healthy controls (T_b=0.03, p=0.73, BF_{01}=5.09; Figure 3C).

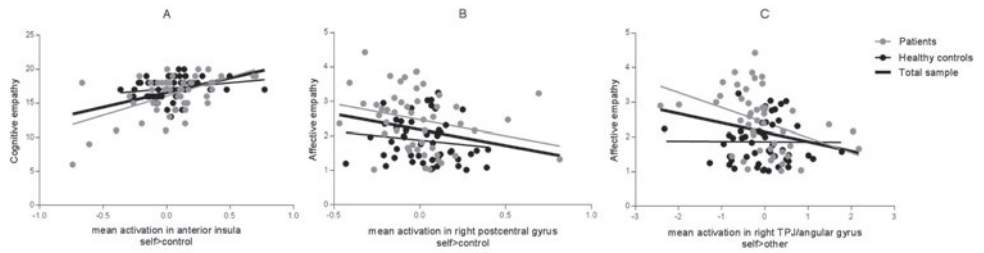


Figure 3. Significant relationships between ROI-activation and empathy with BF^{01}<0.33 (A + B) and significant interaction between ROI-activity and group (C)

Discussion

Previous studies pointed towards impairments in both self-reflective processing as well as empathy in patients with schizophrenia. The aim of the current study was to investigate whether brain activation during self-reflective processing was differentially related to cognitive and affective empathy between patients and healthy individuals. Our main findings are that, in the total sample, cognitive empathy was related to increased activation in the right anterior insula during s elf-reflection (self-reflection versus control) and that affective empathy was negatively related to activity in the right postcentral gyrus. Moreover, affective empathy was negatively associated with TPJ/angular gyrus activation during self-reflection (self-reflection versus other-reflection) in patients only. Furthermore, we showed that patients with schizophrenia, compared with healthy controls, showed less mPFC activation during self-reflective processing, attributed more negative and less positive traits to themselves, and felt increased affective empathy in reaction to film clips.

Group differences in empathy

Instead of standard questionnaires, we used a more ecologically valid experimental set-up to measure affective empathy. It allowed us to measure an individual's feelings when seeing someone else going through an emotional experience. We showed that patients, compared with healthy controls, reported more affective empathy. Given the high consistency between ratings on different emotional experiences that were measured in our task, this was true for

Table 2. Group differences in ROI-activity and the relationship between ROI-activity and empathy

	Group differences		Correlation Cognitive empathy			Affective empathy		
Self>control		BF_{01}		BF_{01}	Group differences		BF_{01}	Group differences
R vMPFC	*t*(100)=-0.75, *p*=0.46	3.73	T_b=0.13, *p*=0.08	1.31	*B*=0.31, *p*=0.51	T_b=0.03, *p*=0.63	6.76	*B*=-0.15, *p*=0.31
L PCC/precuneus	*t*(100)=-1.45, *p*=0.15	1.87	T_b=0.09, *p*=0.22	3.27	*B*=0.55, *p*=0.24	T_b=-0.10, *p*=0.13	2.42	*B*=-0.01, *p*=0.77
L IFG	*t*(100)=-1.04, *p*=0.30	2.95	T_b=0.12, *p*=0.10	1.67	*B*=0.69, *p*=0.10	T_b=0.04, *p*=0.59	6.56	*B*=0.11, *p*=0.42
L TPJ/angular gyrus	*t*(100)=-1.74, *p*=0.09	1.25	T_b=0.02, *p*=0.84	7.51	*B*=-0.1, *p*=0.99	T_b=0.08, *p*=0.24	3.78	*B*=0.03, *p*=0.86
R Anterior insula	*t*(100)=0.04, *p*=0.97	4.78	**T_b=0.24, p=0.001**	**0.01**	*B*=0.95, *p*=0.08	T_b=-0.06, *p*=0.42	5.47	*B*=0.02, *p*=0.89
R Postcental gyrus	*t*(100)=0.95, *p*=0.35	3.21	T_b=-0.03, *p*=0.72	7.17	*B*=-0.30, *p*=0.56	**T_b=-0.18, p=0.01**	**0.22**	*B*=-0.09, *p*=0.57
L MTG	*t*(100)=0.22, *p*=0.83	4.68	T_b=0.02, *p*=0.64	6.82	*B*=0.36, *p*=0.50	T_b=-0.03, *p*=0.65	6.84	*B*=0.04, *p*=0.78
Self>other								
L dACC	*t*(98)=1.73, *p*=0.09	1.27	T_b=0.13, *p*=0.08	1.35	*B*=0.44, *p*=0.49	T_b=-0.06, *p*=0.36	4.95	*B*=0.30, *p*=0.05
L SFG	*t*(98)=1.96, *p*=0.05	0.87	T_b=-0.02, *p*=0.80	7.36	*B*=0.68, *p*=0.29	T_b=-0.04, *p*=0.57	6.42	*B*=0.09, *p*=0.56
L TPJ/angular gyrus	*t*(98)=1.54, *p*=0.13	1.65	T_b=0.03, *p*=0.71	7.06	*B*=0.65, *p*=0.16	T_b=-0.14, *p*=0.05	1.03	*B*=0.13, *p*=0.35
R SFG	*t*(98)=1.92, *p*=0.06	0.94	T_b=-0.05, *p*=0.52	6.01	*B*=0.05, *p*=0.94	T_b=-0.05, *p*=0.47	5.80	*B*=-0.15, *p*=0.47
L Anterior insula	*t*(98)=0.69, *p*=0.49	3.85	T_b=0.02, *p*=0.76	7.23	*B*=0.42, *p*=0.49	T_b=-0.10, *p*=0.17	2.90	*B*=0.01, *p*=0.97
R TPJ/Angular gyrus	*t*(98)=-0.25, *p*=0.80	4.61	T_b=-0.04, *p*=0.62	6.63	*B*=0.59, *p*=0.11	T_b=-0.17, *p*=0.01	0.36	*B*=-0.37, *p*=0.02*
R vMPFC	***t*(98)=2.79, *p*=0.01**	**0.16**	T_b=0.04, *p*=0.59	6.49	*B*=-0.01, *p*=0.99	T_b=-0.08, *p*=0.28	4.18	*B*=-0.01, *p*=0.91
Other>control								
L PCC/precuneus	*t*(99)=-1.06, *p*=0.29	2.88	T_b=0.14, *p*=0.06	1.02	*B*=0.09, *p*=0.86	T_b=-0.03, *p*=0.66	6.85	*B*=0.03, *p*=0.83
L SFG	*t*(99)=-1.69, *p*=0.09	1.34	T_b=0.14, *p*=0.06	1.03	*B*=-0.15, *p*=0.80	T_b=0.06, *p*=0.40	5.32	*B*=-0.12, *p*=0.49
L MTG	*t*(99)=-1.89, *p*=0.06	0.98	T_b=0.04, *p*=0.55	6.25	*B*=-0.43, *p*=0.36	T_b=-0.01, *p*=0.94	7.52	*B*=-0.15, *p*=0.36
L Temporal pole	*t*(99)=-0.21, *p*=0.83	4.67	T_b=-0.03, *p*=0.71	7.09	*B*=-0.08, *p*=0.89	T_b=-0.09, *p*=0.18	3.13	*B*=-0.24, *p*=0.07

R=right; L=left; vMPFC=ventral medial prefrontal cortex; PCC=posterior cingulate cortex; IFG=inferior frontal gyrus; TPJ=temporo-parietal junction; MTG=middle temporal gyrus; dACC=dorsal anterior cingulate cortex; SFG=superior frontal gyrus. Positive t-values under group differences indicate more activation in healthy controls. BF<0.33 in **bold**. *correlation differs significantly between healthy controls and patients.

both positive (i.e., empathic concern) and negative (i.e., personal distress) emotions. One study that used a similar set-up also showed that patients experienced enhanced negative emotions after watching neutral or positively valenced film clips (Kring & Neale, 1996). The authors suggested that despite flattened affect, patients experience similar or even *more* negative emotions than healthy controls (emotion paradox). However, this effect was absent for positive emotions. Together, these results suggest that patients integrate other people's emotions more with their own emotions, which might become dysfunctional or distressing when it is present to a large extent (van der Weiden et al., 2015). It has been hypothesized that this increase in affective empathy, and in particular personal distress, could lead to avoidance of social situations or even social isolation (Corbera et al., 2013; Horan et al., 2015).

Unfortunately, studies using performance-based measures of empathy are scarce and evidence for alterations in empathic abilities in patients mainly comes from studies using questionnaires (Achim, Ouellet, Roy, & Jackson, 2011; Bonfils et al., 2016, 2017; Corbera et al., 2013; Derntl et al., 2009; Smith et al., 2012; Sparks, McDonald, Lino, O'Donnell, & Green, 2010). Interestingly, although these studies report that patients show more personal distress, compared with healthy controls (similar to performance-based studies), they also reported less empathic concern (in contrast with performance-based studies). Together, these results suggest that there might be a discrepancy between how patients reflect on their ability for empathic concern (measured with questionnaires) and their actual experience of empathic concern (performance-based measures).

In contrast with previous work, we found no reduction of cognitive empathy in patients (Bora et al., 2009c; Sprong et al., 2007). In addition to the presence of a ceiling effect, this finding might be explained by differences in sample characteristics. That is, as it has been hypothesized that poor cognitive empathy is state-dependent (Caldiroli, Buoli, Serati, Cahn, & Altamura, 2016; Pousa et al., 2008), the fact that patients in our sample were relatively stable might explain the absence of group differences in the current study. This is further supported by meta-analytic findings of smaller effect sizes in remitted patients compared to non-remitted patients (Bora et al., 2009c).

Group differences in self-reflective processing

In line with other studies using similar tasks, we showed that patients attribute more negative traits to themselves than controls do (J. S. Lee et al., 2016; van der Meer, de Vos, et al., 2013; Zhang, Opmeer, Ruhé, Aleman, & van der Meer, 2015). However, the finding that patients also rated more negative words as 'positive' in the control condition complicates the interpretation of these findings.

In line with previous studies we found a group difference in activation in the ROI consisting of the mPFC (including vACC) during self-reflective processing (compared with other-reflective processing) (Blackwood et al., 2004; Larivière et al., 2017; Pankow et al., 2016; Tan et al., 2015).

More specifically, patients showed less activity in these areas. This is interesting as these areas are particularly important for directing attention to the self and emotional tagging of self-relevant stimuli according to the neuropsychiatric self-reflection model (Murray et al., 2012; van der Meer et al., 2010). As such, our results possibly indicate that problems in evaluating the saliency of stimuli might be central to patients' impairments in self-reflection. This hypothesis is further supported by previous evidence showing a relation between vMPFC activation during self-reflective processing and aberrant salience coding (Pankow et al., 2016). It should be noted that group differences in brain activity have also been shown in other parts of the cortical midline structures, suggesting impairments in additional aspects of self-reflective processing (Blackwood et al., 2004; Larivière et al., 2017; Lee et al., 2016; Menon et al., 2011; Pauly et al., 2014; Tan et al., 2015; van der Meer et al., 2013). For example, alterations in the ACC and PCC might indicate problems in self-directed attention or the integration of autobiographical memories, respectively (van der Meer et al., 2010).

Self-reflective processing and cognitive empathy

We found that activation in the right anterior insula, associated with the self>control contrast, was positively related with cognitive empathy. The anterior insula has strong functional connections with the middle and inferior frontal cortices, ACC, and TPJ (Cauda et al., 2011), and thus, is involved in numerous aspects of human awareness (extensively reviewed by Craig, 2009). Besides its role in the integration of the bodily state during self-reflective processing (van der Meer et al., 2010), the anterior insula is also involved in cognitive control (Craig, 2009). With regard to cognitive control, bilateral insula activation was found to be specifically related to self-perspective inhibition, i.e., the inhibition of information that is known to the subject, but not to the other person who's perspective the subject is taking (Van der Meer, Groenewold, Nolen, Pijnenborg, & Aleman, 2011). Thus, our findings may indicate that increased anterior insula activation point towards inhibition of the self-perspective in order to make inferences about other people's intentions (i.e., cognitive empathy).

Self-reflective processing and affective empathy

We found a negative relation between the postcentral gyrus (or somatosensory cortex) and affective empathy. The somatosensory cortex is involved in maintaining a representation of the body (Tsakiris, Hesse, Boy, Haggard, & Fink, 2007). In line with these findings, it has been suggested that this area is involved in taking a first-person perspective instead of a third-person perspective, which confirms its role in forming a representation of the self (Ruby & Decety, 2003, 2004). More specifically, activation was found particularly during *emotional* first-person perspective taking (Ruby & Decety, 2004). The role of the somatosensory cortex in the processing of emotional stimuli has also been demonstrated in emotional face processing

(Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Sel, Forster, & Calvo-Merino, 2014).

Furthermore, in the self>other contrast we found that activation in the TPJ/angular gyrus was related to affective empathy in patients only. Among other functions, this area is thought to be highly involved in differentiating between the self and others (Blakemore & Frith, 2003; Decety & Lamm, 2007; Santiesteban, Banissy, Catmur, & Bird, 2012). Other evidence for this assumption comes from imaging studies of self-agency, i.e., the ability to discriminate between one's own and other persons' actions, which has been related to activation in the TPJ/angular gyrus in healthy individuals (David, 2012; Farrer & Frith, 2002; Renes, van Haren, Aarts, & Vink, 2015; Ruby & Decety, 2001). As the negative relationship between affective empathy and TPJ/angular gyrus activation was present in patients only, increased affective empathy in this sample might be explained by alterations in underlying neural mechanisms regarding self-other discrimination.

Taken together, the postcentral gyrus and TPJ/angular gyrus are involved in maintaining a representation of the self and in making a distinction between self and others. Therefore, less activity in these areas might contribute to increased integration between self and others, and consequently to increased contagion with other people's emotions (i.e., more affective empathy). These findings support the idea that the ability to distinguish between self and others is important in affective empathy (van der Weiden et al., 2015) and that reflection on self and others are inextricably intertwined (Gallese & Goldman, 1998).

Limitations

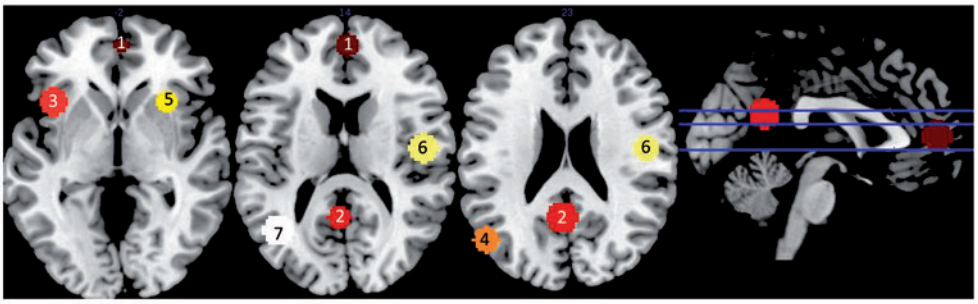
Some limitations need to be taken into account. First, the ceiling effect in the cognitive empathy task, which is most proncounced but not exclusively in healthy controls, impede statistical interpretations (Davidson, Lesser, Parente, & Fiszdon, 2017). A more comprehensive method such as using videoclips depicting short stories might yield more variation in task performance (e.g. part of The Awareness of Social Inference Task (Mcdonald et al., 2003)). Second, in our affective empathy task, we used short film clips. Although these clips might be more realistic than static illustrations that are used in other studies, increasing the duration of the film clips and adding sound would further improve the ecological validity of the task.

Conclusion

We showed that empathy was related to brain activation in the anterior insula and postcentral gyrus during self-reflection in both patients and healthy controls. Although we did not find the predicted mPFC to be involved in this relationship, our results pointed towards other areas that are relevant to self- and other-processing. The fact that these relationships were present in the self>control and self>other contrast, instead of the other>control contrast, further stress the importance of self-processing in empathy. Most importantly, we found that, in patients only,

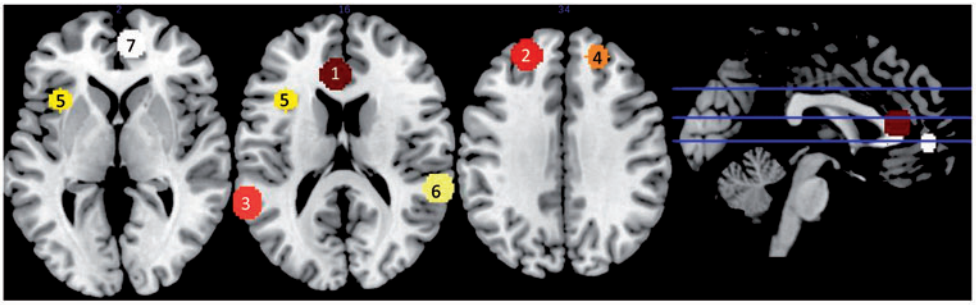
low brain activation in the TPJ/angular gyrus associated with self-reflection was negatively related with affective empathy. As this area is involved in self-other distinction, it confirms the hypothesis that a decrease in self-other distinction might be underlying to enhanced affective empathy in patients. As enhanced affective empathy can induce distress, and might thus become dysfunctional, emotional contagion deserves more attention in the schizoprenia literature. The current study encourages the use of ecologically valid, performance-based measures of empathy in order to further unravel patients' deficits in specific subdomains of empathy.

Supplement 1: ROI definitions



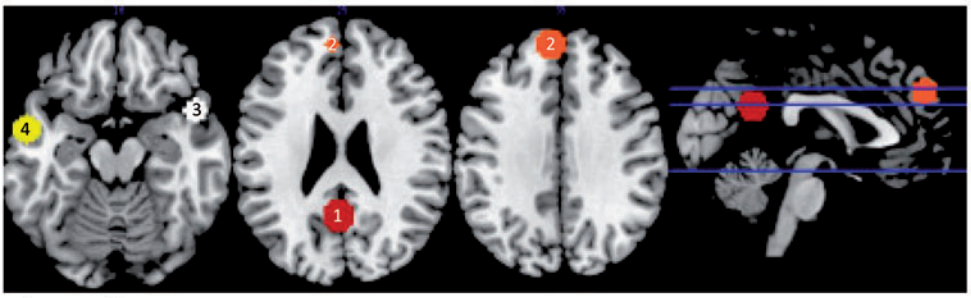
self>control

1= right medial prefrontal cortex; 2= left posterior cingulate cortex/pcc; 3= left inferior frontal gyrus; 4= left temporo-parietal junction; 5= right anterior insula; 6= right postcentral sulcus; 7=left middle temporal gyrus



self>other

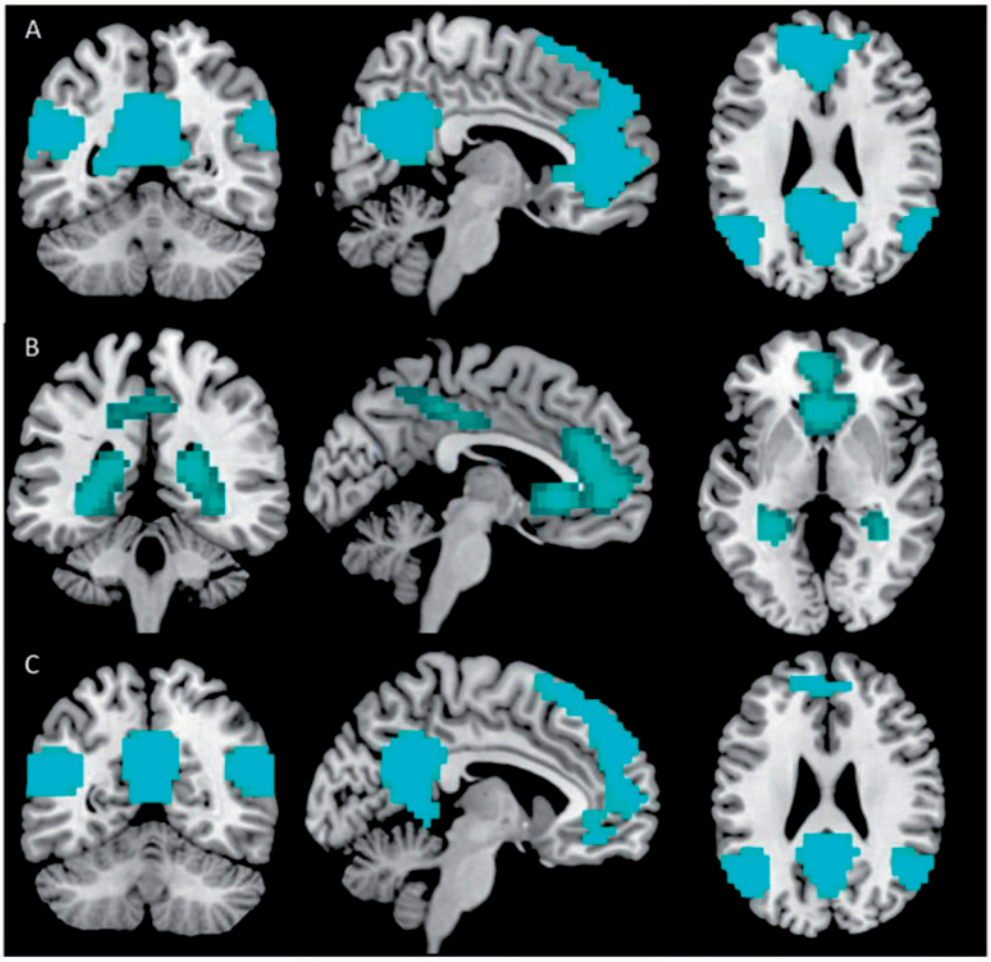
1= left dorsal anterior cingulate cortex; 2= left superior frontal gyrus; 3= left temporo-parietal junction/angular gyrus; 4= right superior frontal gyrus; 5= left anterior insula; 6= right tempo-parietal junction/angular gyrus; 7= right ventromedial prefrontal cortex



other>control

1= left posterior cingulate cortex/precuneus; 2= left superior frontal gyrus; 3= left middle temporal gyrus; 4= right temporal pole

Supplement 2



Supplemental Figure 2. Whole-brain task activation patterns
A. self>control (n=102); B. self>other (n=100); C. other>control (n=101)

Supplemental table 1. Significant whole brain peak activations in each contrast

	brain area	cluster size	t-value	x	y	z
self>control	Precuneus/PCC	578	12.87	-8	-60	20
			12.49	-8	-48	28
	dmPFC/vmPFC/SFC	1166	11.86	-4	60	4
			10.14	-4	52	24
			8.15	-20	40	40
	Angular gyrus/MTG	185	10.13	-48	-72	32
			9.63	-56	-64	24
	MTG/insula	231	8.94	-56	-12	-16
			8.04	-52	4	-28
			7.63	-32	16	-16
	Angular gyrus	82	6.84	56	-60	32
	MTG/iOFC/temporal pole	132	6.42	48	4	-28
			6.00	36	20	-20
			5.62	40	12	-32
			3.63	48	-12	0
self>other	Calcarine/ACC	1225	8.75	-16	-60	16
			8.74	-24	-56	12
			7.46	0	24	0
	MCC/precuneus	133	5.20	-4	-36	44
			4.72	-4	-28	40
			4.61	-16	-44	44
other>control	MTG/iOFC	485	14.93	-56	-8	-16
			12.71	-48	8	-28
			7.36	-44	28	-12
	Precuneus/PCC	454	12.34	4	-56	28
			12.18	-4	-52	24
	MTP/MTG	378	12.17	40	16	-32
			11.11	52	-4	-16
			10.28	60	-8	-12
	Angular gyrus/MTG	199	10.91	-52	-68	28

		10.76	-44	-60	24
Angular gyrus	129	9.82	56	-60	24
dmPFC	674	9.38	8	56	32
		8.96	-4	56	28
		8.52	-8	48	44

PCC=posterior cingulate cortex; dmPFC=dorsomedial prefrontal cortex; vmPFC=ventromedial prefrontal cortex; SFC=superior frontal cortex; MTG=middle temporal gyrus; iOFC=inferior orbitofrontal cortex; ACC=anterior cingulate cortex; MCC=middle cingulate cortex; MTP=middle temporal pole

Supplement 3

Supplemental table 2. Group differences in predefined ROI's with outliers included

	Group differences		Correlation			
Self>control		BF_{01}	Cognitive empathy	BF_{01}	Affective empathy	BF_{01}
R vmPFC	$t(101)=-0.80$, $p=0.43$	3.62	$T_b=0.14$, $p=.06$	1.03	$T_b=0.02$, $p=0.73$	7.18
L PCC/precuneus	$t(101)=-1.57$, $p=0.12$	1.60	$T_b=0.10$, $p=.16$	2.52	$T_b=-0.12$, $p=0.09$	1.80
L IFG	$t(101)=-1.31$, $p=0.19$	2.23	$T_b=0.13$, $p=.07$	1.15	$T_b=0.02$, $p=0.76$	7.28
L TPJ/angular gyrus	$t(101)=-1,95$, $p=0.06$	0.90	$T_b=0.03$, $p=67$	6.99	$T_b=0.06$, $p=0.35$	4.92
R Anterior insula	$t(101)=-0.42$, $p=0.68$	4.45	**$T_b=0.25$, p<.001**	0.01	$T_b=-0.07$, $p=0.30$	4.48
R Postcental gyrus	$t(101)=0.35$, $p=0.73$	4.55	$T_b=-0.01$, $p=.90$	7.66	**$T_b=-0.20$, p=0.004**	0.13
L MTG	$t(101)=0.04$, $p=0.97$	4.80	$T_b=0.05$, $p=.51$	6.03	$T_b=-0.05$, $p=0.50$	6.11
Self>other						
L dACC	$t(101)=1.16$, $p=0.25$	2.65	$T_b=0.14$, $p=.05$	0.94	$T_b=-0.09$, $p=0.21$	3.50
L SFG	$t(101)=1.82$, $p=0.07$	1.12	$T_b=-0.01$, $p=.92$	7.69	$T_b=-0.06$, $p=0.37$	5.09
L TPJ/angular gyrus	$t(101)=0.74$, $p=0.46$	3.77	$T_b=0.04$, $p=.57$	6.43	$T_b=-0.16$, $p=0.02$	0.59
R SFG	$t(101)=1.76$, $p=0.08$	1.23	$T_b=-0.03$, $p=.66$	6.95	$T_b=-0.07$, $p=0.29$	4.42
L Anterior insula	$t(101)=0.25$, $p=0.80$	4.67	$T_b=0.04$, $p=.61$	6.67	$T_b=-0.12$, $p=0.09$	1.86
R TPJ/Angular gyrus	$t(101)=-0.47$, $p=0.64$	4.34	$T_b=-0.02$, $p=.78$	7.41	**$T_b=-0.18$, p=0.01**	0.21
R vmPFC	$t(101)=2.27$, $p=0.03$	0.50	$T_b=0.05$, $p=.45$	5.62	$T_b=-0.10$, $p=0.16$	2.92
Other>control						
L PCC/precuneus	$t(101)=-1.34$, $p=0.19$	2.18	$T_b=0.15$, $p=.04$	0.70	$T_b=-0.01$, $p=0.84$	7.48
L SFG	$t(101)=-2.16$, $p=0.03$	0.62	$T_b=0.14$, $p=.05$	0.90	$T_b=0.08$, $p=0.22$	3.63
L MTG	$t(101)=-2.29$, $p=0.02$	0.93	$T_b=0.05$, $p=.48$	5.84	$T_b=0.02$, $p=0.75$	7.24
L Temporal pole	$t(101)=-0.85$, $p=0.40$	3.49	$T_b=-0.02$, $p=.82$	7.51	$T_b=-0.06$, $p=0.37$	5.14

R=right; L=left; vmPFC=ventral medial prefrontal cortex; PCC=posterior cingulate cortex; IFG=inferior frontal gyrus; TPJ=temporo-parietal junction; MTG=middle temporal gyrus; dACC=dorsal anterior cingulate cortex; SFG=superior frontal gyrus

Summary and general discussion

7

The studies described in this thesis provide insight into self-disturbances in patients with schizophrenia and its relevance for understanding other individuals. This chapter gives an overview of the main findings and implications. First, a summary of the literature review in chapter 2 is given. Then, empirical findings on body ownership, self-agency, and empathy are summarized and discussed. Last, methodological considerations and future directions are described.

Self-other integration and distinction

In chapter 2, a selective literature review described processes involved in self-other distinction and integration and how these processes are affected in patients with schizophrenia. More specifically, mirror neuron functioning, theory of mind, mimicry, self-awareness, and self-agency are discussed in the context of the classic motor prediction model and the cognitive expectation model. Two assumptions were taken into account. First, it was explained that integration and distinction are two sides of the same coin and therefore cannot be treated separately. Second, it was explained how cognitive expectations play a crucial role when reliable motor predictions are absent.

Due to increased motor simulation and an increased temporal binding window, patients with schizophrenia show enhanced integration with other people's behavior and emotions. Moreover, cognitive biases and demands affect their understanding of the more complex emotions and intentions. Conversely, impairments in mirror neuron activation might cause problems in making a distinction between self and others. Together, these conclusions underline the complexity of the balance between self-other integration and distinction. Also, it stresses the importance of examining both sensorimotor *and* cognitive processes in understanding behavior and symptoms related to schizophrenia.

Body ownership

Main findings chapter 3

- In reaction to the Rubber Hand Illusion (RHI), patients with schizophrenia showed subtle alterations in subjective experiences of body ownership, but not in proprioceptive drift
- Body ownership was not affected in individuals at increased familial risk to develop schizophrenia

The impairments in the subjective feeling of body ownership that were found in patients with schizophrenia are in line with other studies that showed that patients experience the illusion faster and stronger and confirm that patients might have a more flexible sense of body ownership (Graham, Martin-Iverson, Holmes, Jablensky, et al., 2014; Lev-Ari et al., 2015;

Peled et al., 2000; Thakkar et al., 2011). A closer look at our findings revealed that patients rated the illusion stronger than healthy controls in the asynchronous condition, but not in the synchronous condition. Interestingly, these findings are in line with the hypothesis that the time window to perceive two stimuli as similar is larger in patients (Foucher et al., 2007). In other words, patients might have perceived asynchronous stroking as more synchronous, and might thus have rated the illusion as stronger, than healthy individuals. Another possible explanation for these findings is that altered subjective RHI experiences in patients might be affected by impaired top-down processes, such as changes in the cognitive representation of the body schema (Tsakiris & Haggard, 2005).

Our study was only the second to assess RHI-induced proprioceptive drift in patients with schizophrenia. The finding that patients did not show impairments herein was in contrast with the previous study, which found a larger proprioceptive drift in patients compared with healthy controls (Thakkar et al., 2011). Importantly, this group difference could be explained by the surprising finding that synchronous or asynchronous stroking did not affect proprioceptive drift in healthy individuals. Given this limitation, replication studies are needed in order confirm our finding that proprioceptive drift is not impaired in patients with schizophrenia.

Furthermore, we did not find evidence for disturbed experiences of body ownership in young individuals at increased familial risk to develop schizophrenia in the future. Although previous research on high-risk populations pointed towards alterations in self-experiences and bodily sensations, our results could not confirm this (Nelson et al., 2012). The highly heterogeneous high-risk sample in the current study, which included many individuals that will not develop a psychotic disorder, might explain these findings. In the future, the longitudinal design of the offspring study described in this thesis will allow us to assess whether self-disturbances *precede* psychosis onset (see also 'Methodological considerations and future directions').

Self-agency

Main findings chapters 4 and 5

- Compared with healthy individuals, patients with schizophrenia showed a smaller effect of primed outcome information on self-agency inferences
- These impairments were not related to decreased neurocognitive functioning or alterations in self-serving bias
- Also, the impairments were not related to symptoms of over- and underattribution of agency in patients
- No significant evidence for impairments in self-agency inferences in siblings of patients were found, although they scored in between patients and healthy individuals

In two samples, we found significant group differences in prime-based agency-inferences, implicating that agency inferences were less informed by primed outcome information in patients (Prikken, van der Weiden, Kahn, Aarts, & van Haren, 2018 (Chapter 4); Renes et al., 2013). In a third sample the effect of group was not significant, but still showed a moderate effect size (Renes, van der Weiden, et al., 2015). Pooling these three independent samples allowed us to perform a highly powered analysis including 180 individuals in total (Prikken et al., 2018 (Chapter 4)). Importantly, this analysis confirmed patients' specific impairments in prime-based agency-inferences, indicating robustness of this effect.

Two potential factors were considered that might explain this impairment. First, it could not be explained by patients' decreased cognitive functioning (Prikken et al., 2018 (Chapter 4)). The absence of such a relationship indicated that prime-based inferences do not necessarily require attentional control, i.e., they occur rather automatically (Hon et al., 2013; Renes, van Haren, & Aarts, 2015). As processing of implicit cues is thought to be important for social cognitive behavior (Nosek et al., 2011), this supports the hypothesis that problems in prime-base agency inferences might be related to problems in social functioning in patients with schizophrenia.

Second, although agency attributions can be affected by cognitive biases and personal beliefs (Aarts & van den Bos, 2011; Desantis et al., 2011), we did not find a relationship between prime-based agency inferences and the self-serving bias. That is, the tendency to attribute positive events to the self and negative events to external sources, did not interfere with prime-based agency inferences. However, this finding does not implicate that agency inferences are not influenced by cognitive biases at all. For example, defeatist beliefs, i.e., the belief that events have no relation to one's own actions at all, might also affect or overrule the influence of primes on agency experiences (van der Weiden et al., 2011). Taken together, we did not find evidence that cognitive functioning or self-serving bias can explain patients' impairments in prime-based agency inferences. An agency inference task that resembles everyday situations might shed new light on the cognitive correlates of these impairments (see also 'Methodological considerations and future directions').

Furthermore, the decreased effect of primes on agency inferences that was found in patients did not relate to the presence of symptoms of over- and underattribution, although patients with symptoms of underattribution gave lower *overall* ratings of self-agency experiences. This finding suggests that these symptoms might not be explained by impairments in prime-based agency inferences. Consequently, it raises the question what other factors might be underlying to these symptoms. For example, there is evidence that motor prediction processes underlying to the sense of agency are related to the presence of symptoms of underattribution (also referred to as first-rank or passivity symptoms; Daprati et al., 1997; Franck et al., 2001; Synofzik et al., 2010). Also, increased attention to (delusional) agents or other external sources possibly decreases agency attribution to the self. As this is also

relevant in the context of social information processing (White et al., 2016), it is an interesting direction for future research.

The fact that 31% of the patients in our study showed symptoms of underattribution as well as symptoms of overattribution in the past month indicates that the direction of self-agency disturbances might vary depending on the context or available information. Of note, it is still unclear how both of these symptom categories can occur simultaneously. It has been suggested that unreliable motor predictions lead to an unstable basis for agency experiences, thereby causing patients to rely more on alternative agency cues (Synofzik et al., 2013). Situation-specific influence of some of these cues, such as emotional valence attribution, might change the weighting process of agency cues. Consequently, this weighting process might result in symptoms of overattribution as well as underattribution. Further exploration of the influence of alternative agency cues is recommended to gain more insight in this topic.

In contrast to patients with schizophrenia, non-psychotic adult siblings of patients did not show impairments in prime-based agency processing, although they scored in between patients and healthy individuals at trend level significance. These findings are in line with a previous study that showed self-reported self-disturbances in patients, while these were absent in unaffected siblings of patients (Heering et al., 2016). However, others found that unaffected siblings, compared with healthy individuals, showed impairments in action-monitoring (Hommes et al., 2012; Versmissen et al., 2007), which is closely related to attributions of self-agency. In contrast to the agency inference task described in this thesis, the action monitoring tasks used in these two previous studies require motor prediction, which might explain the different findings. That is, these results suggest that motor prediction, but not cognitive processes underlying agency experiences might be a vulnerability marker for schizophrenia. This is also confirmed by unpublished preliminary results from one of our ongoing studies that indicated no impairments in prime-based agency inferences in adolescent offspring of patients with schizophrenia. Importantly, as the sample sizes of both this offspring sample and the sibling sample described in this thesis were small (n<20 per group), caution must be applied regarding this hypothesis.

Empathy

Main findings chapter 6

- Patients with schizophrenia showed alterations in affective, but not in cognitive empathic abilities
- In patients only, activation in the temporoparietal junction (TPJ)/angular gyrus was related with affective empathy during self-reflection (compared with other-reflection)
- In both patients and healthy controls, activation during self-reflection (compared with a control condition) in the anterior insula and postcentral gyrus was related with cognitive and affective empathy, respectively

Compared with healthy controls, patients with schizophrenia showed enhanced affective empathy, i.e., they showed more empathy in reaction to watching a film clip of another person going though an experience. Increased affective empathy, and mainly personal distress, has been shown before in patients (Bonfils et al., 2017). As personal distress in reaction to others might cause patients to avoid social situations, this is an important topic (Horan et al., 2015). Results of the current study suggest that increased affective empathy in patients might partly be explained by differences in brain activation underlying self-reflection. That is, more affective empathy (i.e., emotional contagion) was related with decreased activation in the TPJ/angular gyrus in patients only. These areas are involved in distinguishing between self and others (e.g., Blakemore & Frith, 2003; Renes, van Haren, Aarts, et al., 2015). Consequently, decreased activation in the TPJ/angular gyrus, and thus less distinction between self and others, might explain the finding of increased affective empathy in patients.

Furthermore, cognitive and affective empathy were differentially related with activity during self-referential processing. That is, *cognitive* empathy was positively related with activity during self-reflection in the anterior insula in both patients and healthy controls. Among others, the anterior insula is involved in the inhibition of the self-perspective when taking *another* person's perspective (van der Meer, Groenewold, Pijnenborg, & Aleman, 2013). Thus, this might suggest that stronger inhibition of the self-perspective is related with more cognitive empathy. Conversely, *affective* empathy was negatively related with activity during self-reflection in the postcentral gyrus in the total sample. As part of the somatosensory cortex, it is involved in maintaining a representation of the self (Ruby & Decety, 2003, 2004; Tsakiris, Hesse, et al., 2007). Therefore, less activity in this area could indicate a weaker representation of the self, which may in turn lead to more affective empathy. Together, these findings confirm a connection between self-processing and reflection on others.

Methodological considerations and future directions

When interpreting the findings of the current thesis, some methodological issues need to be considered. Issues that are specific to a certain chapter are described in the discussion section of that chapter. However, there were also general methodological considerations, which are described below. In relation to these methodological issues future directions are suggested.

First, the studies that included patients with schizophrenia had long protocols, taking five hours (data from chapter 5) or two times four and a half hours (data from chapter 3 – 6) to administer. Consequently, all the empirical studies that are described in this thesis included patients with schizophrenia that were clinically stable and were cognitively able to complete study participation. Indeed, multiple patients dropped out because the study was too demanding. This resulted in a relatively high functioning patient sample. Including patients at a more severe stage of the illness might lead to more pronounced group differences.

Second, the offspring study allows for prospective assessment of individuals at a relatively high conversion rate. Consequently, potential endophenotypes for schizophrenia can be studied. However, using *cross-sectional* data from this cohort (Chapter 3) has its limitations. For example, results give no information about the *prediction* of conversion to schizophrenia, as this is only possible with longitudinal data. The offspring study is still ongoing and longitudinal data is currently being collected. Consequently, in the future it will be possible to investigate differences between converters and non-converters at baseline, which provides the opportunity to re-examine self-disturbances as a potential vulnerability marker for schizophrenia. Furthermore, similar to our adult patient sample, our familial high-risk sample might be a biased selection of the general population. That is, the families that participated might be better functioning with higher socioeconomic status and do generally include treatment-seeking families.

Third, we did not find any correlates of patients' impairments in prime-based agency inferences. There was no relation with attributional style (chapter 4), neurocognitive functioning (chapter 4), and symptoms of over- and underattribution (chapter 5). Furthermore, unpublished results showed that the impairments did not correlate with a self-report questionnaire of social functioning (Social Functioning Scale; Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). Together, this confirms that the agency-inference task, like many experimental (computer) tasks, has low ecological validity. Importantly, patients' impairments in prime-based agency inferences were demonstrated in three independent samples, implicating that it is a robust effect. The next step would be to examine its relevance for social functioning in patients with schizophrenia. In doing so, self-agency inferences could be measured in ways that resemble real-life situations to a greater extent. For example, it is possible to assess experiences of agency over someone else's *emotions* instead of actions (Ruys & Aarts, 2012). Such a task might resemble real-life social behavior to a larger extent compared to the button presses in our current experiment.

Conclusion

Taken together, the research described in this thesis contributes to our understanding of self-disturbances in patients with schizophrenia. Instead of using questionnaires, experimental set-ups were used in order to increase our knowledge of underlying cognitive mechanisms of self-disturbances. Research was not limited to patients and healthy controls, but also included high-risk samples. In empirical studies we confirmed the presence of basic self-disturbances in patients with schizophrenia and provided evidence for a relation between self- and other-processing. The findings implicate that the presence of these disturbances should not be ignored in clinical practice and stimulate future studies to increase knowledge about its clinical and behavioral relevance.

References

Aarts, H. (2007). Unconscious authorship ascription: The effects of success and effect-specific information priming on experienced authorship. *Journal of Experimental Social Psychology*, *43*(1), 119–126.

Aarts, H., Custers, R., & Marien, H. (2009). Priming and authorship ascription: when nonconscious goals turn into conscious experiences of self-agency. *Journal of Personality and Social Psychology*, *96*(5), 967–979.

Aarts, H., Custers, R., & Wegner, D. M. (2005). On the inference of personal authorship: enhancing experienced agency by priming effect information. *Consciousness and Cognition*, *14*(3), 439–458.

Aarts, H., Gollwitzer, P. M., & Hassin, R. R. (2004). Goal contagion: perceiving is for pursuing. *Journal of Personality and Social Psychology*, *87*(1), 23–37.

Aarts, H., & van den Bos, K. (2011). On the foundations of beliefs in free will: intentional binding and unconscious priming in self-agency. *Psychological Science*, *22*(4), 532–537.

Abdulkarim, Z., & Ehrsson, H. H. (2016). No causal link between changes in hand position sense and feeling of limb ownership in the rubber hand illusion. *Attention, Perception, & Psychophysics*, *78*(2), 707–720.

Abu-Akel, A. (1999). Impaired theory of mind in schizophrenia. *Pragmatics & Cognition*, *7*(2), 1125–1129.

Abu-Akel, A., & Shamay-Tsoory, S. G. (2013). Characteristics of Theory of Mind Impairments in Schizophrenia. In *Social cognition in schizophrenia: From evidence to treatment* (pp. 196–214).

Achim, A. M., Ouellet, R., Roy, M. A., & Jackson, P. L. (2011). Assessment of empathy in first-episode psychosis and meta-analytic comparison with previous studies in schizophrenia. *Psychiatry Research*, *190*(1), 3–8.

Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology*, *11*(2), 231–239.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *The Journal of Neuroscience*, *20*(7), 2683–2690.

Aimola Davies, A. M., White, R. C., & Davies, M. (2013). Spatial limits on the nonvisual self-touch illusion and the visual rubber hand illusion: Subjective experience of the illusion and proprioceptive drift. *Consciousness and Cognition*, *22*(2), 613–636.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. *American Journal of Psychiatry* (5th ed.). Washington, DC: American Psychiatric Assosication.

Amminger, G. P., Schäfer, M. R., Papageorgiou, K., Klier, C. M., Schlögelhofer, M., Mossaheb, N., McGorry, P. D. (2012). Emotion recognition in individuals at clinical high-risk for schizophrenia. *Schizophrenia Bulletin*, *38*(5), 1030–1039.

An, S. K., Kang, J. I., Park, J. Y., Kim, K. R., Lee, Y., & Lee, E. (2010). Attribution Bias in Ultra-High Risk for Psychosis and First-Episode Schizophrenia. *Schizophrenia Research*, *118*(1–3), 54–61.

Anderson, N. H. (1968). Likableness ratings of 555 personality-trait words. *Journal of Personality and Social Psychology*, *9*(3), 272–279.

Andreasen, N. C., Flaum, M., & Arndt, S. (1992). The Comprehensive Assessment of Symptoms and History (CASH). *Archives of General Psychiatry*, *49*(8), 615–623.

Asai, T., Mao, Z., Sugimori, E., & Tanno, Y. (2011). Rubber hand illusion, empathy, and schizotypal experiences in terms of self-other representations. *Consciousness and Cognition*, *20*(4), 1744–1750.

Ashton–James, C., Baaren, R. B. van, Chartrand, T. L., Decety, J., & Karremans, J. (2007). Mimicry and Me: The Impact of Mimicry on Self–Construal. *Social Cognition*, *25*(4), 518–535.

Balconi, M. (2010). *Neuropsychology of the Sense of Agency*. Milan: Springer-Verlag.

Bargh, J. A., & Morsella, E. (2008). The Unconscious Mind. *Perspectives on Psychological Science*, *3*(1), 73–79.

Bedford, N. J., Surguladze, S., Giampietro, V., Brammer, M. J., & David, A. S. (2012). Self-evaluation in schizophrenia: an fMRI study with implications for the understanding of insight. *BMC Psychiatry*, *12*(1), 106.

Belayachi, S., & Van der Linden, M. (2010). Feeling of doing in obsessive–compulsive checking. *Consciousness and Cognition*, *19*(2), 534–546.
Bell, C. C. (2001). Memory-based expectations in electrosensory systems. *Current Opinion in Neurobiology*, *11*(4), 481–487.
Bell, M., Tsang, H. W. H., Greig, T. C., & Bryson, G. J. (2009). Neurocognition, social cognition, perceived social discomfort, and vocational outcomes in schizophrenia. *Schizophrenia Bulletin*, *35*(4), 738–747.
Bender, S., Schröder, J., Freitag, C., Roessner, V., Resch, F., & Weisbrod, M. (2012). Movement-related potentials point towards an impaired tuning of reafferent sensory feedback by preceding motor activation in schizophrenia. *Psychiatry Research: Neuroimaging*, *202*(1), 65–73.
Bentall, R. P., Kinderman, P., & Kaney, S. (1994). The self, attributional processes and abnormal beliefs: Towards a model of persecutory delusions. *Behaviour Research and Therapy*, *32*(3), 331–341.
Berry, K., Bucci, S., Kinderman, P., Emsley, R., & Corcoran, R. (2015). An investigation of attributional style, theory of mind and executive functioning in acute paranoia and remission. *Psychiatry Research*, *226*(1), 84–90.
Birchwood, M., Smith, J., Cochrane, R., Wetton, S., & Copestake, S. (1990). The Social Functioning Scale. The development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. *The British Journal of Psychiatry*, *157*(6), 853–859.
Blackwood, N. J., Bentall, R. P., Ffytche, D. H., Simmons, A., Murray, R. M., & Howard, R. J. (2004). Persecutory delusions and the determination of self-relevance: an fMRI investigation. *Psychological Medicine*, *34*(4), 591–596.
Blakemore, S. J., & Frith, C. D. (2003). Self-awareness and action. *Current Opinion in Neurobiology*, *13*(2), 219–224.
Blakemore, S. J., Smith, J., Steel, R., Johnstone, E. C., & Frith, C. D. (2000). The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychological Medicine*, *30*(5), 1131–1139.
Blakemore, S. J., Wolpert, D. M., & Frith, C. D. (1998). Central cancellation of self-produced tickle sensation. *Nature Neuroscience*, *1*(7), 635–640.
Bleuler, E. (1911). Dementia praecox oder Gruppe der Schizophrenien. *Handbuch Der Psychiatrie*.
Bonfils, K. A., Lysaker, P. H., Minor, K. S., & Salyers, M. P. (2016). Affective empathy in schizophrenia: a meta-analysis. *Schizophrenia Research*, *175*(1–3), 109–117.
Bonfils, K. A., Lysaker, P. H., Minor, K. S., & Salyers, M. P. (2017). Empathy in schizophrenia: A meta-analysis of the Interpersonal Reactivity Index. *Psychiatry Research*, *249*, 293–303.
Bonini, L., Ferrari, P. F., & Fogassi, L. (2013). Neurophysiological bases underlying the organization of intentional actions and the understanding of others' intention. *Consciousness and Cognition*, *22*(3), 1095–1104.
Bora, E., Eryavuz, A., Kayahan, B., Sungu, G., & Veznedaroglu, B. (2006). Social functioning, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. *Psychiatry Research*, *145*(2–3), 95–103.
Bora, E., Vahip, S., Gonul, a S., Akdeniz, F., Alkan, M., Ogut, M., & Eryavuz, A. (2005). Evidence for theory of mind deficits in euthymic patients with bipolar disorder. *Acta Psychiatrica Scandinavica*, *112*(2), 110–6.
Bora, E., Yucel, M., & Pantelis, C. (2009a). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: Meta-analytic study. *British Journal of Psychiatry*, *195*(6), 475–482.
Bora, E., Yucel, M., & Pantelis, C. (2009b). Theory of mind impairment: A distinct trait-marker for schizophrenia spectrum disorders and bipolar disorder? *Acta Psychiatrica Scandinavica*, *120*(4), 253–264.
Bora, E., Yucel, M., & Pantelis, C. (2009c). Theory of mind impairment in schizophrenia: Meta-analysis. *Schizophrenia Research*, *109*(1–3), 1–9.

Bosia, M., Riccaboni, R., & Poletti, S. (2012). Neurofunctional correlates of theory of mind deficits in schizophrenia. *Current Topics in Medicinal Chemistry*, *12*(21), 2284–2302.
Botvinick, M. (2004). Neuroscience. Probing the neural basis of body ownership. *Science*, *305*(5685), 782–783.
Botvinick, M., & Cohen, J. (1998). Rubber hands "feel" touch that eyes see. *Nature*, *391*(6669), 756.
Bourgeois, P., & Hess, U. (2008). The impact of social context on mimicry. *Biological Psychology*, *77*(3), 343–352.
Brennan, A. M., Harris, A. W. F., & Williams, L. M. (2014). Neural processing of facial expressions of emotion in first onset psychosis. *Psychiatry Research*, *219*(3), 477–485.
Brown, E. C., Tas, C., Can, H., Esen-Danaci, A., & Brüne, M. (2014). A Closer Look at the Relationship Between the Subdomains of Social Functioning, Social Cognition and Symptomatology in Clinically Stable Patients with Schizophrenia. *Comprehensive Psychiatry*, *55*(1), 25–32.
Brüne, M. (2003). Theory of mind and the role of IQ in chronic disorganized schizophrenia, *60*, 57–64.
Brüne, M. (2005a). Emotion recognition, "theory of mind," and social behavior in schizophrenia. *Psychiatry Research*, *133*(2–3), 135–147.
Brüne, M. (2005b). "Theory of mind" in schizophrenia: A review of the literature. *Schizophrenia Bulletin*, *31*(1), 21–42.
Brüne, M., Abdel-Hamid, M., Lehmkämper, C., & Sonntag, C. (2007). Mental State Attribution, Neurocognitive Functioning, and Psychopathology: What Predicts Poor Social Competence in Schizophrenia Best? *Schizophrenia Research*, *92*(1–3), 151–159.
Brunelin, J., D'Amato, T., Brun, P., Bediou, B., Kallel, L., Senn, M., … Saoud, M. (2007). Impaired verbal source monitoring in schizophrenia: An intermediate trait vulnerability marker? *Schizophrenia Research*, *89*(1–3), 287–292.
Buehner, M. J., & Humphreys, G. R. (2009). Causal binding of actions to their effects. *Psychological Science*, *20*(10), 1221–1228.
Bulot, V., Thomas, P., & Delevoye-Turrell, Y. (2007). A pre-reflective indicator of an impaired sense of agency in patients with Schizophrenia. *Experimental Brain Research*, *183*(1), 115–126.
Caldiroli, A., Buoli, M., Serati, M., Cahn, W., & Altamura, A. C. (2016). General and social cognition in remitted first-episode schizophrenia patients: a comparative study. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(7), 639–647.
Cardno, A. G., Marshall, E. J., Coid, B., Macdonald, A. M., Ribchester, T. R., Davies, N. J., … Murray, R. M. (1999). Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Archives of General Psychiatry*, *56*(2), 162–168.
Carpenter, W. T., Strauss, J. S., & Muleh, S. (1973). Are there pathognomonic symptoms in schizophrenia? An empiric investigation of Schneider's first-rank symptoms. *Archives of General Psychiatry*, *28*(6), 847–852.
Carr, L., Iacoboni, M., Dubeau, M.-C., Mazziotta, J. C., & Lenzi, G. L. (2003). Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(9), 5497–5502.
Cattaneo, L., & Rizzolatti, G. (2009). The mirror neuron system. *Archives of Neurology*, *66*(5), 557–560.
Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., & Vercelli, A. (2011). Functional connectivity of the insula in the resting brain. *NeuroImage*, *55*(1), 8–23.
Cella, M., Hamid, S., Butt, K., & Wykes, T. (2015). Cognition and social cognition in non-psychotic siblings of patients with schizophrenia. *Cognitive Neuropsychiatry*, *20*(3), 232–242.
Chartrand, T. L., & Bargh, J. A. (1999). The chameleon effect: The perception–behavior link and social interaction. *Journal of Personality and Social Psychology*, *76*(6), 893–910.
Chartrand, T. L., Maddux, W. W., & Lakin, J. L. (2005). Beyond the Perception-Behavior Link: The Ubiquitous Utility and Motivational Moderators of Nonconscious Mimicry. In R. R. Hassin, J. S. Uleman, & J. A. Bargh (Eds.), *The new unconscious* (pp. 334–361). New York, NY: Oxford University Press.

Cheng, C. M., & Chartrand, T. L. (2003). Self-Monitoring Without Awareness: Using Mimicry as a Nonconscious Affiliation Strategy. *Journal of Personality and Social Psychology*, *85*(6), 1170–1179.
Chung, Y. S., Kang, D.-H., Shin, N. Y., Yoo, S. Y., & Kwon, J. S. (2008). Deficit of theory of mind in individuals at ultra-high-risk for schizophrenia. *Schizophrenia Research*, *99*(1–3), 111–118.
Cochin, S., Barthelemy, C., Lejeune, B., Roux, S., & Martineau, J. (1998). Perception of motion and qEEG activity in human adults. *Electroencephalography and Clinical Neurophysiology*, *107*(4), 287–295.
Cochin, S., Barthelemy, C., Roux, S., & Martineau, J. (1999). Observation and execution of movement: similarities demonstrated by quantified electroencephalography. *European Journal of Neuroscience*, *11*(5), 1839–1842.
Colonius, H., & Diederich, A. (2004). Multisensory interaction in saccadic reaction time: a time-window-of-integration model. *Journal of Cognitive Neuroscience*, *16*(6), 1000–1009.
Corbera, S., Wexler, B. E., Ikezawa, S., & Bell, M. D. (2013). Factor structure of social cognition in schizophrenia: is empathy preserved? *Schizophrenia Research and Treatment*, *2013*.
Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social inference: Investigating "theory of mind" in people with schizophrenia. *Schizophrenia Research*, *17*(1), 5–13.
Corlett, P. R., Honey, G. D., & Fletcher, P. C. (2007). From prediction error to psychosis: ketamine as a pharmacological model of delusions. *Journal of Psychopharmacology*, *21*(3), 238–252.
Corlett, P. R., Taylor, J. R., Wang, X.-J., Fletcher, P. C., & Krystal, J. H. (2010). Toward a neurobiology of delusions. *Progress in Neurobiology*, *92*(3), 345–369.
Costantini, M., Robinson, J., Migliorati, D., Donno, B., Ferri, F., & Northoff, G. (2016). Temporal limits on rubber hand illusion reflect individuals ' temporal resolution in multisensory perception. *Cognition*, *157*, 39–48.
Cowie, D., Makin, T. R., & Bremner, A. J. (2013). Children's Responses to the Rubber-Hand Illusion Reveal Dissociable Pathways in Body Representation. *Psychological Science*, *24*(5), 762–769.
Cowie, D., Sterling, S., & Bremner, A. J. (2016). The development of multisensory body representation and awareness continues to 10 years of age: Evidence from the rubber hand illusion. *Journal of Experimental Child Psychology*, *142*, 230–238.
Craig, A. D. (2009). How do you feel — now? The anterior insula and human awareness. *Nature Reviews Neuroscience*, *10*(1), 59–70.
Cravo, A. M., Claessens, P. M. E., & Baldo, M. V. C. (2009). Voluntary action and causality in temporal binding. *Experimental Brain Research*, *199*(1), 95–99.
Custers, R., & Aarts, H. (2010). The Unconscious Will : How the Pursuit of Goals Operates Outside of Conscious Awareness. *Science*, *329*(5987), 47–51.
Dannenberg, L., Förster, J., & Jostmann, N. B. (2012). "If only…": when counterfactual thoughts can reduce illusions of personal authorship. *Consciousness and Cognition*, *21*(1), 456–463.
Daprati, E., Franck, N., Georgieff, N., Proust, J., Pacherie, E., Daléry, J., & Jeannerod, M. (1997). Looking for the agent: an investigation into consciousness of action and self-consciousness in schizophrenic patients. *Cognition*, *65*(1), 71–86.
David, N. (2012). New frontiers in the neuroscience of the sense of agency. *Frontiers in Human Neuroscience*, *6*(161).
Davidson, C. A., Lesser, R., Parente, L. T., & Fiszdon, J. M. (2017). Psychometrics of social cognitive measures for psychosis treatment research. *Schizophrenia Research*.
de Achával, D., Costanzo, E. Y., Villarreal, M., Jáuregui, I. O., Chiodi, A., Castro, M. N., Guinjoan, S. M. (2010). Emotion processing and theory of mind in schizophrenia patients and their unaffected first-degree relatives. *Neuropsychologia*, *48*(5), 1209–1215.
Decety, J., & Lamm, C. (2007). The role of the right temporoparietal junction in social interaction: how low-level computational processes contribute to meta-cognition. *The Neuroscientist*, *13*(6), 580–593.
Decety, J., & Lamm, C. (2011). Empathy versus personal distress: Recent evidence from social neuroscience. In *The Social Neuroscience of Empathy* (pp. 199–213).

Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: a social developmental neuroscience account. *Development and Psychopathology*, *20*(4), 1053–1080.
Del Cul, A., Dehaene, S., & Leboyer, M. (2006). Preserved subliminal processing and impaired conscious access in schizophrenia. *Archives of General Psychiatry*, *63*(12), 1313–1323.
Dempsey-Jones, H., & Kritikos, A. (2014). Higher-order cognitive factors affect subjective but not proprioceptive aspects of self-representation in the rubber hand illusion. *Consciousness and Cognition*, *26*(1), 74–89.
Derntl, B., Finkelmeyer, A., Toygar, T. K., Hülsmann, A., Schneider, F., Falkenberg, D. I., & Habel, U. (2009). Generalized deficit in all core components of empathy in schizophrenia. *Schizophrenia Research*, *108*(1–3), 197–206.
Desantis, A., Roussel, C., & Waszak, F. (2011). On the influence of causal beliefs on the feeling of agency. *Consciousness and Cognition*, *20*(4), 1211–1220.
Desantis, A., Weiss, C., Schütz-Bosbach, S., & Waszak, F. (2012). Believing and Perceiving: Authorship Belief Modulates Sensory Attenuation. *PLoS ONE*, *7*(5), e37959.
Dewey, J. A., & Knoblich, G. (2014). Do Implicit and Explicit Measures of the Sense of Agency Measure the Same Thing? *PLoS ONE*, *9*(10), e110118.
Diez-Alegría, C., Vázquez, C., Nieto-Moreno, M., Valiente, C., & Fuentenebro, F. (2006). Personalizing and externalizing biases in deluded and depressed patients: are attributional biases a stable and specific characteristic of delusions? *The British Journal of Clinical Psychology*, *45*(4), 531–544.
Dimaggio, G., Lysaker, P. H., Carcione, A., Nicolò, G., & Semerari, A. (2008). Know yourself and you shall know the other... to a certain extent: multiple paths of influence of self-reflection on mindreading. *Consciousness and Cognition*, *17*(3), 778–789.
Donohoe, G., Spoletini, I., McGlade, N., Behan, C., Hayden, J., O'Donoghue, T., … Corvin, A. (2008). Are relational style and neuropsychological performance predictors of social attributions in chronic schizophrenia? *Psychiatry Research*, *161*(1), 19–27.
Eagleman, D. M., & Holcombe, A. O. (2002). Motor-sensory recalibration leads to an illusory reversal of action and sensation. *Trends in Cognitive Sciences*, *6*(8), 323–325.
Ebert, J. P., & Wegner, D. M. (2010). Time warp: authorship shapes the perceived timing of actions and events. *Consciousness and Cognition*, *19*(1), 481–489.
Ehrsson, H. H. (2012). The Concept of Body Ownership and Its Relation to Multisensory Integration. In *The New Handbook of Multisensory Processes* (pp. 775–792).
Ehrsson, H. H., Spence, C., & Passingham, R. E. (2004). That's My Hand! Activity in Premotor Cortex Reflects Feeling of Ownership of a Limb. *Science*, *305*(5685), 875–877.
Farrer, C., & Franck, N. (2007). Self-Monitoring in Schizophrenia. *Current Psychiatry Reviews*, *3*(4), 243–251.
Farrer, C., & Frith, C. D. (2002). Experiencing oneself vs another person as being the cause of an action: The neural correlates of the experience of agency. *NeuroImage*, *15*(3), 596–603.
Ferri, F., Costantini, M., Salone, A., Di Iorio, G., Martinotti, G., Chiarelli, A., … Gallese, V. (2014). Upcoming tactile events and body ownership in schizophrenia. *Schizophrenia Research*, *152*(1), 51–57.
Fett, A. K. J., Viechtbauer, W., Dominguez, M., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, *35*(3), 573–588.
First, M. B. et, Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *SCID I gestructureerd Klinisch Interview voor de vaststelling van DSM-IV As I Stoornissen (Groenestijn, Akkerhuis, Kupka, Schneider, & Nolen, trans.)*. New York: Biometrics Research, New York State Psychiatric Institute.
Fischer-Lokou, J., Martin, A., Guéguen, N., & Lamy, L. (2011). Mimicry and propagation of prosocial behavior in a natural setting. *Psychological Reports*, *108*(2), 599–605.
Fitch, G. (1970). Effects of self-esteem, perceived performance, and choice on causal attributions. *Journal of Personality and Social Psychology*, *16*(2), 311–315.

Ford, J. M., Gray, M., Faustman, W. O., Roach, B. J., & Mathalon, D. H. (2007). Dissecting corollary discharge dysfunction in schizophrenia. *Psychophysiology*, *44*(4), 522–529.
Ford, J. M., & Mathalon, D. H. (2012). Anticipating the future: Automatic prediction failures in schizophrenia. *International Journal of Psychophysiology*, *83*(2), 232–239.
Ford, J. M., Palzes, V. A., Roach, B. J., & Mathalon, D. H. (2013). Did I Do That? Abnormal Predictive Processes in Schizophrenia When Button Pressing to Deliver a Tone. *Schizophrenia Bulletin*, *40*(4), 804–812.
Ford, J. M., Roach, B. J., Faustman, W. O., & Mathalon, D. H. (2008). Out-of-synch and out-of-sorts: dysfunction of motor-sensory communication in schizophrenia. *Biological Psychiatry*, *63*(8), 736–743.
Foucher, J. R., Lacambre, M., Pham, B. T., Giersch, A., & Elliott, M. A. (2007). Low time resolution in schizophrenia. Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophrenia Research*, *97*(1–3), 118–127.
Fourneret, P., & Jeannerod, M. (1998). Limited conscious monitoring of motor performance in normal subjects. *Neuropsychologia*, *36*(11), 1133–1140.
Franck, N., Farrer, C., Georgieff, N., Marie-Cardine, M., Daléry, J., D'Amato, T., & Jeannerod, M. (2001). Defective recognition of one's own actions in patients with schizophrenia. *American Journal of Psychiatry*, *158*(3), 454–459.
Frijda, N. H. (2010). Impulsive action and motivation. *Biological Psychology*, *84*(3), 570–579.
Frith, C. D. (2005). The neural basis of hallucinations and delusions. *Comptes Rendus Biologies*, *328*(2), 169–175.
Frith, C. D. (2012). Explaining delusions of control: the comparator model 20 years on. *Consciousness and Cognition*, *21*(1), 52–54.
Frith, C. D. (2013a). Action, agency and responsibility. *Neuropsychologia*, *55*, 137–124.
Frith, C. D. (2013b). The psychology of volition. *Experimental Brain Research*, *229*(3), 289–299.
Frith, C. D., Blakemore, S. J., & Wolpert, D. M. (2000a). Abnormalities in the awareness and control of action. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *355*(1404), 1771–1788.
Frith, C. D., Blakemore, S. J., & Wolpert, D. W. (2000b). Explaining the symptoms of schizophrenia: Abnormalities in the awareness of action. *Brain Research Reviews*, *31*(2–3), 357–363.
Frith, C. D., & Done, D. J. (2013). Experiences of alien control in schizophrenia reflect a disorder in the central monitoring of action. *Psychological Medicine*, *19*(2), 359.
Gallace, A., & Spence, C. (2010). The science of interpersonal touch: an overview. *Neuroscience and Biobehavioral Reviews*, *34*(2), 246–259.
Gallagher, S. (2000). Philosophical conceptions of the self: implications for cognitive science. *Trends in Cognitive Sciences*, *4*(1), 14–21.
Gallese, V. (2003). The Roots of Empathy: The Shared Manifold Hypothesis and the Neural Basis of Intersubjectivity. *Psychopathology*, *36*(4), 171–180.
Gallese, V., Fadiga, L., Fogassi, L., & Rizzolatti, G. (1996). Action recognition in the premotor cortex. *Brain*, *119*(2), 593–609.
Gallese, V., & Goldman, A. I. (1998). Mirror neurons and the simulation theory of mind-reading. *Trends in Cognitive Sciences*, *2*(12), 493–501.
Gardner, A., Cotton, S. M., Allott, K., Filia, K. M., Hester, R., & Killackey, E. (2017). Social inclusion and its interrelationships with social cognition and social functioning in first-episode psychosis. *Early Intervention in Psychiatry*.
Garety, P. A., & Freeman, D. (1999). Cognitive approaches to delusions: A critical review of theories and evidence. *British Journal of Clinical Psychology*, *38*(2), 113–154.
Gentsch, A., & Schütz-Bosbach, S. (2011). I did it: unconscious expectation of sensory consequences modulates the experience of self-agency and its functional signature. *Journal of Cognitive Neuroscience*, *23*(12), 3817–3828.

Germine, L., Benson, T. L., Cohen, F., & Hooker, C. I. (2013). Psychosis-proneness and the rubber hand illusion of body ownership. *Psychiatry Research*, *207*(1–2), 45–52.
Goldman, A. I. (1989). Interpretation Psychologized. *Mind & Language*, *4*(3), 161–185.
Goldman, A. I. (2009). Mirroring, Simulating and Mindreading. *Mind & Language*, *24*(2), 235–252.
Gopnik, A., & Wellman, H. M. (1992). Why the Child's Theory of Mind Really Is a Theory. *Mind & Language*, *7*(1–2), 145–171.
Gori, M., Del Viva, M., Sandini, G., & Burr, D. C. (2008). Young Children Do Not Integrate Visual and Haptic Form Information. *Current Biology*, *18*(9), 694–698.
Gorwood, P., Burns, T., Juckel, G., Rossi, A., San, L., Hargarter, L., & Schreiner, A. (2013). Psychiatrists' perceptions of the clinical importance, assessment and management of patient functioning in schizophrenia in Europe, the Middle East and Africa. *Annals of General Psychiatry*, *12*(1), 8.
Gould, L. N. (1948). Verbal hallucinations and activity of vocal musculature; an electromyographic study. *The American Journal of Psychiatry*, *105*, 367–372.
Graham-Schmidt, K. T., Martin-Iverson, M. T., & Waters, F. A. V. (2017). Self- and other-agency in people with passivity (first rank) symptoms in schizophrenia. *Schizophrenia Research*, *192*, 75–81.
Graham, K. T., Martin-Iverson, M. T., Holmes, N. P., Jablensky, A., & Waters, F. (2014). Deficits in agency in schizophrenia, and additional deficits in body image, body schema, and internal timing, in passivity symptoms. *Frontiers in Psychiatry*, *5*, 126.
Graham, K. T., Martin-Iverson, M. T., Holmes, N. P., & Waters, F. A. (2014). The projected hand illusion: component structure in a community sample and association with demographics, cognition, and psychotic-like experiences. *Attention, Perception & Psychophysics*, *77*(1), 207–219.
Graziano, M. S. A., & Botvinick, M. M. (2002). How the brain represents the body: insights from neurophysiology and psychology. *Common Mechanisms in Perception and Action (Attention and Performance XIX)*, *19*, 136–157.
Green, M. F., Bearden, C. E., Cannon, T. D., Fiske, A. F., Hellemann, G., Horan, W. P., … Nuechterlein, K. H. (2012). Social Cognition in Schizophrenia, Part 1: Performance Across Phase of Illness. *Schizophrenia Bulletin*, *38*(4), 854–864.
Green, M. F., Horan, W. P., & Lee, J. (2015). Social cognition in schizophrenia. *Nature Reviews. Neuroscience*, *16*(1), 620–631.
Green, M. F., & Kinsbourne, M. (1990). Subvocal activity and auditory hallucinations: Clues for behavioral treatments? *Schizophrenia Bulletin*, *16*(4), 617–625.
Green, M. J., Waldron, J. H., Simpson, I., & Coltheart, M. (2008). Visual processing of social context during mental state perception in schizophrenia. *Journal of Psychiatry & Neuroscience : JPN*, *33*(1), 34–42.
Green, M. J., Williams, L. M., & Hemsley, D. R. (2010). Cognitive Theories of Delusion Formation: The Contribution of Visual Scanpath Research. *Cognitive Neuropsychiatry*, *5*(1), 63–74.
Guéguen, N., Martin, A., & Meineri, S. (2011). Mimicry and helping behavior: an evaluation of mimicry on explicit helping request. *The Journal of Social Psychology*, *151*(1), 1–4.
Haggard, P., & Clark, S. (2003). Intentional action: Conscious experience and neural prediction. *Consciousness and Cognition*, *12*(4), 695–707.
Haggard, P., Clark, S., & Kalogeras, J. (2002). Voluntary action and conscious awareness. *Nature Neuroscience*, *5*(4), 382–385.
Haggard, P., Martin, F., Taylor-Clarke, M., Jeannerod, M., & Franck, N. (2003). Awareness of action in schizophrenia. *NeuroReport*, *14*(7), 1081–1085.
Haker, H., & Rössler, W. (2009). Empathy in schizophrenia: impaired resonance. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(6), 352–61.
Hampshire, A., Chamberlain, S. R., Monti, M. M., Duncan, J., & Owen, A. M. (2010). The role of the right inferior frontal gyrus: inhibition and attentional control. *NeuroImage*, *50*(3), 1313–1319.
Hari, R., Forss, N., Avikainen, S., Kirveskari, E., Salenius, S., & Rizzolatti, G. (1998). Activation of human primary motor cortex during action observation: A neuromagnetic study. *Proceedings of the National Academy of Sciences*, *95*(25), 15061–15065.

Hauser, M., Knoblich, G., Repp, B. H., Lautenschlager, M., Gallinat, J., Heinz, A., & Voss, M. (2011). Altered sense of agency in schizophrenia and the putative psychotic prodrome. *Psychiatry Research*, *186*(2–3), 170–176.

Heering, H. D., Goedhart, S., Bruggeman, R., Cahn, W., De Haan, L., Kahn, R. S., … Wiersma, D. (2016). Disturbed experience of self: Psychometric analysis of the Self-Experience Lifetime Frequency Scale (SELF). *Psychopathology*, *49*(2), 69–76.

Heering, H. D., van Haren, N. E. M., & Derks, E. M. (2013). A two-factor structure of first rank symptoms in patients with a psychotic disorder. *Schizophrenia Research*, *147*(2–3), 269–274.

Heinks-Maldonado, T. H., Mathalon, D. H., Houde, J. F., Gray, M., Faustman, W. O., & Ford, J. M. (2007). Relationship of Imprecise Corollary Discharge in Schizophrenia to Auditory Hallucinations. *Archives of General Psychiatry*, *64*(3), 286–296.

Heinrichs, R., & Zakzanis, K. (1998). Neurocognitive Deficit in Schizophrenia: A Quantitative Review of the Evidence. *Neuropsychology*, *12*(3), 426–445.

Hemsley, D. R. (1998). The disruption of the "sense of self" in schizophrenia: potential links with disturbances of information processing. *The British Journal of Medical Psychology*, *71*(2), 115–124.

Hemsley, D. R. (2005a). The development of a cognitive model of schizophrenia: placing it in context. *Neuroscience and Biobehavioral Reviews*, *29*(6), 977–988.

Hemsley, D. R. (2005b). The schizophrenic experience: taken out of context? *Schizophrenia Bulletin*, *31*(1), 43–53.

Hemsley, D. R., & Zawada, S. L. (1976). "Filtering" and the cognitive deficit in schizophrenia. *The British Journal of Psychiatry, 128*(5), 456–461.

Hess, U., & Fischer, A. (2013). Emotional mimicry as social regulation. *Personality and Social Psychology Review*, *17*(2), 142–157.

Hickok, G. (2009). Eight Problems for the Mirror Neuron Theory of Action Understanding in Monkeys and Humans. *Journal of Cognitive Neuroscience*, *21*(7), 1229–1243.

Hickok, G., & Hauser, M. (2010). (Mis)understanding mirror neurons. *Current Biology*, *20*(14), R593-594.

Hillock-Dunn, A., & Wallace, M. T. (2012). Developmental changes in the multisensory temporal binding window persist into adolescence. *Developmental Science*, *15*(5), 688–696.

Hirstein, W., & Sifferd, K. (2011). The legal self: executive processes and legal theory. *Consciousness and Cognition*, *20*(1), 156–171.

Hommes, J., Krabbendam, L., Versmissen, D., Kircher, T., van Os, J., & van Winkel, R. (2012). Self-monitoring as a familial vulnerability marker for psychosis: an analysis of patients, unaffected siblings and healthy controls. *Psychological Medicine*, *42*(2), 235–245.

Hon, N., Poh, J. H., & Soon, C. S. (2013). Preoccupied minds feel less control: Sense of agency is modulated by cognitive load. *Consciousness and Cognition*, *22*(2), 556–561.

Horan, W. P., Foti, D., Hajcak, G., Wynn, J. K., & Green, M. F. (2012). Impaired neural response to internal but not external feedback in schizophrenia. *Psychological Medicine*, *42*(8), 1637–1647.

Horan, W. P., Reise, S. P., Kern, R. S., Lee, J., Penn, D. L., & Green, M. F. (2015). Structure and correlates of self-reported empathy in schizophrenia, *14*(11), 871–882.

Hoshi, E., & Tanji, J. (2006). Differential involvement of neurons in the dorsal and ventral premotor cortex during processing of visual signals for action planning. *Journal of Neurophysiology*, *95*(6), 3596–3616.

Hughes, G., & Waszak, F. (2011). ERP correlates of action effect prediction and visual sensory attenuation in voluntary action. *NeuroImage*, *56*(3), 1632–1640.

Hur, J. W., Kwon, J. S., Lee, T. Y., & Park, S. (2014). The crisis of minimal self-awareness in schizophrenia: a meta-analytic review. *Schizophrenia Research*, *152*(1), 58–64.

Iacoboni, M. (2009). Imitation, empathy, and mirror neurons. *Annual Review of Psychology*, *60*, 653–70.

IJsselsteijn, W. A., de Kort, Y. A. W., & Haans, A. (2006). Is This My Hand I See Before Me? The Rubber Hand Illusion in Reality, Virtual Reality, and Mixed Reality. *Presence: Teleoperators and Virtual Environments*, *15*(4), 455–464.

Inzlicht, M., Gutsell, J. N., & Legault, L. (2012). Mimicry reduces racial prejudice. *Journal of Experimental Social Psychology*, *48*(1), 361–365.
Janssen, I., Krabbendam, L., Jolles, J., & van Os, J. (2003). Alterations in theory of mind in patients with schizophrenia and non-psychotic relatives. *Acta Psychiatrica Scandinavica*, *108*(2), 110–117.
Janssen, I., Versmissen, D., Campo, J. A., Myin-Germeys, I., van Os, J., & Krabbendam, L. (2006). Attribution style and psychosis: evidence for an externalizing bias in patients but not in individuals at high risk. *Psychological Medicine*, *36*(6), 771–778.
Jardri, R., Delevoye-Turrell, Y., Lucas, B., Pins, D., Bulot, V., Delmaire, C., … Goeb, J.-L. (2009). Clinical practice of rTMS reveals a functional dissociation between agency and hallucinations in schizophrenia. *Neuropsychologia*, *47*(1), 132–138.
Jardri, R., Pins, D., Lafargue, G., Very, E., Ameller, A., Delmaire, C., & Thomas, P. (2011). Increased overlap between the brain areas involved in self-other distinction in schizophrenia. *PloS One*, *6*(3), e17500.
Johns, L. C., Allen, P., Valli, I., Winton-Brown, T., Broome, M., Woolley, J., … McGuire, P. (2010). Impaired verbal self-monitoring in individuals at high risk of psychosis. *Psychological Medicine*, *40*(9), 1433–42.
Johns, L. C., Rossell, S., Frith, C. D., Ahmad, F., Hemsley, D., Kuipers, E., & McGuire, P. K. (2001). Verbal self-monitoring and auditory verbal hallucinations in patients with schizophrenia. *Psychological Medicine*, *31*(4), 705–715.
Jones, S. H., Hemsley, D. R., & Gray, J. A. (1991). Contextual effects on choice reaction time and accuracy in acute and chronic schizophrenics. Impairment in selective attention or in the influence of prior learning? *The British Journal of Psychiatry*, *159*(3), 415–421.
Kahn, R. S., & Keefe, R. S. E. (2013). Schizophrenia Is a Cognitive Illness. *JAMA Psychiatry*, *70*(10), 1107.
Kail, R. (1991). Development of processing speed in childhood and adolescence. *Advances in Child Development and Behavior*, *23*(23), 151–185.
Kállai, J., Hegedüs, G., Feldmann, Á., Rózsa, S., Darnai, G., Herold, R., Szolcsányi, T. (2015). Temperament and psychopathological syndromes specific susceptibility for rubber hand illusion. *Psychiatry Research*, *229*(1–2), 410–419.
Kammers, M. P. M., de Vignemont, F., Verhagen, L., & Dijkerman, H. C. (2009). The rubber hand illusion in action. *Neuropsychologia*, *47*(1), 204–211.
Kaney, S., & Bentall, R. P. (1992). Persecutory Delusions and the Self-Serving Bias. Evidence from a contingency judgment task. *The Journal of Nervous and Mental Disease*, *180*(12), 773–780.
Kaplan, J. T., & Iacoboni, M. (2006). Getting a grip on other minds: mirror neurons, intention understanding, and cognitive empathy. *Social Neuroscience*, *1*(3–4), 175–183.
Kapur, S., Mizrahi, R., & Li, M. (2005). From dopamine to salience to psychosis-linking biology, pharmacology and phenomenology of psychosis. *Schizophrenia Research*, *79*, 59–68.
Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(7), 980–988.
Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.
Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenoud, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research*, *68*(2–3), 283–297.
Kendler, K. S., Pedersen, N. L., Neale, M. C., & Mathé, A. A. (1995). A Pilot Swedish Twin Study of Affective Illness Including Hospital- and Population-Ascertained Subsamples: Results of Model Fitting. *Behavior Genetics*, *25*(3), 217–232.
Kilner, J. M., Friston, K. J., & Frith, C. D. (2009). Predictive coding: an account of the mirror neuron system. *Cognitive Processing*, *8*(3), 159–166.

Kinderman, P., & Bentall, R. P. (1996). New Measure of Causal Locus: the Internal, Personal and Situational Attributions Questionnaire. *Personality and Individual Differences*, *20*(2), 261–264.
Klaver, M., & Dijkerman, H. C. (2016). Bodily Experience in Schizophrenia : Factors Underlying a Disturbed Sense of Body Ownership. *Frontiers in Human Neuroscience*, *10*, 305.
Klingberg, S., Wittorf, A., Sickinger, S., Buchkremer, G., & Wiedemann, G. (2008). Course of cognitive functioning during the stabilization phase of schizophrenia. *Journal of Psychiatric Research*, *42*(4), 259–267.
Knoblich, G., Stottmeister, F., & Kircher, T. (2004). Self-monitoring in patients with schizophrenia. *Psychological Medicine*, *34*(8), 1561–1569.
Korver, N., Quee, P. J., Boos, H. B. M., Simons, C. J. P., de Haan, L., & GROUPinvestigators. (2012). Genetic Risk and Outcome of Psychosis (GROUP), a multi site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International Journal of Methods in Psychiatric Research*, *21*(3), 205–221.
Kring, A. M., & Campellone, T. R. (2012). Emotion Perception in Schizophrenia: Context Matters. *Emotion Review*, *4*(2), 182–186.
Kring, A. M., & Elis, O. (2013). Emotion deficits in people with schizophrenia. *Annual Review of Clinical Psychology*, *9*, 409–433.
Kring, A. M., Kerr, S. L., & Earnst, K. S. (1999). Schizophrenic patients show facial reactions to emotional facial expressions. *Psychophysiology*, *36*(2), 186–192.
Kring, A. M., & Neale, J. M. (1996). Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *Journal of Abnormal Psychology*, *105*(2), 249–257.
Króliczak, G., McAdam, T. D., Quinlan, D. J., & Culham, J. C. (2008). The human dorsal stream adapts to real actions and 3D shape processing: a functional magnetic resonance imaging study. *Journal of Neurophysiology*, *100*(5), 2627–2639.
Kuperberg, G., & Heckers, S. (2000). Schizophrenia and cognitive function. *Current Opinion in Neurobiology*, *10*(2), 205–210.
Lakin, J. L., & Chartrand, T. L. (2003). Using Nonconscious Behavioral Mimicry to Create Affiliation and Rapport. *Psychological Science*, *14*(4), 334–339.
Lakin, J. L., Chartrand, T. L., & Arkin, R. M. (2008). I am too just like you: nonconscious mimicry as an automatic behavioral response to social exclusion. *Psychological Science*, *19*(8), 816–822.
Langdon, R., Coltheart, M., & Ward, P. B. (2006). Empathetic perspective-taking is impaired in schizophrenia: evidence from a study of emotion attribution and theory of mind. *Cognitive Neuropsychiatry*, *11*(2), 133–155.
Langdon, R., Corner, T., McLaren, J., Ward, P. B., & Coltheart, M. (2006). Externalizing and personalizing biases in persecutory delusions: the relationship with poor insight and theory-of-mind. *Behaviour Research and Therapy*, *44*(5), 699–713.
Langdon, R., Ward, P. B., & Coltheart, M. (2010). Reasoning anomalies associated with delusions in schizophrenia. *Schizophrenia Bulletin*, *36*(2), 321–30.
Larivière, S., Lavigne, K. M., Woodward, T. S., Gerretsen, P., Graff-Guerrero, A., & Menon, M. (2017). Altered functional connectivity in brain networks underlying self-referential processing in delusions of reference in schizophrenia. *Psychiatry Research - Neuroimaging*, *263*, 32–43.
Lavoie, M. A., Plana, I., Bédard Lacroix, J., Godmaire-Duhaime, F., Jackson, P. L., & Achim, A. M. (2013). Social cognition in first-degree relatives of people with schizophrenia: A meta-analysis. *Psychiatry Research*, *209*(2), 129–135.
Lee, J., & Park, S. (2005). Working Memory Impairments in Schizophrenia: A Meta-Analysis. *Journal of Abnormal Psychology*, *114*(4), 599–611.

Lee, J. S., Kim, E. S., Kim, E. J., Kim, J., Kim, E., Lee, S. K., & Kim, J. J. (2016). The relationship between self-referential processing-related brain activity and anhedonia in patients with schizophrenia. *Psychiatry Research - Neuroimaging*, *254*, 112–118.

Lee, K. H., Farrow, T. F. D., Spence, S. A., & Woodruff, P. W. R. (2004). Social cognition, brain networks and schizophrenia. *Psychological Medicine*, *34*(3), 391–400.

Leube, D. T., Knoblich, G., Erb, M., Schlotterbeck, P., & Kircher, T. T. J. (2010). The neural basis of disturbed efference copy mechanism in patients with schizophrenia. *Cognitive Neuroscience*, *1*(2), 111–117.

Lev-Ari, L., Hirschmann, S., Dyskin, O., Goldman, O., & Hirschmann, I. (2015). The Rubber Hand Illusion paradigm as a sensory learning process in patients with schizophrenia. *European Psychiatry*, *30*(7), 868–873.

Lewkowicz, D. J., & Flom, R. (2014). The audiovisual temporal binding window narrows in early childhood. *Child Development*, *85*(2), 685–694.

Lincoln, T. M., Mehl, S., Kesting, M. L., & Rief, W. (2011). Negative symptoms and social cognition: Identifying targets for psychological interventions. *Schizophrenia Bulletin*, *37*(SUPPL. 2), s23–s32.

Lind, E. A., Kanfer, R., & Earley, P. C. (1990). Voice, control, and procedural justice: Instrumental and noninstrumental concerns in fairness judgments. *Journal of Personality and Social Psychology*, *59*(5), 952–959.

Liu, J., Corbera, S., & Wexler, B. E. (2014). Neural activation abnormalities during self-referential processing in schizophrenia: an fMRI study. *Psychiatry Research*, *222*(3), 165–171.

Ma, K., & Hommel, B. (2015). Body-ownership for actively operated non-corporeal objects. *Consciousness and Cognition*, *36*, 75–86.

Maat, A., Fett, A. K., Derks, E., & Investigators, G. (2012). Social cognition and quality of life in Sschizophrenia. *Schizophrenia Research*, *137*(1–3), 212–218.

Maeda, T., Kato, M., Muramatsu, T., Iwashita, S., Mimura, M., & Kashima, H. (2012). Aberrant sense of agency in patients with schizophrenia: forward and backward over-attribution of temporal causality during intentional action. *Psychiatry Research*, *198*(1), 1–6.

Maeda, T., Takahata, K., Muramatsu, T., Okimura, T., Koreki, A., Iwashita, S., … Kato, M. (2013). Reduced sense of agency in chronic schizophrenia with predominant negative symptoms. *Psychiatry Research*, *209*(3), 386–892.

Mahy, C. E. V, Moses, L. J., & Pfeifer, J. H. (2014). How and where: theory-of-mind in the brain. *Developmental Cognitive Neuroscience*, *9*, 68–81.

Maister, L., Sebanz, N., Knoblich, G., & Tsakiris, M. (2013). Experiencing ownership over a dark-skinned body reduces implicit racial bias. *Cognition*, *128*(2), 170–178.

Malenka, R. C., Angel, R. W., Hampton, B., & Berger, P. A. (1982). Impaired Central Error-Correcting Behavior in Schizophrenia. *Archives of General Psychiatry*, *39*(1), 101–107.

Marjoram, D., Miller, P., McIntosh, A. M., Cunningham Owens, D. G., Johnstone, E. C., & Lawrie, S. (2006). A neuropsychological investigation into "Theory of Mind" and enhanced risk of schizophrenia. *Psychiatry Research*, *144*(1), 29–37.

Martin, J. A., & Penn, D. L. (2002). Attributional style in schizophrenia: An investigation in outpatients with and without persecutory delusions. *Schizophrenia Bulletin*, *28*(1), 131–141.

Matthews, N., Gold, B. J., Sekuler, R., & Park, S. (2013). Gesture imitation in schizophrenia. *Schizophrenia Bulletin*, *39*(1), 94–101.

Mattingley, J. B., Husain, M., Rorden, C., Kennard, C., & Driver, J. (1998). Motor role of human inferior parietal lobe revealed in unilateral neglect patients. *Nature*, *392*(6672), 179–182.

Maurer, R. E., & Tindall, J. H. (1983). Effect of postural congruence on client's perception of counselor empathy. *Journal of Counseling Psychology*, *30*(2), 158–163.

McCormick, L. M., Brumm, M. C., Beadle, J. N., Paradiso, S., Yamada, T., & Andreasen, N. C. (2012). Mirror neuron function, psychosis, and empathy in schizophrenia. *Psychiatry Research: Neuroimaging*, *201*(3), 233–239.

Mcdonald, S., Flanagan, S., Psychology, M., Rollins, J., Science, B. A., Pathology, S., & Kinch, J. (2003). A New Clinical Tool for Assessing Social Perception after Traumatic Brain Injury. *Journal of Head Trauma Rehabilitation*, *18*(3), 219–238.

Medalia, A., & Thysen, J. (2010). A comparison of insight into clinical symptoms versus insight into neuro-cognitive symptoms in schizophrenia. *Schizophrenia Research*, *118*(1–3), 134–139.

Mehl, S., Landsberg, M. W., Schmidt, A., Cabanis, M., Bechdolf, A., Herrlich, J., … Wagner, M. (2014). Why do bad things happen to me? attributional style, depressed mood, and persecutory delusions in patients with schizophrenia. *Schizophrenia Bulletin*, *40*(6), 1338–1346.

Mehta, U. M., Thirthalli, J., Aneelraj, D., Jadhav, P., Gangadhar, B. N., & Keshavan, M. S. (2014). Mirror neuron dysfunction in schizophrenia and its functional implications: A systematic review. *Schizophrenia Research*, *160*(1), 9–19.

Mehta, U. M., Thirthalli, J., Bhagyavathi, H. D., Keshav Kumar, J., Subbakrishna, D. K., Gangadhar, B. N., … Keshavan, M. S. (2014). Similar and contrasting dimensions of social cognition in schizophrenia and healthy subjects. *Schizophrenia Research*, *157*(1–3), 70–77.

Menon, M., Schmitz, T. W., Anderson, A. K., Graff, A., Korostil, M., Mamo, D., … Kapur, S. (2011). Exploring the neural correlates of delusions of reference. *Biological Psychiatry*, *70*(12), 1127–1133.

Metcalfe, J., Van Snellenberg, J. X., DeRosse, P., Balsam, P., & Malhotra, A. K. (2012). Judgements of agency in schizophrenia: an impairment in autonoetic metacognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1594), 1391–1400.

Miller, D. T., & Ross, M. (1975). Self-serving biases in the attribution of causality: Fact or fiction? *Psychological Bulletin*, *82*(2), 213–225.

Mishara, A. L., Lysaker, P. H., & Schwartz, M. A. (2014). Self-disturbances in schizophrenia: History, phenomenology, and relevant findings from research on metacognition. *Schizophrenia Bulletin*, *40*(1), 5–12.

Molenberghs, P., Cunnington, R., & Mattingley, J. B. (2012). Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neuroscience and Biobehavioral Reviews*, *36*(1), 341–349.

Montag, C., Heinz, A., Kunz, D., & Gallinat, J. (2007). Self-reported empathic abilities in schizophrenia. *Schizophrenia Research*, *92*(1–3), 85–89.

Montag, C., Neuhaus, K., Lehmann, A., Krüger, K., Dziobek, I., Heekeren, H. R., Gallinat, J. (2012). Subtle deficits of cognitive theory of mind in unaffected first-degree relatives of schizophrenia patients. *European Archives of Psychiatry and Clinical Neuroscience*, *262*(3), 217–226.

Moore, J. W., & Haggard, P. (2008). Awareness of action: Inference and prediction. *Consciousness and Cognition*, *17*(1), 136–144.

Moore, J. W., Wegner, D. M., & Haggard, P. (2009). Modulating the sense of agency with external cues. *Consciousness and Cognition*, *18*(4), 1056–1064.

Moretto, G., Walsh, E., & Haggard, P. (2011). Experience of agency and sense of responsibility. *Consciousness and Cognition*, *20*(4), 1847–54.

Moskowitz, G. B. (2002). Preconscious effects of temporary goals on attention. *Journal of Experimental Social Psychology*, *38*(4), 397–404.

Mukamel, R., Ekstrom, A. D., Kaplan, J., Iacoboni, M., & Fried, I. (2010). Single-Neuron Responses in Humans during Execution and Observation of Actions. *Current Biology*, *20*(8), 750–756.

Murphy, E. R., Brent, B. K., Benton, M., Pruitt, P., Diwadkar, V., Rajarethinam, R. P., & Keshavan, M. S. (2010). Differential processing of metacognitive evaluation and the neural circuitry of the self and others in schizophrenia: A pilot study. *Schizophrenia Research*, *116*(2–3), 252–258.

Murray, R. J., Schaer, M., & Debbané, M. (2012). Degrees of separation: a quantitative neuroimaging meta-analysis investigating self-specificity and shared neural activation between self- and other-reflection. *Neuroscience and Biobehavioral Reviews*, *36*(3), 1043–1059.

Nathaniel-James, D. A., & Frith, C. D. (2009). Confabulation in schizophrenia: evidence of a new form? *Psychological Medicine*, *26*(2), 391–399.

Nelson, B., Sass, L. A., Thompson, A., Yung, A. R., Francey, S. M., Amminger, G. P., & McGorry, P. D. (2009). Does Disturbance of Self Underlie Social Cognition Deficits in Schizophrenia and Other Psychotic Disorders? *Early Intervention in Psychiatry*, *3*(2), 83–93.

Nelson, B., Thompson, A., & Yung, A. R. (2012). Basic Self-Disturbance Predicts Psychosis Onset in the Ultra High Risk for Psychosis "Prodromal" Population. *Schizophrenia Bulletin*, *38*(6), 1277–1287.

Nelson, B., Whitford, T. J., Lavoie, S., & Sass, L. A. (2014). What are the neurocognitive correlates of basic self-disturbance in schizophrenia?: Integrating phenomenology and neurocognition. Part 1 (Source monitoring deficits). *Schizophrenia Research*, *152*(1), 12–9.

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain-A meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457.

Nosek, B. A., Hawkins, C. B., & Frazier, R. S. (2011). Implicit social cognition: From measures to mechanisms. *Trends in Cognitive Sciences*, *15*(4), 152–159.

Oberman, L. M., Winkielman, P., & Ramachandran, V. S. (2007). Face to face: blocking facial mimicry can selectively impair recognition of emotional expressions. *Social Neuroscience*, *2*(3–4), 167–178.

Obhi, S. S., & Hall, P. (2011a). Sense of agency and intentional binding in joint action. *Experimental Brain Research.*, *211*(3–4), 655–662.

Obhi, S. S., & Hall, P. (2011b). Sense of agency in joint action: influence of human and computer co-actors. *Experimental Brain Research*, *211*(3–4), 663–670.

Ocampo, B., & Kritikos, A. (2011). Interpreting actions: the goal behind mirror neuron function. *Brain Research Reviews*, *67*(1–2), 260–267.

Pankow, A., Katthagen, T., Diner, S., Deserno, L., Boehme, R., Kathmann, N., … Schlagenhauf, F. (2016). Aberrant salience is related to dysfunctional self-referential processing in psychosis. *Schizophrenia Bulletin*, *42*(1), 67–76.

Park, S., Matthews, N., & Gibson, C. (2008). Imitation, simulation, and schizophrenia. *Schizophrenia Bulletin*, *34*(4), 698–707.

Park, S., & Nasrallah, H. a. (2014). The varieties of anomalous self experiences in schizophrenia: splitting of the mind at a crossroad. *Schizophrenia Research*, *152*(1), 1–4.

Parnas, J., Carter, J., & Nordgaard, J. (2014). Premorbid self-disorders and lifetime diagnosis in the schizophrenia spectrum: a prospective high-risk study. *Early Intervention in Psychiatry*, *10*(1), 45–53.

Parnas, J., & Handest, P. (2003). Phenomenology of Anomalous Self-Experience in Early Schizophrenia. *Comprehensive Psychiatry*, *44*(2), 121–134.

Parnas, J., Raballo, A., Handest, P., Jansson, L., Vollmer-Larsen, A., & Saebye, D. (2011). Self-experience in the early phases of schizophrenia: 5-year follow-up of the Copenhagen Prodromal Study. *World Psychiatry*, *10*(3), 200–204.

Patterson, M. L., Powell, J. L., & Lenihan, M. G. (1986). Touch, compliance, and interpersonal affect. *Journal of Nonverbal Behavior*, *10*(1), 41–50.

Patterson, T. L., Moscona, S., McKibbin, C. L., Davidson, K., & Jeste, D. V. (2001). Social Skills Performance Assessment Among Older Patients with Schizophrenia. *Schizophrenia Research*, *48*(2), 351–360.

Pauly, K. D., Kircher, T. T. J., Schneider, F., & Habel, U. (2014). Me, myself and I: Temporal dysfunctions during self-evaluation in patients with schizophrenia. *Social Cognitive and Affective Neuroscience*, *9*(11), 1779–1788.

Peled, A., Pressman, A., Geva, A. B., & Modai, I. (2003). Somatosensory evoked potentials during a rubber-hand illusion in schizophrenia. *Schizophrenia Research*, *64*(2–3), 157–163.

Peled, A., Ritsner, M., Hirschmann, S., Geva, A. B., & Modai, I. (2000). Touch feel illusion in schizophrenic patients. *Biological Psychiatry*, *48*(11), 1105–1108.

Penn, D. L., Lawrence, S. J., Roberts, L., Sanna, L. J., & Roberts, D. L. (2008). Social Cognition in Schizophrenia: An Overview. *Schizophrenia Bulletin*, *34*(3), 408–411.

Penn, D. L., Ritchie, M., Francis, J., Combs, D., & Martin, J. (2002). Social perception in schizophrenia: the role of context. *Psychiatry Research*, *109*(2), 149–159.
Perner, J., & Howes, D. (1992). "He Thinks He Knows": And More Developmental Evidence Against the Simulation (Role Taking) Theory. *Mind & Language*, *7*(1–2), 72–86.
Pinkham, A. E., & Penn, D. L. (2006). Neurocognitive and Social Cognitive Predictors of Interpersonal Skill in Schizophrenia. *Psychiatry Research*, *143*(2), 167–178.
Pinkham, A. E., Penn, D. L., Perkins, D. O., Graham, K. A., & Siegel, M. (2007). Emotion Perception and Social Skill Over the Course of Psychosis: a Comparison of Individuals "at-Risk" for Psychosis and Individuals with Early and Chronic Schizophrenia Spectrum Illness. *Cognitive Neuropsychiatry*, *12*(3), 198–212.
Poulet, J. F. A., & Hedwig, B. (2002). A corollary discharge maintains auditory sensitivity during sound production. *Nature*, *418*(6900), 872–876.
Pousa, E., Duñó, R., Brébion, G., David, A. S., Ruiz, A. I., & Obiols, J. E. (2008). Theory of mind deficits in chronic schizophrenia: evidence for state dependence. *Psychiatry Research*, *158*(1), 1–10.
Prikken, M., van der Weiden, A., Kahn, R. S., Aarts, H., & van Haren, N. E. M. (2018). Impaired self-agency inferences in schizophrenia: The role of cognitive capacity and causal reasoning style. *European Psychiatry*, *47*, 27–34.
Prikken, M., van der Weiden, A., Renes, R. A., Koevoets, G. J. C., Heering, H. D., Kahn, R. S., … van Haren, N. E. M. (2017). Abnormal agency experiences in schizophrenia patients: Examining the role of psychotic symptoms and familial risk. *Psychiatry Research*, *250*.
Renes, R. A., van der Weiden, A., Prikken, M., Kahn, R. S., Aarts, H., & van Haren, N. E. M. (2015). Abnormalities in the experience of self-agency in schizophrenia: A replication study. *Schizophrenia Research*, *164*(1–3), 210–213.
Renes, R. A., van Haren, N. E. M., & Aarts, H. (2015). Attentional control and inferences of agency: Working memory load differentially modulates goal-based and prime-based agency experiences. *Consciousness and Cognition*, *38*, 38–49.
Renes, R. A., van Haren, N. E. M., Aarts, H., & Vink, M. (2015). An exploratory fMRI study into inferences of self-agency. *Social Cognitive and Affective Neuroscience*, *10*(5), 708–712.
Renes, R. A., Vermeulen, L., Kahn, R. S., Aarts, H., & van Haren, N. E. M. (2013). Abnormalities in the establishment of feeling of self-agency in schizophrenia. *Schizophrenia Research*, *143*(1), 50–54.
Rizzolatti, G., & Craighero, L. (2005). Mirror neuron: A neurological approach to empathy. In J.-P. Changeux, A. R. Damasio, W. Singer, & Y. Christen (Eds.), *Neurobiology of Human Values* (pp. 107–123). Berlin/Heidelberg: Springer-Verlag.
Rizzolatti, G., Fadiga, L., Gallese, V., & Fogassi, L. (1996). Premotor cortex and the recognition of motor actions. *Cognitive Brain Research*, *3*(2), 131–141.
Rohde, M., Luca, M., & Ernst, M. O. (2011). The rubber hand illusion: Feeling of ownership and proprioceptive drift Do not go hand in hand. *PLoS ONE*, *6*(6), e21659.
Roncone, R., Falloon, I. R. H., Mazza, M., De Risio, A., Pollice, R., Necozione, S., … Casacchia, M. (2002). Is Theory of Mind in Schizophrenia More Strongly Associated with Clinical and Social Functioning than with Neurocognitive Deficits? *Psychopathology*, *35*(5), 280–288.
Rotter, J. B. (1966). Generalized Expectancies for Internal Versus External Control of Reinforcement. *Psychological Monographs: General and Applied*, *80*(1), 1–28.
Roussel, C., Hughes, G., & Waszak, F. (2013). A preactivation account of sensory attenuation. *Neuropsychologia*, *51*(5), 922–929.
Ruby, P., & Decety, J. (2001). Effect of subjective perspective taking during simulation of action: a PET investigation of agency. *Nature Neuroscience*, *4*(5), 546–550.
Ruby, P., & Decety, J. (2003). What you believe versus what you think they believe: A neuroimaging study of conceptual perspective-taking. *European Journal of Neuroscience*, *17*(11), 2475–2480.

Ruby, P., & Decety, J. (2004). How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *Journal of Cognitive Neuroscience*, *16*(6), 988–999.

Ruys, K. I., & Aarts, H. (2012). I didn't mean to hurt you! Unconscious origins of experienced self-agency over others' emotions. *Emotion*, *12*(1), 132–141.

Rychlowska, M., Cañadas, E., Wood, A., Krumhuber, E. G., Fischer, A., & Niedenthal, P. M. (2014). Blocking mimicry makes true and false smiles look the same. *PloS One*, *9*(3), e90876.

Santiesteban, I., Banissy, M. J., Catmur, C., & Bird, G. (2012). Enhancing social ability by stimulating right temporoparietal junction. *Current Biology*, *22*(23), 2274–2277.

Sarfati, Y., Hardy-Baylé, M.-C., Brunet, E., & Widlöcher, D. (1999). Investigating theory of mind in schizophrenia: influence of verbalization in disorganized and non-disorganized patients. *Schizophrenia Research*, *37*(2), 183–190.

Sass, L. A. (2014). Self-disturbance and schizophrenia: structure, specificity, pathogenesis (Current issues, New directions). *Schizophrenia Research*, *152*(1), 5–11.

Sass, L. A., & Parnas, J. (2003). Schizophrenia, consciousness, and the self. *Schizophrenia Bulletin*, *29*(3), 427–444.

Sato, A. (2009). Both motor prediction and conceptual congruency between preview and action-effect contribute to explicit judgment of agency. *Cognition*, *110*(1), 74–83.

Savla, G. N., Vella, L., Armstrong, C. C., Penn, D. L., & Twamley, E. W. (2013). Deficits in domains of social cognition in schizophrenia: A meta-analysis of the empirical evidence. *Schizophrenia Bulletin*, *39*(5), 979–992.

Saxe, R., Moran, J. M., Scholz, J., & Gabrieli, J. (2006). Overlapping and non-overlapping brain regions for theory of mind and self reflection in individual subjects. *Social Cognitive and Affective Neuroscience*, *1*(3), 229–234.

Scherer, K. R. (2009). The dynamic architecture of emotion: Evidence for the component process model. *Cognition & Emotion*, *23*(7), 1307–1351.

Schimansky, J., David, N., Wulf, R., & Haker, H. (2010). Sense of agency and mentalizing: Dissociation of subdomains of social cognition in patients with schizophrenia. *Psychiatry Research*, *178*(1), 39–45.

Schmand, B., Bakker, D., Saan, R., & Louman, J. (1991). The Dutch Reading Test for Adults: a measure of premorbid intelligence level. *Tijdschrift Voor Gerontologische Geriatrie*, *22*(1), 15–19.

Schneider, K. (1939). *Psychischer Befund und psychiatrische Diagnose*. Leipzig: Thieme.

Seidman, L. J., Hellemann, G., Nuechterlein, K. H., Greenwood, T. a, Braff, D. L., Cadenhead, K. S., … Green, M. F. (2015). Factor structure and heritability of endophenotypes in schizophrenia: Findings from the Consortium on the Genetics of Schizophrenia (COGS-1). *Schizophrenia Research*, *163*(1–3), 73–79.

Sel, A., Forster, B., & Calvo-Merino, B. (2014). The Emotional Homunculus: ERP Evidence for Independent Somatosensory Responses during Facial Emotional Processing. *Journal of Neuroscience*, *34*(9), 3263–3267.

Serra, A. M., Jones, S. H., Toone, B., & Gray, J. A. (2001). Impaired associative learning in chronic schizophrenics and their first-degree relatives: A study of latent inhibition and the Kamin blocking effect. *Schizophrenia Research*, *48*(2–3), 273–289.

Shamay-Tsoory, S. G. (2011). The Neural Bases for Empathy. *The Neuroscientist*, *17*(1), 18–24.

Shamay-Tsoory, S. G., Shur, S., Barcai-Goodman, L., Medlovich, S., Harari, H., & Levkovitz, Y. (2007). Dissociation of cognitive from affective components of theory of mind in schizophrenia. *Psychiatry Research*, *149*(1–3), 11–23.

Shamay-Tsoory, S. G., Tomer, R., Goldsher, D., Berger, B. D., & Aharon-Peretz, J. (2004). Impairment in cognitive and affective empathy in patients with brain lesions: Anatomical and cognitive correlates. *Journal of Clinical and Experimental Neuropsychology*, *26*(8), 1113–1127.

Shergill, S. S., Samson, G., Bays, P. M., Frith, C. D., & Wolpert, D. W. M. (2005). Evidence for Sensory Prediction Deficits in Schizophrenia. *American Journal of Psychiatry*, *162*(12), 2384–2386.

Shimada, S., Fukuda, K., & Hiraki, K. (2009). Rubber hand illusion under delayed visual feedback. *PLoS ONE*, *4*(7), e6185.
Smith, M. J., Horan, W. P., Karpouzian, T. M., Abram, S. V., Cobia, D. J., & Csernansky, J. G. (2012). Self-reported empathy deficits are uniquely associated with poor functioning in schizophrenia. *Schizophrenia Research*, *137*(1–3), 196–202.
Smith, M. J., Schroeder, M. P., Abram, S. V, Goldman, M. B., Parrish, T. B., Wang, X., … Breiter, H. C. (2014). Alterations in Brain Activation During Cognitive Empathy Are Related to Social Functioning in Schizophrenia. *Schizophrenia Bulletin*, *41*(1), 211–222.
Sober, S. J., & Sabes, P. N. (2003). Multisensory Integration during Motor Planning. *Journal of Neuroscience*, *23*(18), 6982–6992.
Sobhani, M., Fox, G. R., Kaplan, J., & Aziz-Zadeh, L. (2012). Interpersonal liking modulates motor-related neural regions. *PloS One*, *7*(10), e46809.
Soon, C. S., Brass, M., Heinze, H.-J., & Haynes, J.-D. (2008). Unconscious determinants of free decisions in the human brain. *Nature Neuroscience*, *11*(5), 543–545.
Sparks, A., McDonald, S., Lino, B., O'Donnell, M., & Green, M. J. (2010). Social cognition, empathy and functional outcome in schizophrenia. *Schizophrenia Research*, *122*(1–3), 172–178.
Sprong, M., Schothorst, P., Vos, E., Hox, J., Engeland, H. Van, & Engeland, H. V. A. N. (2007). Theory of mind in schizophrenia : Meta-analysis. *British Journal of Psychiatry*, *191*, 5–13.
Stanghellini, G. (2009). Embodiment and schizophrenia. *World Psychiatry*, *8*(1), 56–59.
Stanghellini, G., Ballerini, M., Blasi, S., Mancini, M., Presenza, S., Raballo, A., & Cutting, J. (2014). The bodily self: A qualitative study of abnormal bodily phenomena in persons with schizophrenia. *Comprehensive Psychiatry*, *55*(7), 1703–1711.
Steinhorst, A., & Funke, J. (2014). Mirror neuron activity is no proof for action understanding. *Frontiers in Human Neuroscience*, *8*, 333.
Stel, M., van Baaren, R. B., & Vonk, R. (2008). Effects of mimicking: acting prosocially by being emotionally moved. *European Journal of Social Psychology*, *38*(6), 965–976.
Stel, M., & Vonk, R. (2010). Mimicry in social interaction: benefits for mimickers, mimickees, and their interaction. *British Journal of Psychology*, *101*(2), 311–323.
Stetson, C., Cui, X., Montague, P. R., & Eagleman, D. M. (2006). Motor-sensory recalibration leads to an illusory reversal of action and sensation. *Neuron*, *51*(5), 651–659.
Strack, F., Martin, L. L., & Stepper, S. (1988). Inhibiting and facilitating conditions of the human smile: A nonobtrusive test of the facial feedback hypothesis. *Journal of Personality and Social Psychology*, *54*(5), 768–777.
Suzuki, K., Garfinkel, S. N., Critchley, H. D., & Seth, A. K. (2013). Multisensory integration across exteroceptive and interoceptive domains modulates self-experience in the rubber-hand illusion. *Neuropsychologia*, *51*, 2909–2917.
Świtaj, P., Anczewska, M., Chrostek, A., Sabariego, C., Cieza, A., Bickenbach, J., & Chatterji, S. (2012). Disability and schizophrenia: a systematic review of experienced psychosocial difficulties. *BMC Psychiatry*, *12*(1), 193.
Synofzik, M., Thier, P., Leube, D. T., Schlotterbeck, P., & Lindner, A. (2010). Misattributions of agency in schizophrenia are based on imprecise predictions about the sensory consequences of one's actions. *Brain*, *133*(1), 262–271.
Synofzik, M., Vosgerau, G., & Lindner, A. (2009). Me or not me--an optimal integration of agency cues? *Consciousness and Cognition*, *18*(4), 1065–1068.
Synofzik, M., Vosgerau, G., & Newen, A. (2008). Beyond the comparator model: A multifactorial two-step account of agency. *Consciousness and Cognition*, *17*(1), 219–239.
Synofzik, M., Vosgerau, G., & Voss, M. (2013). The experience of agency: an interplay between prediction and postdiction. *Frontiers in Psychology*, *4*, 127.

Tan, S., Zhao, Y., Fan, F., Zou, Y., Jin, Z., Zen, Y., … Zhou, D. (2015). Brain correlates of self-evaluation deficits in schizophrenia: A combined functional and structural MRI study. *PLoS ONE*, *10*(9), e0138737.

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008). Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia Research*, *102*(1), 1–18.

Tettamanti, M., Rognoni, E., Cafiero, R., Costa, T., Galati, D., & Perani, D. (2012). Distinct pathways of neural coupling for different basic emotions. *NeuroImage*, *59*(2), 1804–1817.

Thakkar, K. N., Nichols, H. S., McIntosh, L. G., & Park, S. (2011). Disturbances in Body Ownership in Schizophrenia: Evidence from the Rubber Hand Illusion and Case Study of a Spontaneous Out-of-Body Experience. *PLoS ONE*, *6*(10), e27089.

Thakkar, K. N., Peterman, J. S., & Park, S. (2014). Altered Brain Activation During Action Imitation and Observation in Schizophrenia: A Translational Approach to Investigating Social Dysfunction in Schizophrenia. *American Journal of Psychiatry*, *171*(5), 539–548.

Thompson, A., Papas, A., Bartholomeusz, C., Allott, K., Amminger, G. P., Nelson, B., … Yung, A. (2012). Social cognition in clinical "at risk" for psychosis and first episode psychosis populations. *Schizophrenia Research*, *141*(2–3), 204–209.

Thompson, A., Papas, A., Bartholomeusz, C., Nelson, B., & Yung, A. (2013). Externalized attributional bias in the Ultra High Risk (UHR) for psychosis population. *Psychiatry Research*, *206*(2–3), 200–205.

Timm, J., Sanmiguel, I., Keil, J., Schröger, E., & Schönwiesner, M. (2014). Motor Intention Determines Sensory Attenuation of Brain Responses to Self-initiated Sounds. *Journal of Cognitive Neuroscience*, *26*(7), 1481–1489.

Tsakiris, M. (2010). My body in the brain: A neurocognitive model of body-ownership. *Neuropsychologia*, *48*(3), 703–712.

Tsakiris, M. (2017). The multisensory basis of the self: From body to identity to others. *Quarterly Journal of Experimental Psychology*, *70*(4), 597–609.

Tsakiris, M., & Haggard, P. (2005). The rubber hand illusion revisited: visuotactile integration and self-attribution. *Journal of Experimental Psychology. Human Perception and Performance*, *31*(1), 80.

Tsakiris, M., Hesse, M. D., Boy, C., Haggard, P., & Fink, G. R. (2007). Neural signatures of body ownership: A sensory network for bodily self-consciousness. *Cerebral Cortex*, *17*(10), 2235–2244.

Tsakiris, M., Schütz-Bosbach, S., & Gallagher, S. (2007). On agency and body-ownership: Phenomenological and neurocognitive reflections. *Consciousness and Cognition*, *16*(3), 645–660.

Urgesi, C., Maieron, M., Avenanti, A., Tidoni, E., Fabbro, F., & Aglioti, S. M. (2010). Simulating the future of actions in the human corticospinal system. *Cerebral Cortex*, *20*(11), 2511–2521.

Van Buuren, M., Gladwin, T. E., Zandbelt, B. B., Kahn, R. S., & Vink, M. (2010). Reduced functional coupling in the default-mode network during self-referential processing. *Human Brain Mapping*, *31*(8), 1117–1127.

van der Gaag, M. (2006). A neuropsychiatric model of biological and psychological processes in the remission of delusions and auditory hallucinations. *Schizophrenia Bulletin*, *32 Suppl 1*(suppl_1), S113–S122.

van der Meer, L., Costafreda, S., Aleman, A., & David, A. S. (2010). Self-reflection and the brain: a theoretical review and meta-analysis of neuroimaging studies with implications for schizophrenia. *Neuroscience and Biobehavioral Reviews*, *34*(6), 935–946.

van der Meer, L., de Vos, A. E., Stiekema, A. P. M., Pijnenborg, G. H. M., van Tol, M.-J., Nolen, W. a, … Aleman, A. (2013). Insight in schizophrenia: involvement of self-reflection networks? *Schizophrenia Bulletin*, *39*(6), 1288–1295.

Van der Meer, L., Groenewold, N. A., Nolen, W. A., Pijnenborg, M., & Aleman, A. (2011). Inhibit yourself and understand the other: Neural basis of distinct processes underlying Theory of Mind. *NeuroImage*, *56*(4), 2364–2374.

van der Meer, L., Groenewold, N. A., Pijnenborg, M., & Aleman, A. (2013). Psychosis-Proneness and Neural Correlates of Self-Inhibition in Theory of Mind. *PLoS ONE*, *8*(7), e67774.
van der Weiden, A., Aarts, H., & Ruys, K. I. (2010). Reflecting on the action or its outcome: Behavior representation level modulates high level outcome priming effects on self-agency experiences. *Consciousness and Cognition*, *19*(1), 21–32.
van der Weiden, A., Aarts, H., & Ruys, K. I. (2011). Prime and probability: Causal knowledge affects inferential and predictive effects on self-agency experiences. *Consciousness and Cognition*, *20*(4), 1865–1871.
van der Weiden, A., Aarts, H., & Ruys, K. I. (2013). On the nature of experiencing self-agency: the role of goals and primes in inferring oneself as the cause of behavior. *Social and Personality Psychology Compass*, *7*(12), 888–904.
van der Weiden, A., Prikken, M., & van Haren, N. E. M. (2015). Self-Other Integration and Distinction in Schizophrenia : A theoretical analysis and a review of the evidence. *Neuroscience and Biobehavioral Reviews*, *57*, 220–237.
van der Weiden, A., Ruys, K. I., & Aarts, H. (2013). A matter of matching: How goals and primes affect self-agency experiences. *Journal of Experimental Psychology: General*, *142*(3), 954–966.
Van Overwalle, F. (2009). Social cognition and the brain: A meta-analysis. *Human Brain Mapping*, *30*(3), 829–858.
Varcin, K. J., Bailey, P. E., & Henry, J. D. (2010). Empathic deficits in schizophrenia: the potential role of rapid facial mimicry. *Journal of the International Neuropsychological Society*, *16*(4), 621–629.
Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, a L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophrenia Research*, *25*(1), 21–31.
Veluw, S. J., & Chance, S. A. (2013). Differentiating between self and others: an ALE meta-analysis of fMRI studies of self-recognition and theory of mind. *Brain Imaging and Behavior*, *8*(1), 24–38.
Versmissen, D., Myin-Germeys, I., Janssen, I., Franck, N., Georgieff, N., Campo, J. A., … Krabbendam, L. (2007). Impairment of self-monitoring: Part of the endophenotypic risk for psychosis. *British Journal of Psychiatry*, *191*(51), s58-62.
Vöhringer, P. A., Barroilhet, S. A., Amerio, A., Reale, M. L., Alvear, K., Vergne, D., & Ghaemi, S. N. (2013). Cognitive impairment in bipolar disorder and schizophrenia: A systematic review. *Frontiers in Psychiatry*, *4*(87).
Vosgerau, G., & Synofzik, M. (2012). Weighting models and weighting factors. *Consciousness and Cognition*, *21*(1), 55–58.
Voss, M., Moore, J. W., Hauser, M., Gallinat, J., Heinz, A., & Haggard, P. (2010). Altered awareness of action in schizophrenia: a specific deficit in predicting action consequences. *Brain*, *133*(10), 3104–3112.
Vroomen, J., & Keetels, M. (2010). Perception of intersensory synchrony: a tutorial review. *Attention, Perception & Psychophysics*, *72*(4), 871–884.
Walston, F., Blennerhassett, R. C., & Charlton, B. G. (2000). "Theory of mind", persecutory delusions and the somatic marker mechanism. *Cognitive Neuropsychiatry*, *5*(3), 161–174.
Walter, H., Ciaramidaro, A., Adenzato, M., Vasic, N., Ardito, R. B., Erk, S., & Bara, B. G. (2009). Dysfunction of the social brain in schizophrenia is modulated by intention type: an fMRI study. *Social Cognitive and Affective Neuroscience*, *4*(2), 166–176.
Waszak, F., Cardoso-Leite, P., & Hughes, G. (2012). Action effect anticipation: neurophysiological basis and functional consequences. *Neuroscience and Biobehavioral Reviews*, *36*(2), 943–959.
Waters, F. A. V., & Badcock, J. C. (2010). First-Rank Symptoms in Schizophrenia: Reexamining Mechanisms of Self-recognition. *Schizophrenia Bulletin*, *36*(3), 510–517.
Wegner, D. M. (2002). *The Illusion of Conscious Will*. Cambridge, MA: MIT Press.

Wegner, D. M., & Wheatley, T. (1999). Apparent Mental Causation: Sources of the Experience of Will. *American Psychologist*, *54*(7), 480–492.
Weiss, C., Herwig, A., & Schütz-Bosbach, S. (2011). The Self in Social Interactions: Sensory Attenuation of Auditory Action Effects Is Stronger in Interactions with Others. *PLoS ONE*, *6*(7), e22723.
White, T. P., Borgan, F., Ralley, O., & Shergill, S. S. (2016). You looking at me?: Interpreting social cues in schizophrenia. *Psychological Medicine*, *46*(1), 149–160.
Willis, F. N., & Hamm, H. K. (1980). The use of interpersonal touch in securing compliance. *Journal of Nonverbal Behavior*, *5*(1), 49–55.
Wittorf, A., Giel, K. E., Hautzinger, M., Rapp, A., Schönenberg, M., Wolkenstein, L., Klingberg, S. (2012). Specificity of jumping to conclusions and attributional biases: a comparison between patients with schizophrenia, depression, and anorexia nervosa. *Cognitive Neuropsychiatry*, *17*(3), 262–286.
Wohlschlager, A., Haggard, P., Gesierich, B., & Prinz, W. (2003). The perceived onset time of self- and other-generated actions. *Psychological Science*, *14*(6), 586–591.
Wolpert, D. M., & Flanagan, J. R. (2001). Motor prediction. *Current Biology*, *11*(18), R729–R732.
Woodward, T. S., Moritz, S., Cuttler, C., & Whitman, J. C. (2006). The contribution of a cognitive bias against disconfirmatory evidence (BADE) to delusions in schizophrenia. *Journal of Clinical and Experimental Neuropsychology*, *28*(4), 605–617.
Yung, A. R., Phillips, L. J., Yuen, H. P., & McGorry, P. D. (2004). Risk factors for psychosis in an ultra high-risk group: Psychopathology and clinical features. *Schizophrenia Research*, *67*(2–3), 131–142.
Zhang, L., Opmeer, E. M., Ruhé, H. G., Aleman, A., & van der Meer, L. (2015). Brain activation during self- and other-reflection in bipolar disorder with a history of psychosis: Comparison to schizophrenia. *NeuroImage: Clinical*, *8*, 202–209.
Zhang, L., van der Meer, L., Opmeer, E. M., Marsman, J. B. C., Ruhé, H. G., & Aleman, A. (2016). Altered functional connectivity during self- and close other-reflection in patients with bipolar disorder with past psychosis and patients with schizophrenia. *Neuropsychologia*, *93*, 97–105.
Zhu, C.-Y., Lee, T. M. C., Li, X.-S., Jing, S.-C., Wang, Y.-G., & Wang, K. (2007). Impairments of social cues recognition and social functioning in Chinese people with schizophrenia. *Psychiatry and Clinical Neurosciences*, *61*(2), 149–158.

Nederlandse samenvatting

Een groot deel van de patiënten met schizofrenie ondervindt problemen bij het begrijpen van gedrag, gedachten of intenties van andere mensen (i.e., sociale cognitie). Daardoor is het voor deze patiënten soms lastig om relaties aan te gaan of om een baan te behouden. Omdat dit de kwaliteit van leven negatief beïnvloedt is het belangrijk om te onderzoeken waar de problemen in sociale cognitie vandaan komen. Een belangrijk aspect van sociale cognitie is de manier waarop we onszelf waarnemen en begrijpen. Immers, hoe is het mogelijk om anderen te begrijpen wanneer wij onze eigen ervaringen en belevingen niet begrijpen?

Al in 1911 erkende Eugene Bleuler dat 'het zelf' nooit intact was bij patiënten met schizofrenie. Ook een meer recente wetenschappelijke visie gaat er vanuit dat zelf-stoornissen ten grondslag liggen aan de ziekte. Dergelijke stoornissen komen naar voren bij verschillende psychotische symptomen. Zo kunnen patiënten bijvoorbeeld het idee hebben dat iemand anders controle heeft over hun gedachten of bewegingen (i.e., beïnvloedingswanen) of dat zij invloed hebben op gebeurtenissen die zij met geen mogelijkheid kunnen sturen (i.e., grootheidswanen). De grens tussen zelf en anderen is hierbij vervaagd, wat het vormen en behouden van een stabiel zelfbeeld en sociale interactie bemoeilijkt.

De relatie tussen zelf en anderen

De literatuurstudie in hoofdstuk 2 beschrijft welke processen onderliggend zijn aan het vormen van een relatie tussen zelf en anderen en hoe deze processen mogelijk verstoord zijn bij patiënten met schizofrenie. De relatie tussen zelf en ander wordt in de literatuur op twee manieren bekeken: een deel van het onderzoek richt zich op het begrijpen van anderen in relatie tot onszelf en een deel richt zich op het begrijpen van onszelf in relatie tot anderen. Dit onderscheid wordt gehanteerd in hoofdstuk 2 en wordt hieronder toegelicht.

Bij processen die bijdragen aan het begrijpen van anderen is een rol weggelegd voor spiegelneuronen. Deze neuronen zijn actief wanneer we zelf een bepaalde actie uitvoeren, zoals het reiken naar een object, maar ook wanneer we observeren dat iemand anders deze actie uitvoert. Bij gezonde individuen zijn spiegelneuronen actiever tijdens zelf uitgevoerde acties vergeleken met het observeren van anderen die deze actie uitvoeren, waardoor een onderscheid tussen acties van zelf en anderen gemaakt kan worden. Echter, doordat dit verschil in activatie bij patiënten met schizofrenie kleiner is, draagt dit mogelijk bij aan verminderde differentiatie tussen zelf en anderen. Door deze verstoringen op motorisch niveau zijn patiënten meer afhankelijk van (misleidende) overtuigingen over gedrag en gedachten van anderen. Tezamen kan dit bijdragen aan een verminderd begrip van anderen (Theory Of Mind).

Daarnaast worden processen beschreven die betrekking hebben op het begrijpen van onszelf in relatie tot anderen. Het motorische systeem speelt hierbij een belangrijke rol. Het 'comparator model' legt uit dat wanneer we een actie uitvoeren (zoals het drukken op een knop) er kopieën worden opgeslagen van de verwachte motorische consequenties van

deze actie (vingers raken een knop). Omdat bij patiënten met schizofrenie deze motorische predictie verstoord is, zorgt dit voor problemen in het onderscheiden van eigen en andermans acties, oftewel het gevoel van zelf-causatie. Daarnaast hebben onnauwkeurige motorische predicties bij patiënten tot gevolg dat het maken van een onderscheid tussen zelf en ander in grotere mate wordt beïnvloed door *cognitieve* verwachtingen.

In de hoofdstukken 3 tot en met 6 wordt dieper ingegaan op zelf-stoornissen en de relatie tussen zelf en anderen. Twee concepten die hierbij een hoofdrol spelen, omdat zij sterk bijdragen aan het 'ik-gevoel', zijn het lichamelijk bewustzijn ('het is *mijn* hand dat naar een glas reikt') en het gevoel van zelf-causatie ('ik heb het gevoel dat *ik* ervoor zorg dat mijn hand naar een glas reikt'). Daarnaast wordt ingegaan op verminderde empatische vermogens bij patiënten, een belangrijke voorspeller van functioneren.

Lichamelijk bewustzijn ('body ownership')

Patiënten met schizofrenie hebben soms ervaringen waarbij de grenzen van het lichaam lijken vervaagd of waarbij lichaamsdelen niet eigen lijken. Echter, er zijn weinig empirische studies die kijken naar de herkomst van deze ervaringen. In hoofdstuk 3 wordt een studie beschreven waarbij ik het lichamelijk bewustzijn heb onderzocht met behulp van de Rubber Hand Illusie (RHI). In dit experiment worden een onzichtbare linkerhand en een zichtbare linker nephand aangeraakt met een zachte kwast om de illusie te creëren dat de nephand onderdeel van het eigen lichaam is. Uit dit onderzoek bleek dat patiënten met schizofrenie een sterkere subjectieve ervaring van de illusie hadden vergeleken met gezonde onderzoeksdeelnemers. Deze resultaten sluiten aan bij eerder onderzoek en bevestigen dat de integratie van sensorische informatie vanuit verschillende modaliteiten, ofwel 'multisensorische integratie', een proces onderliggend aan de RHI, verstoord lijkt te zijn bij patiënten. Daarnaast werd bevestigd dat de illusie mogelijk samenhangt met positieve symptomen bij patiënten, wat suggereert dat er sprake kan zijn van gedeelde onderliggende mechanismen.

Erfelijkheid speelt een grote rol bij de ontwikkeling van schizofrenie. Er is dan ook een groot aantal kenmerken van de ziekte dat gerelateerd is aan een familiair of genetisch risico op het ontwikkelen van de ziekte. Deze kenmerken, ofwel endofenotypes, kunnen gebruikt worden om in te schatten of een individu risico heeft op het ontwikkelen van een ziekte. Een tweede vraag die wordt behandeld in hoofdstuk 3 betreft de mogelijkheid dat de aanwezigheid van zelf-stoornissen een mogelijk endofenotype is voor schizofrenie. Omdat kinderen van patiënten met schizofrenie een verhoogde kans hebben op het ontwikkelen van deze ziekte, heb ik de uitkomsten van de RHI in deze populatie vergeleken met uitkomsten bij kinderen van patiënten met een bipolaire stoornis en kinderen zonder ouders met schizofrenie of een bipolaire stoornis. Ik vond geen verschillen tussen deze drie groepen, wat impliceert dat in deze studie geen bewijs werd gevonden voor een afwijkende RHI als endofenotype voor

schizofrenie. Echter, longitudinale data kan meer inzicht geven in dit onderwerp. Wanneer we in een later stadium weten welke individuen schizofrenie ontwikkelen, kan retrospectief worden gekeken of uitkomsten op de RHI een voorspellende waarde hebben.

Zelf-causatie ('self-agency')

Het gevoel van zelf-causatie is het gevoel dat we verantwoordelijk zijn voor onze eigen acties en de gevolgen ervan. Dit lijkt voor de meeste mensen erg vanzelfsprekend: je weet dat *jij* een blikje frisdrank uit een automaat hebt laten komen na het drukken op een knop en je weet dat *jij* ervoor hebt gezorgd dat er een geluid klinkt na het gebruiken van je fietsbel. Echter, er zijn ook situaties te bedenken wanneer dit gevoel iets minder vanzelfsprekend is. Neem bijvoorbeeld een situatie waarin jij en een vriend tegelijk een lichtknop indrukken en er een lamp aan gaat. De betrouwbaarheid van het gevoel van zelf-causatie is in dit geval verminderd, omdat er twee mogelijke verklaringen zijn voor het aangaan van de lamp.

Het gevoel van zelf-causatie kan op verschillende manieren tot stand komen. In dit proefschrift stond de rol van inferenties centraal. Afhankelijk van het soort gedrag kunnen twee vormen van inferenties van belang zijn. Ten eerste kan bij *doelgericht* gedrag een gevoel van zelf-causatie afgeleid worden van vooraf gestelde doelen. Wanneer het doel van een actie overeenkomt met de uitkomst van een actie, treed een gevoel van zelf-causatie op. Ten tweede, bij *niet-doelgericht* gedrag kan dit gevoel worden afgeleid van impliciete informatie over de uitkomsten van een actie. Hierbij geldt hetzelfde principe: wanneer deze informatie over een uitkomst overeenkomt met de daadwerkelijke uitkomst, ontstaat een gevoel van zelf-causatie.

Uit eerder onderzoek is gebleken dat patiënten met schizofrenie niet effectief gebruiken van de impliciete informatie bij de totstandkoming van het een gevoel van zelf-causatie. Omdat een groot deel van ons sociale gedrag niet doelgericht is, en dus afhankelijk is van impliciete informatie, zou dit mede kunnen verklaren waarom patiënten met schizofrenie problemen ondervinden in sociale informatieverwerking. Daarom gaan de hoofdstukken 4 en 5 dieper in op de afwijkende impliciete informatieverwerking bij de totstandkoming van het gevoel van zelf-causatie.

Relatie tussen zelf-causatie, neurocognitief functioneren en attributiestijl

Het gevoel van zelf-causatie wordt niet alleen door impliciete informatie beïnvloed, maar tal van andere factoren kunnen daarnaast een rol spelen. In hoofdstuk 4 beschrijft een onderzoek naar twee mogelijke factoren. Ten eerste werd onderzocht of verminderde neurocognitieve functies bij patiënten kunnen verklaren waarom zij de impliciete informatie niet effectief gebruiken om tot een gevoel van zelf-causatie te komen. De afwezigheid van een relatie tussen het gebruik van impliciete informatie en neurocognitieve functies bevestigt de hypothese dat de invloed van impliciete informatie op zelf-causatie een automatisch proces is.

Daarnaast is het concept van zelf-causatie gerelateerd aan attributiestijl, oftewel een algemene neiging om gevolgen van gedrag te verklaren in termen van interne of externe oorzaken. Eerdere studies toonden aan dat patiënten een afwijkende attributiestijl hadden. Daarom toetst het onderzoek beschreven in hoofdstuk 4 of dit de verminderde efficiëntie in het gebruik van impliciete informatie in de totstandkoming van een gevoel van zelf-causatie kan verklaren. Een dergelijk verband werd echter niet gevonden. Dit suggereert dat de onderliggende processen die gemeten zijn met de zelf-causatie taak in de huidige studie wellicht niet direct betrekking hebben op algemene ervaringen van causatie in het dagelijks leven. Concluderend, hoewel de bevindingen laten zien dat er op cognitief niveau veranderingen zijn, blijft het onduidelijk wat ervoor zorgt dat patiënten impliciete informatie minder effectief gebruiken om tot een gevoel van zelf-causatie te komen.

Relatie tussen het gevoel van zelf-causatie en psychotische symptomen

Het is niet verrassend dat het gevoel van zelf-causatie veel is onderzocht bij patiënten met schizofrenie, omdat psychotische symptomen waarbij dit gevoel een rol speelt vaak aanwezig zijn bij patiënten met schizofrenie. Patiënten kunnen ervaringen hebben die gerelateerd zijn aan zowel een overmatig gevoel van zelf-causatie (i.e., overattributie van zelf-causatie; bij grootheidswanen, schuldwanen of betrekkingswanen) als een verminderd gevoel van zelf-causatie (i.e., onderattributie van zelf-causatie; bij beïnvloedingswanen, gedachteninbrenging, gedachtenonttrekking of auditieve (verbale) hallucinaties). Hoofdstuk 5 beschrijft een studie waarin wordt onderzocht hoe impliciete informatieverwerking onderliggend aan het gevoel van zelf-causatie samenhangt met deze symptomen. Resultaten suggereren dat symptomen van onder- en overattributie niet gerelateerd zijn aan veranderingen in impliciete informatieverwerking bij het gevoel van zelf-causatie. In hoofdstuk 5 worden andere mogelijke verklaringen voor de symptomen met betrekking tot over- en onderattributie besproken.

Het gevoel van zelf-causatie en familiair risico

Eerder onderzoek suggereerde dat zelf-stoornissen mogelijk een endofenotype voor schizofrenie zijn. Daarom onderzoekt de studie in hoofdstuk 5 of verminderde efficiëntie van het gebruik van impliciete informatieverwerking bij de totstandkoming van een gevoel van zelf-causatie een mogelijk endofenotype kan zijn. De resultaten laten zien dat broers en zussen van patiënten hoger scoren dan gezonde controles en lager dan patiënten, maar dat deze verschillen geen statistische significantie bereiken. Een belangrijk punt bij de interpretatie van deze resultaten is dat het gebruik van een kleine steekproef van broers en zussen van patiënten heeft geleid tot onvoldoende statistische power. Samenvattend, uit de huidige resultaten kan niet geconcludeerd worden dat verminderde efficiëntie van het gebruik van impliciete informatieverwerking bij de totstandkoming van een gevoel van zelf-causatie een endofenotype is.

Empathie

Empathie is een onderwerp dat uitgebreid is onderzocht bij patiënten met schizofrenie. Doorgaans wordt daarbij onderscheid gemaakt tussen cognitieve en affectieve empathie. Terwijl cognitieve empathie gaat over het begrijpen van andermans *gedachten* en *intenties*, gaat affectieve empathie over het begrijpen van andermans *emoties*. Eerdere studies vonden dat patiënten in beide domeinen veranderingen lieten zien en dat dit een relatie heeft met de mate van sociaal functioneren.

Het begrijpen en interpreteren van anderen wordt volgens de 'simulatie-theorie' gevormd door kennis over ons zelf. Daarom beschrijft hoofdstuk 6 een studie waarin wordt onderzocht of zelf-stoornissen een relatie hebben met empathische vermogens bij patiënten en gezonde personen. Dit heb ik bekeken door hersenactiviteit bij onderzoeksdeelnemers te meten terwijl op zichzelf reflecteerden. Daarnaast heb ik cognitieve en affectieve empathische vermogens getest.

Vergeleken met gezonde controles rapporteerden patiënten met schizofrenie meer affectieve empathie na het zien van een filmfragment. Zij gaven daarbij aan zowel meer positieve (bijvoorbeeld 'warmte' of 'sentimenteel') als negatieve (bijvoorbeeld 'verdrietig'of 'overstuur') emoties te ervaren. Omdat met name verhoogde affectieve empathie met betrekking tot negatieve emoties ervoor kan zorgen dat patiënten sociale situaties ontwijken, is dit een relevante bevinding.

Een tweede belangrijke bevinding in deze studie is dat bij patiënten een relatie werd gevonden tussen verhoogde affectieve empathie en verminderde brein activatie in de temporo-pariëtale cortex/gyrus angularis tijdens zelfreflectie. Eerder onderzoek toonde aan dat deze hersengebieden zijn betrokken bij het onderscheid maken tussen zelf en anderen. De resultaten uit de huidige studie suggereren daardoor dat de verminderde breinactivatie in deze gebieden mogelijk een verklaring geeft voor verhoogde affectieve empathie bij patiënten.

Conclusie

Het onderzoek dat werd beschreven in dit proefschrift draagt bij aan onze kennis over zelf-stoornissen bij patiënten met schizofrenie. In dit onderzoek is, in plaats van vragenlijsten, gebruik gemaakt van experimentele methodes om onderliggende cognitieve processen van deze stoornissen in kaart te brengen. Het onderzoek werd niet alleen uitgevoerd bij patiënten en gezonde controles, maar ook bij populaties met een verhoogd familiair risico op het ontwikkelen van schizofrenie. De aanwezigheid van zelf-stoornissen bij schizofrenie werd bevestigd en een volgende stap werd gezet in het begrijpen van het gevoel van zelf-causatie. Het beschreven werk stimuleert verder onderzoek naar de gedragsmatige en klinische relevantie van stoornissen in zelfperceptie.

Dankwoord
List of publications
Curriculum Vitae

10

Dankwoord

Meteen na mijn master kreeg ik de kans om te promoveren op de afdeling psychiatrie van het UMCU. Ik heb hier ontzettend veel geleerd, waardevolle contacten opgedaan en nieuwe vrienden gemaakt. In de afgelopen vijf jaar heeft een groot aantal mensen mij geholpen bij de totstandkoming van dit proefschrift en bij mijn persoonlijke ontwikkeling en deze mensen wil ik dan ook graag via deze weg bedanken voor hun bijdrage.

Allereerst, veel dank aan mijn promotors en co-promotor: **prof. dr. Neeltje van Haren, prof. dr. Henk Aarts en dr. Anouk van der Weiden.**

Neeltje, wat was ik blij dat ik in jouw onderzoeksgroep was aangenomen! Ik heb ontzettend veel van jou geleerd. Jij leerde me alle ins en outs van het wetenschappelijk onderzoek en liet me ondertussen vrij in het vormgeven van mijn eigen stukje binnen jouw project. Naast de inhoudelijke kennis die je aan me hebt overgedragen heb ik ook veel geleerd van jouw manier van leiding geven. Jij weet mensen op een heel natuurlijke manier op hun gemak te stellen, te enthousiasmeren en motiveren, wat er voor zorgt dat er altijd een goede sfeer is als jij er bent. Daarnaast waardeer ik ontzettend hoe je altijd open stond voor mijn wens om me naast de wetenschap ook op klinisch gebied te ontwikkelen. Dankjewel dat je me de kans hebt gegeven in jouw onderzoeksgroep te promoveren. Door jou heb ik een mooie start in mijn carrière kunnen maken!

Henk, dankzij jouw kritische blik wist je mijn ideeën altijd uit te dagen en wist je me aan het denken te zetten. Jij weet hoe je mensen het beste uit zichzelf kunt laten halen. Daarnaast heb ik mede dankzij jou mijn statistische kennis flink uitgebreid. We hadden vaak interessante discussies over de verschillen tussen wetenschappelijk onderzoek binnen de psychologie en psychiatrie, welke ertoe hebben geleid dat ik in mijn proefschrift deze twee disciplines heb kunnen samenbrengen.

Anouk, vanaf het moment dat ik in het UMCU werkte heb ik altijd tegen je op gekeken. Door de passie waarmee jij aan wetenschappelijk onderzoek werkte wist je me te enthousiasmeren voor jouw ideeën. Door onze verschillende achtergronden leek het bij het schrijven van ons review soms alsof we een andere taal spraken, maar dit werkte uiteindelijk in ons voordeel en heeft tot een prachtig eindresultaat geleid. Ik heb ontzettend veel van je geleerd op het gebied van wetenschappelijk schrijven, statistiek en het opzetten van studies. Ontzettend veel dank voor je betrokkenheid!

Prof. dr. Kahn, ik wil u bedanken voor de periode waarin u mijn promotor bent geweest en voor de kans om onderzoek te doen op uw afdeling. De grote hoeveelheid kennis en expertise op deze afdeling hebben mij tot een betere onderzoeker gemaakt. Bedankt voor de samenwerking in de afgelopen jaren en ik wens u veel succes toe in New York.

Veel dank gaat uit naar de beoordelingscommissie van mijn promotie: **prof. dr. Chris Dijkerman, prof. dr. Wiepke Cahn, prof. dr. Iris Sommer, prof. dr. André Aleman en dr. Martine van Zandvoort.** Bedankt voor de tijd die jullie hebben vrijgemaakt om mijn werk te lezen en beoordelen.

Voor het superviseren van mijn werk wil ik nog een aantal mensen bedanken: **dr. Matthijs Vink, prof. dr. Manon Hillegers, prof. dr. Iris Sommer en dr. Tamar van Raalten**.

Matthijs, ontzettend veel dank voor alles wat je me geleerd hebt over functionele MRI. Jij hebt me een kijkje gegeven in de wereld van het programmeren en wist me op de juiste manier handvatten te geven om hiermee aan de slag te gaan. De meetings met jou waren, naast dat ze leerzaam waren, ook altijd gezellig. Voor een dosis goede humor kon ik altijd bij je terecht. Wat vond ik het dan ook jammer dat je het UMCU inruilde voor de UU! Gelukkig bleef onze samenwerking bestaan en heb ik mede dankzij jou een mooi fMRI-paper kunnen schrijven. Dankjewel!

Manon, bedankt voor de prettige samenwerking tussen onze onderzoeksgroepen. Ik vond het erg leerzaam om ons werk te integreren in het BRIDGE-onderzoek. Daarnaast heb je me veel geleerd over diagnostiek bij de kwetsbare jongerenpopulatie waarmee je werkt. Ik kijk op naar de manier waarop je onderzoek en kliniek combineert en ik weet zeker dat je in Rotterdam het succes van jouw werk zult voorzetten.

Iris, ik heb het afgelopen jaar met heel veel plezier in jouw onderzoeksgroep gewerkt. Ik ben onder de indruk van alle projecten waar je mee bezig bent en de vele ideeën die je hebt. Dankjewel dat je me de kans hebt gegeven om in een post-doc functie mee te werken aan een website over cognitieve stoornissen en herstel. Ik twijfel er niet over dat je vanuit Groningen deze website tot een succes weet te maken!

Tamar, dankzij jou heb ik tijdens mijn promotie mijn klinische vaardigheden nog verder kunnen ontwikkelen. Bedankt voor deze waardevolle ervaring, welke zeker goed van pas gaat komen in mijn verdere carrière. Esther Mesman, ook jou wil ik in dit kader hartelijk bedanken!

Daarnaast wil ik natuurlijk de ruim 200 deelnemers van ons onderzoek bedanken. Zonder hun bereidwilligheid en openheid had dit onderzoek niet kunnen bestaan.

Paranimfen **Judith en Sonja,** jullie mentale support richting de afronding van het proefschrift is natuurlijk onmisbaar geweest! Ook vond ik het ontzettend fijn dat we onze dagelijkse promotieperikelen en -successen hebben kunnen delen op de kantoortuin. Tot mijn grote vreugd zorgde jullie komst op ons kantoor voor nog meer lol, meer geklets over planten en pizza's en meer vrijdagmiddagborrels. Judith, bedankt voor alle fijne gesprekken tijdens onze wandelingetjes, je betrokkenheid en je hulp bij mijn fMRI-analyses. Jouw oprechtheid en droge humor maken jou tot een fantastisch mens! Sonja, ik heb genoten van je opgewekte

humeur en daarbij behorende lach en onze geweldige mini-roadtrip rond San Diego. Ik hoop dat we elkaar blijven zien in Amsterdam!

Martijn, wij kennen elkaar al sinds mijn sollicitatie bij SCIP en ik heb met heel veel plezier met je samengewerkt. Mede door de combinatie van jouw technische en mijn klinische kennis hebben we ons onderzoek tot een succes weten te maken. Sorry dat ik niet altijd meewerkte wanneer je moeilijke namen van onze stagiaires moest onthouden ;) Bedankt voor alles wat je me geleerd hebt over imaging, maar ook voor je enthousiasme, random wist-je-datjes, de baksels van Christine en gezelligheid tijdens alle tripjes naar congressen in Florence en de VS.

Heel veel dank aan al mijn kamergenoten van KT1 in de afgelopen jaren: **Judith, Sonja, Martijn, Bart, Jessica, Pascal, Marc, Jalmar, Thalia en Sven**. Zonder jullie was het een stuk minder gezellig geweest! Bart, speciale dank aan jou voor alle goede muziek die je met me hebt gedeeld en voor je huisgebrouwen biertjes die we mochten testen. Pascal, bedankt voor al je hulp bij imaging-vragen!

Ruby, ik leerde jou in één van mijn eerste weken in het UMCU kennen bij de k-sads training en daarna heb ik een aantal jaren met heel veel plezier met je mogen samenwerken. Ik ben ontzettend blij dat jij er was deze jaren, want jij wist me er doorheen te slepen als het even niet mee zat en ik kon altijd bij je terecht voor een goed gesprek en gezelligheid. Ik vond het dan ook ontzettend jammer dat je het UMCU verliet, maar het was een leuke tijd!

Philippine, onze samenwerking bij SCIP verliep altijd vlekkeloos, omdat we altijd op één lijn zaten. We waren een ontzettend goed team en ik waardeer wat je voor ons onderzoek hebt betekend. Bedankt voor alle leuke momenten, gesprekken, de lol die we hadden en de gezonde lunches samen!

Dan wil ik ook graag oud-collega's van het SCIP onderzoek bedanken: **Natascha, Robert, Myrthel en Jet**. Natascha, heel veel dank voor je inzet voor het onderzoek en voor de manier waarop je alles hebt georganiseerd de afgelopen jaren. Robert en Myrthel, van jullie kreeg ik mijn eerste lessen over self-agency en sociaal psychologische experimenten. Bedankt dat ik hiervoor altijd bij jullie terecht kon en voor alles wat jullie me hierover hebben geleerd.

Wie niet in dit rijtje mogen ontbreken zijn alle **stagiaires** die hebben meegewerkt om het onderzoek tot een succes te maken. Zonder jullie hulp was het niet mogelijk geweest om alle onderzoeksdeelnemers binnen afzienbare tijd te zien. Veel dank voor jullie interesse, motivatie en betrokkenheid.

Nikita en Heleen, bedankt voor de fijne samenwerking tussen onze onderzoeksgroepen. Tijdens onze gezamenlijke meetings heb ik veel geleerd over jongeren met een kwetsbaarheid voor het ontwikkelen van psychopathologie. Daarnaast wil ik jullie bedanken voor alle gezellige momenten tijdens borrels, feestjes en meetings. Nikita, ik vind het ontzettend knap hoe je de coördinatie van het grote BRIDGE-onderzoek, de begeleiding van stagiaires en je PhD weet te combineren. Heleen, ik vond het erg leuk dat je als één van onze eerste stagiaires bij het SCIP-onderzoek doorstroomde naar de functie van research assistant bij BRIDGE. Bedankt voor je bijdrage aan mijn artikel over de rubber hand illusie!

Met veel plezier heb ik het afgelopen jaar in de onderzoeksgroep van Iris Sommer mogen werken. **Marieke B., Maya, Mascha, Janna, Igne, Meenakshi, Sanne SK, Alban, Jasper, Jantina, Lyliana, Ilse, Hidde en Priscilla**, bedankt dat ik in jullie groep werd opgenomen alsof ik er al jaren bij hoorde. Marieke, dankzij jouw lessen over het uitvoeren van meta-analyses heb ik het afgelopen jaar een mooi paper kunnen schrijven. Janna, in recordtempo publiceerden wij samen een meta-analyse, en met succes! Dankjewel voor de samenwerking hierin.

Tijdens onderzoeksoverleggen, congressen, de Zandvoortdagen, vrijdagmiddagborrels, summer schools en andere bijeenkomsten heb ik ook andere collega's van de afdeling psychiatrie leren kennen. **Elizabeth, Anna, Joyce, Sanne V, Lucija, Annabel, Lieke H, Hans, Remmelt, Kim, Branko, Caitlyn, Jan, Chantal, Ania, Iris en Dorinde**, bedankt!
Marieke H. en Anouk, bedankt voor de fijne samenwerking bij het geven van de Circuits training. Ik wens jullie heel veel succes bij het afronden van jullie studie!
Paula, veel dank voor je hulp bij het werven van onze onderzoeksdeelnemers.
Tjen, Mirjam en Janneke, bedankt voor al jullie secretariële ondersteuning!

Ook mijn lieve vrienden en vriendinnen **Marlie, Sanne, Marie-Anne, Elvira, Marielle, Andrea, Anne-Gerlin, Femke, Lieke OV, Jessie, Janita, Anne, Marloes, Ruben** en **Marten,** jullie wil ik ontzettend bedanken voor jullie betrokkenheid bij mijn promotie en alle leuke weekenden en avonden vol gezelligheid! **Iris B**, uiteraard een speciaal bedankje naar jou voor het ontwerpen van de voorkant van mijn proefschrift. Met je opleiding tot allround stylist op het gebied van mode, interieur en media was jij hier natuurlijk de aangewezen persoon voor ;) Ik ben blij dat we elkaar nog steeds zien en samen kunnen lachen, gieren en brullen! **Annemarie**, bedankt voor de gezelligheid tijdens congressen en ons tripje naar New York. Hopelijk blijven we elkaar tegenkomen!

Marc, Dian, Tim, Bas, Puck, Evelyn en Nicky, bedankt voor jullie betrokkenheid en interesse in wat ik doe. Ik voel me altijd welkom bij jullie en geniet van de gezelligheid tijdens avondjes samen en niet te vergeten de wintersport!

Lieve **papa en mama**, bedankt voor het oneindige vertrouwen dat jullie altijd in mij hebben gehad. Jullie stimuleerden mij om zelf keuzes te maken en hebben mij hier altijd vrij in gelaten. Dit, samen met jullie onvoorwaardelijke steun, hebben ervoor gezorgd dat ik kan doen wat ik nu doe. Ik ben ontzettend blij met jullie als ouders!
Loes, lieve zus, dankjewel voor alles! Ik geniet van onze goede gesprekken en de lol die we samen hebben. Dat we dezelfde stem, hetzelfde lachje en dezelfde maniertjes hebben maakt ons echte zussen ;) Ik wens jou en **Willem** al het geluk van de wereld toe.
Oma, ontzettend bedankt dat je altijd zo trots op mij bent en interesse hebt in alles wat ik doe. Ik ben blij met een oma zoals jij!

Lieve **Koen**, wat ben ik blij dat ik jou heb ontmoet! Jouw vrolijkheid en positiviteit maken mij iedere dag heel gelukkig. Ook als het leven eventjes geen ponykamp was de afgelopen jaren wist jij me altijd weer op te vrolijken met één van je ijzersterke grappen, oneliners of zelfbedachte spreekwoorden. Bedankt dat ik bij jou altijd mezelf kan zijn en ik hoop dat we samen nog veel mooie avonturen gaan beleven!

List of publications

Published

Prikken, M., van der Weiden, A., Kahn, R.S., Aarts, H., & van Haren N.E.M. (2018) Impaired self-agency inferences in schizophrenia: the role of cognitive capacity and causal reasoning style. *European Psychiatry, 47,* 27-34

De Boer, J., **Prikken, M.**, Lei, W.U., Begemann, M.J.H., & Sommer, I.E.C. (2018) The effect of raloxifene augmentation in men and women with a schizophrenia spectrum disorder: a systematic review and meta-analysis. *NPJ Schizophrenia, 4*(1), 1

Prikken, M., van der Weiden, A., Renes, R.A., Koevoets, M.G.J.C., Heering, H.D., Kahn, R.S., Aarts, H., & van Haren, N.E.M. (2017). Abnormal agency experiences in schizophrenia patients: the role of psychotic symptoms and familial risk. *Psychiatry Research, 250,* 270-276

Renes, R.A., Vink, M., van der Weiden, A., **Prikken, M.**, Koevoets, M.G.J.C., Kahn, R.S., Aarts, H., & van Haren, N.E.M. (2016). Impaired frontal processing during agency inferences in schizophrenia. *Psychiatry Research: Neuroimaging, 248,* 134-141

van der Weiden, A., Aarts, H., **Prikken, M.**, & van Haren, N.E.M. (2016). Individual differences in action co-representation: not personal distress or subclinical psychotic experiences but sex composition modulates joint action performance. *Experimental Brain Research, 234*(2), 499-510

van der Weiden A., **Prikken M**., & van Haren N.E.M. (2015). Self-other integration and distinction in schizophrenia: A theoretical analysis and a review of the evidence. *Neuroscience and Biobehavioral Reviews*, *57.* 220-237

Renes, R.A., van der Weiden, A., **Prikken, M.**, Kahn, R.S., Aarts, H., & van Haren, N.E.M. (2015). Abnormalities in the experience of self-agency in schizophrenia: A replication study. *Schizophrenia Research, 164*(1), 210-213

In preparation

Prikken, M., van der Meer, L., Koevoets, M.G.J.C., den Bleijker, N.M., Vink, M., van der Weiden, A., Kahn, R.S., Aarts. H., & van Haren, N.E.M. The role of the self-reflection network in cognitive and affective empathy in schizophrenia and healthy individuals *(under review)*

Prikken, M., van der Weiden, A., Baalbergen, H., Hillegers, M.H.J., Kahn, R.S., Aarts, H., van Haren N.E.M. Multisensory integration underlying body ownership experiences in schizophrenia and individuals at high risk to develop psychosis: a study using the rubber hand illusion paradigm *(under review)*

Prikken, M., Konings, M.J, Lei, W.U., Begemann, M.H.J., Sommer, I.E.C. The efficacy of computerized cognitive drill and practice training for schizophrenia: a meta-analysis *(in revision)*

Sinkeviciute, I., Begemann, M.J.H., **Prikken, M.**, Oranje, B., Johnsen, E., Lei, W.U., Hugdahl, K., Kroken, R., Rau, C., Jacobs, J., Mattaroccia, S., Sommer, I.E.C. Efficacy of different types of cognitive enhancers for patients with schizophrenia-spectrum disorders; a meta-analysis *(in revision)*

Koevoets, M.G.J.C., Hagenaar, D., **Prikken, M.**, van Haren, N.E.M. White matter differences related to emotion recognition, contagion, and their interaction *(in preparation)*

Koevoets, M.G.J.C., de Nijs, J., **Prikken, M.**, Kahn,R.S., Cahn, W., van Haren, N.E.M. White and grey matter modalities integration in schizophrenia in relation to emotion *(in preparation)*

Koevoets, M.G.J.C., de Nijs, J., **Prikken, M.**, Kahn, R.S., Cahn, W., van Haren, N.E.M. Micro to macro level of white and grey matter modalities integration in schizophrenia *(in preparation)*

Curriculum Vitae

Merel Prikken was born on November 19th in Havelte. After she finished her secondary education at C.S.G. Dingstede in Meppel she started studying psychology in 2007 at Groningen University. During her bachelor she became interested in neuropsychology. Therefore, after finishing her bachelor's degree in 2010 she started a master in neuropsychology at Groningen University. During a research internship at the NeuroImaging Center of the University Medical Center Groningen she developed an interest in psychiatry, particularly in schizophrenia. During this internship she studied the neural effects (using functional MRI) of an intervention that aims to improve insight in schizophrenia. During her master Merel also completed a master's honours program (focused on leadership) and was active as a board member of the study association of psychology. After finishing her master's degree in 2013 she started her PhD at the department of psychiatry of the University Medical Center Utrecht. Under supervision of prof. dr. Van Haren, prof. dr. Aarts, and dr. Van der Weiden she studied self-disturbances and social cognition in patients with schizophrenia. In 2017 Merel combined her work as a PhD-student with a research position in Iris Sommer's lab at the same department. In this lab she focused on improving neurocognitive functioning in patients with schizophrenia and other brain diseases. Currently, Merel is working as a psychologist at GGZ Ingeest in Amsterdam.

Brain Center Rudolf Magnus

Universiteit Utrecht

ISBN 978-94-6299-957-2