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The effects of aging on insight into illness in schizophrenia: a review†

Philip Gerretsen, **Eric Plitman**, **Tarek K. Rajji**, and **Ariel Graff-Guerrero**

University of Toronto and the Centre for Addiction and Mental Health, Toronto, ON Canada

Abstract

Objectives—Impaired insight into illness is a prevalent feature of schizophrenia, which negatively influences treatment adherence and clinical outcomes. Little is known about the effects of aging on insight impairment. We aimed to review the available research literature on the effects of aging on insight into illness in schizophrenia, in relation to positive, negative, and cognitive symptoms. Ultimately, we propose a trajectory of insight in schizophrenia across the lifespan.

Method—A systematic Medline® literature search was conducted, searching for English language studies describing the relationship of insight into illness in schizophrenia with aging.

Results—We identified 62 studies. Insight impairment is associated with illness severity, premorbid intellectual function (i.e. IQ), executive function, and memory. Insight impairment improves modestly during midlife, worsening again in late life. It tends to fluctuate with each episode of psychosis, likely in relation to worsening positive symptoms that improve with antipsychotic treatment. The relationship between insight impairment and cognitive dysfunction appears to attenuate with age, while the relationship with lower premorbid intellectual function is preserved. The association between impaired insight and negative symptoms is unclear.

Conclusions—The available literature suggests that the course of insight impairment follows a U-shaped curve, where insight impairment is severe during the first episode of psychosis, modestly improves over midlife, and declines again in late life. Future studies are required to investigate the trajectory of insight into illness and its core domains across the lifespan from prodromal phase to late life.

Keywords

age; aging; insight; schizophrenia; illness awareness; denial

Introduction

Schizophrenia is a chronic brain disorder characterized by impaired insight into illness. Insight into illness is recognized as a multidimensional construct consisting of having

†Names of the institutions at which the research was conducted: Centre for Addiction and Health and University of Toronto.

Correspondence to: P. Gerretsen, MD, MSW, FRCPC, philgerretsen@yahoo.com; philip.gerretsen@camh.ca.

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awareness of a mental disorder, its symptoms, its implications, and need for treatment (David, 1990; Lincoln *et al*., 2007). Moderate-to-severe insight impairment occurs in over 50% of patients with schizophrenia (Amador *et al*., 1994; Schwartz *et al*., 1997) and is associated with medication non-adherence and poor clinical and functional outcomes (Amador *et al*., 1994; Schwartz, 1998b; Lysaker *et al*., 2002; Smith *et al*., 2002; Buckley *et al*., 2007; Saravanan *et al*., 2010; Segarra *et al*., 2012). Moreover, impaired insight has limited responsiveness to pharmacological and psychological interventions, including cognitive behavioral therapy (CBT) and psychoeducation (Mojtabai *et al*., 1998; Pijnenborg *et al*., 2013). Although the significance of insight into illness is evident, it is poorly understood. Recently, insight into illness in schizophrenia has received more attention in the research literature (Mintz *et al*., 2003; Ouzir *et al*., 2012). Yet, despite the increasing number of older patients with schizophrenia (Cohen *et al*., 2000), the effects of aging on insight impairment, and to an even lesser degree, its role in late life, remain largely unexplored.

Insight into illness in schizophrenia appears to fluctuate with illness severity, worsening with an acute psychotic episode and improving with treatment and recovery (Schwartz, 1994; Weiler *et al*., 2000; Wiffen *et al*., 2010b; Parellada *et al*., 2011; Comparelli *et al*., 2013; Koren *et al*., 2013). Impaired insight is independently associated with illness severity and cognitive function, namely executive function, premorbid intellectual function (i.e. IQ), memory, and to a lesser degree, attention (Mintz *et al*., 2003; Aleman *et al*., 2006; Shad *et al*., 2006; Orfei *et al*., 2008; De Hert *et al*., 2009; Mohamed *et al*., 2009; Trevisi *et al*., 2012; Gerretsen *et al*., 2013b, 2013a; Mingrone *et al*., 2013). Positive symptoms attenuate and cognitive function appears to decline with age, while the effects of aging on negative symptoms are mixed (Cohen *et al*., 2000, 2008; Rajji and Mulsant, 2008; Rajji *et al*., 2013). As such, one's insight into illness may change as a function of the aging process.

The aims of this review are to discuss the following: (1) the multidimensional construct of insight into illness in schizophrenia; (2) the explanatory models of insight into illness and their relation to aging; (3) the effects of aging on the course of schizophrenia, in terms of the interaction among insight into illness and positive, negative, and cognitive symptoms; (4) the effects of episode of psychosis on changes in insight into illness; (5) the influence of phase of illness on insight into illness; (6) a proposed trajectory of insight into illness in schizophrenia across the lifespan; and (7) future directions.

Methods

A systematic Medline® literature search (1949–December 2013) was conducted, searching for English language case reports, studies, or reviews describing the relationship of insight into illness in schizophrenia with aging. The search was performed using the terms “schizophrenia” or “psychotic disorders” and “aging” or “age” (“age of onset” OR “Age factors” OR “Age distribution”), which were cross-referenced with the terms “insight,” “illness awareness,” “denial,” “awareness,” “anosognosia,” and “agnosia.” All MeSH terms were explored, and all subheadings were included. Reference sections were gleaned for relevant articles overlooked by the search strategy.

Results

This search identified 83 publications. All of the titles or abstracts were read by two of the authors (P. G. and E. P.), and 28 relevant papers were selected and reviewed. We identified an additional 57 articles from reviewing cited and citing articles. We retained all studies (n = 62) that reported on insight impairment in schizophrenia spectrum disorders and aging. The data are summarized in Table 1. The majority of cross-sectional studies did not find an association between insight into illness and age; however, results from the few longitudinal studies were mixed.

Insight into illness in schizophrenia: a multidimensional construct

Insight into illness in schizophrenia has evolved from the dichotomous notion of being "present" or "not present" to a multidimensional construct that exists on a continuum (David, 1990). There are several different definitions of insight into illness, and although not exactly alike, they generally share their acknowledgement of four core domains: (1) awareness of having a severe brain disorder; (2) awareness and appropriate attribution of symptoms to mental illness; (3) acceptance of the need for treatment, most commonly with an antipsychotic medication; and (4) awareness of social, occupational, legal, or other negative consequences attributable to the mental disorder (David, 1990; Orfei *et al*., 2008). Intriguingly, awareness in one domain does not ensure awareness in another domain (Bota *et al*., 2006).

A number of instruments are available for the quantitative measurement of insight into illness and its domains, including single-item measures that provide a global assessment of insight into illness and multiple-item measures that can be divided into clinician-rated (McEvoy *et al*., 1989; Amador and Strauss, 1990; David, 1990; Medalia and Thysen, 2008) and self-report scales (Markova and Berrios, 1992; Selten *et al*., 1993; Birchwood *et al*., 1994; Hayashi *et al*., 1999; Marks *et al*., 2000; Beck *et al*., 2004).

Explanatory models of impaired insight in schizophrenia

There are generally four explanatory models of impaired insight into illness in schizophrenia: (1) psychological; (2) cognitive or neuropsychological; (3) clinical/psychopathological; and (4) neuroanatomical. A fifth, (5) lack of information/education, may also play an influential role in illness awareness deficits in patients with schizophrenia.

According to the (1) psychological model, impaired insight into illness, or illness denial, serves as a defense mechanism that acts as a coping strategy for the emotional consequences of acknowledging a severe mental illness (McGlashan and Carpenter, 1976; Moore *et al*., 1999). Although results are mixed, some research has shown that greater insight into illness is associated with hopelessness, lower self-esteem, depression, and suicidal ideation, along with other negative effects (Carroll *et al*., 1999, 2004; Cunningham Owens *et al*., 2001; Drake *et al*., 2004; Cooke *et al*., 2007a, 2007b). This model of illness denial appears to be applicable across the lifespan with arguably greater influence in the early phases of schizophrenia, where there exists the strongest risk for depression and suicide in relation to developing insight into illness (Melle and Barrett, 2012).

The (2) cognitive/neuropsychological model suggests that an underlying cognitive dysfunction mediates impaired insight. The greatest evidence in support of this theory is the association between insight impairment and executive dysfunction, especially set-shifting, as measured by the Wisconsin Card Sorting Test or Trail Making Test B, and lower premorbid intellectual function (Young *et al*., 1993; Lysaker and Bell, 1994; Keshavan *et al*., 2004; Aleman *et al*., 2006; Shad *et al*., 2006; Nair *et al*., 2014). Impaired insight, according to this model, is thought to result from mental rigidity, faulty error monitoring, and the inability to entertain alternative hypotheses for the etiology of delusional experiences. Memory and attention deficits have also been associated with impaired insight (Voruganti *et al*., 1997; Keshavan *et al*., 2004; Nair *et al*., 2014). The effects of aging on cognition will be discussed later (*see* Section on Aging, cognitive function, and insight into illness).

The related construct of “cognitive insight” proposes that one's degree of self-certainty and self-reflectiveness dictate one's capacity for illness awareness (Beck *et al*., 2004). Studies on the whole suggest that cognitive insight explains at most a modest portion of the variance of insight into illness (Pedrelli *et al*., 2004; Warman *et al*., 2007; Uchida *et al*., 2009b; Greenberger and Serper, 2010; Nair *et al*., 2014). To understand this, individuals with schizophrenia may have significant rigidity about their illness beliefs, but relatively preserved mental flexibility and self-reflectiveness in other domains.

The (3) clinical/psychopathological model considers impaired insight to be a product of the severity of one's clinical psychopathology, in particular positive symptoms (Cuesta and Peralta, 1994; Collins *et al*., 1997; Cuesta *et al*., 2006). More frequent, intense hallucinations, greater delusional severity, and duration of untreated psychosis lead to greater insight impairment (Sevy *et al*., 2004; Parellada *et al*., 2011) (see Section on Aging, Positive Symptoms, and Insight into Illness).

The (4) neuroanatomical model posits that structural alterations underlie insight impairment. Anosognosia or impaired illness awareness can occur with right hemisphere brain lesions secondary to stroke, traumatic brain injury, and dementia (Orfei *et al*., 2008). To explain the role of the right hemisphere in illness awareness, the cerebral hemispheres are thought to serve distinct functions when confronted with discrepant cognitive or sensory stimuli (Ramachandran *et al*., 2007). Impaired illness awareness in these contexts is thought to arise from interhemispheric imbalance and serves as a model for understanding impaired insight in other neuropsychiatric disorders, such as schizophrenia (Ramachandran, 1995; Ramachandran *et al*., 2007; Shad *et al*., 2007).

Volume-based analyses using a region of interest approach support the neuroanatomical model of impaired insight by reporting reduced right hemisphere volume in the right frontal lobe, including the orbitofrontal cortex, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortices (Flashman *et al*., 2001; Shad *et al*., 2004, 2006), and the right parietal lobe (Shad *et al*., 2007). However, voxel-based morphometry studies using a whole brain approach have produced mixed results (Ha *et al*., 2004; Bassitt *et al*., 2007; Cooke *et al*., 2008; Morgan *et al*., 2010; Berge *et al*., 2011). A more recent study, exploring hemisphere asymmetry, found relatively less right hemisphere volume in the DLPFC, and parietal and anteroinferior temporal lobe in relation to impaired insight (Gerretsen *et al*., 2013a). In a

study of first-episode patients, cortical thickness, but not voxel-based morphometry, was associated with regional thinning in the left middle frontal and inferior temporal gyri (Buchy *et al*., 2011). Other studies have associated impaired insight with the following: reduced brain volume, particularly within the frontal and parietal regions (Flashman *et al*., 2000; Laroi *et al*., 2000; Sapara *et al*., 2007; Parellada *et al*., 2011); reduced white matter volume (Gerretsen *et al*., 2013a); white matter deficits as measured with diffusion tensor imaging (Antonius *et al*., 2011); and right posterior insula structural alterations (Palaniyappan *et al*., 2011). Age-related cerebral atrophy may enhance the relationship between structural changes and impaired insight, particularly in late life, where there may be greater insight impairment than in midlife (Wiffen *et al*., 2010b). Studies are required to test this hypothesis.

A final explanation for impaired insight in schizophrenia is the notion that (5) lack of information/education contributes to unawareness of illness. According to this model, patients often do not have the knowledge base required to score high on assessments of insight into illness. Upon gaining information about schizophrenia, insight into illness may improve in a subset of patients (Chan *et al*., 2009; Aho-Mustonen *et al*., 2011; Pijnenborg *et al*., 2013).

None of these models seem to explain impaired insight in its entirety; at the same time, they are not mutually exclusive. All models may coexist and contribute to a fuller understanding of the complex construct of insight into illness. For example, the functional aspects of illness denial as a defense mechanism may involve the same brain structures that are damaged in anosognosia secondary to a cerebral lesion.

The interaction among aging, symptoms, and insight into illness in schizophrenia

Aging, positive symptoms, and insight into illness—Impaired insight into illness is consistently associated with severity of positive symptoms in a number of cross-sectional studies (David *et al*., 1992; Amador *et al*., 1993; Young *et al*., 1993; Collins *et al*., 1997; Schwartz, 1998a; Chan *et al*., 2012), longitudinal studies (Weiler *et al*., 2000; Saeedi *et al*., 2007) and a meta-analytic review (Mintz *et al*., 2003). However, some studies have failed to find a relationship between positive symptoms and insight into illness (Cuesta and Peralta, 1994; Smith *et al*., 1998; Carroll *et al*., 1999; Braw *et al*., 2012).

The research literature suggests that positive symptoms improve with age in schizophrenia (McGlashan and Fenton, 1993; Davidson *et al*., 1995; Cohen *et al*., 2000, 2008; Harrison *et al*., 2001; Jeste *et al*., 2003; Bankole *et al*., 2008; Shepherd *et al*., 2012). In a sample 40 to 85 years, there was a trend towards improvement of positive symptoms in older patients with schizophrenia (Jeste *et al*., 2003). The decline in positive symptoms is proposed to represent “burnout” (Jeste *et al*., 2003), resulting from age-related degeneration of the dopaminergic system (Schultz *et al*., 1997), countering the hyperdopaminergic state hypothesized to cause psychosis (Howes and Kapur, 2009). Dopaminergic neuronal and receptor loss may manifest in a reduction of positive symptom severity. Age-related decreases in striatal D2 receptors (Volkow *et al*., 1996; Kaasinen *et al*., 2000) likely contribute to the increased antipsychotic drug sensitivity of older adults (Jeste *et al*., 2003; Uchida *et al*., 2009a; Leon *et al*., 2010) and the need for lower doses to achieve remission of

positive symptoms. The observation of age-related improvement in positive symptoms is used to argue that schizophrenia does not follow a debilitating course, as in Alzheimer's disease or other dementias, with clinical deterioration usually limited to the first 5 years after onset (Lieberman, 1999; Levine *et al*., 2011). There exists, however, heterogeneity among different illness course trajectories, with a minority of patients deteriorating over time (Harding, 1988; Olesen and Mortensen, 2002; Rabinowitz *et al*., 2007).

Overall, there appears to be an improvement of insight into illness with age, at least during midlife, in conjunction with the attenuation of positive symptoms that may be related, in part, to dopaminergic system "burnout." It is important to note that longitudinal data on the effects of aging on insight into illness and its relationship to symptomatology are, for the most part, limited to samples less than 65 years.

Aging, negative symptoms, and insight into illness—The relationship among aging, insight into illness, and negative symptoms is unclear, seemingly as a result of the inconsistent association between negative symptoms and aging, and similarly, negative symptoms and impaired insight.

Positive symptoms have traditionally characterized the early course of schizophrenia with negative symptoms emerging later in life, dominating the clinical picture with age (Pfohl and Winokur, 1982; McGlashan and Johannessen, 1996). However, explorations of the literature on the effects of age on negative symptoms suggest that findings are mixed. In earlier reports, negative symptom severity was observed to increase with age (Soni and Mallik, 1993; Davidson *et al*., 1995; Gur *et al*., 1996). Conversely, subsequent and more recent studies have indicated that negative symptoms stabilize or attenuate with age (Schultz *et al*., 1997; Jeste *et al*., 2003; Cohen *et al*., 2013). One review reported that negative symptoms were prevalent in 50–90% of first-episode patients, with only 20–40% of patients experiencing persistent negative symptoms that remained stable in long-term follow-up studies (Makinen *et al*., 2008).

The findings of studies reporting on the relationship between impaired insight and negative symptoms are also mixed. Impaired insight and negative symptoms are modestly associated in a number of cross-sectional studies (Nakano *et al*., 2004; De Hert *et al*., 2009; Braw *et al*., 2012; Chan *et al*., 2012) and longitudinal studies (Kemp and Lambert, 1995; Saeedi *et al*., 2007). Similarly, the results of a meta-analysis found a modest but significant relationship between impaired insight and negative symptoms (Mintz *et al*., 2003). Conversely, other cross-sectional (Amador *et al*., 1994; Collins *et al*., 1997; Schwartz, 1998a) and longitudinal studies (Smith *et al*., 1998; Carroll *et al*., 1999) have failed to find a relationship between impaired insight and negative symptoms.

Aging, cognitive function, and insight into illness—Impaired insight is negatively correlated with cognitive function in cross-sectional (Young *et al*., 1993; Drake and Lewis, 2003; Goodman *et al*., 2005) and longitudinal studies (Lysaker and Bell, 1994). Other studies, however, have failed to find a relationship between cognitive function and insight into illness (Cuesta and Peralta, 1994; David *et al*., 1995; Kemp and David, 1996; Collins *et al*., 1997; Aleman *et al*., 2002; Cuesta *et al*., 2006). In two comprehensive meta-analyses,

global cognitive function, premorbid intellectual function (i.e. IQ), executive function, and memory were the cognitive domains associated with insight into illness (Aleman *et al*., 2006; Nair *et al*., 2014).

The normal aging process is associated with cognitive decline, particularly with attention and executive function, while the relationship with premorbid intellectual function is preserved (Hedden and Gabrieli, 2004; Dickinson and Hiscock, 2010). Reports on the course of cognitive function are mixed in schizophrenia and may depend on the sample studied. Individuals with schizophrenia tend to score 1 to 3 standard deviations below normal healthy controls on tests of cognition (Saykin *et al*., 1991; Wilk *et al*., 2004; Frangou, 2010; Rajji *et al*., 2013) and have lower premorbid intellectual function as assessed with measures of IQ prior to the onset of the first episode of psychosis (Woodberry *et al*., 2008). Some studies report that cognitive function progressively declines (Bilder *et al*., 1992; Sheitman *et al*., 2000), while other studies suggest that cognitive function remains stable, especially among community-dwelling patients (Gold *et al*., 1999; Heaton *et al*., 2001; Kurtz, 2005; Keefe *et al*., 2006; Bonner-Jackson *et al*., 2010). In studies of community-dwelling patients, age-related cognitive decline occurs at a similar rate to healthy controls (Jeste *et al*., 2003; Rajji *et al*., 2013). However, as a result of having less cognitive reserve, individuals with schizophrenia may experience “premature aging” (Rajji *et al*., 2013). By comparison, the rate of cognitive decline is accelerated in institutionalized patients and in those with more severe psychopathology (Kurtz, 2005; Rajji and Mulsant, 2008). This suggests that these patients may have less “cognitive reserve” than community-dwelling patients or the possibility of a neurodegenerative process (Cohen *et al*., 2008).

Recent preliminary research suggests that aging in late life (greater than 60 years) attenuates the relationship between insight impairment and measures of cognitive dysfunction seen in younger samples, while its relationship with premorbid intellectual function is preserved (Gerretsen *et al*., 2013b). In contrast to the modest improvement in insight into illness observed in younger adults, a cross-sectional study that measured insight at different points across the lifespan found the greatest insight impairment in the >56 years group (Wiffen *et al*., 2010a). The reason for this decline may be related to the effects of “premature aging”; however, this study did not assess cognition.

The effects of medications in late life, particularly high doses of antipsychotics and the use of drugs with anticholinergic properties, may contribute to cognitive impairment and possibly insight impairment (Leon *et al*., 2010; Gerretsen and Pollock, 2013). The effects of drugs on insight impairment remain to be studied.

Insight into illness and episode of psychosis

To understand the relationship between aging and insight into illness, it is important to distinguish it from its relation to an episode of psychosis. At any point across the lifespan, a patient with schizophrenia can experience a new psychotic episode or an exacerbation of preexisting psychotic symptoms, during which insight may fluctuate considerably. During a psychotic episode, insight impairment tends to worsen in conjunction with worsening psychosis and then improves with hospitalization and initiation of antipsychotic treatment (David *et al*., 1995; Kemp and Lambert, 1995; Smith *et al*., 1998; Weiler *et al*., 2000;

Parellada *et al*., 2011; Schennach *et al*., 2012; Koren *et al*., 2013). With recovery, insight into illness appears to either remain stable or continue to improve. The greatest degree of insight improvement may occur during the acute phase of treatment and may be influenced by multiple factors, including psychosocial stressors, medication adherence, IQ, age, duration of untreated psychosis, severity, and phase of illness (Buckley *et al*., 2007; Wiffen *et al*., 2010b; Parellada *et al*., 2011; Quee *et al*., 2011).

Insight into illness and phase of illness

We are not aware of any cohort studies that have measured insight impairment longitudinally over the course of schizophrenia from the prodromal phase or first episode of psychosis to late life. However, the progression of insight impairment at each phase of illness (i.e. prodromal, first episode of psychosis, and chronic, including late life) may be characteristically different, providing some clarity regarding the effects of aging. A caveat to this approach is the likelihood that some, although few, patients may experience their first episode of psychosis in mid-to-late life. The following section discusses the course of insight into illness during the different phases of schizophrenia.

Prodromal phase of schizophrenia—Little is known about the relationship between impaired insight into illness and the prodromal phase of schizophrenia. Prior to the onset of the first episode of psychosis, patients with schizophrenia experience subsyndromal symptoms (e.g. ideas of reference, persecutory ideation, and perceptual disturbances) for which they have greater capacity for mental flexibility, discernment, and insight than during subsequent phases of psychosis. We are aware of just one study that has explored insight into illness during the prodrome of schizophrenia, which consisted of a retrospective analysis of 24 participants diagnosed with schizophrenia within a 2-year period (Bota *et al*., 2006). The investigators reported that insight into illness is usually maintained during the initial perceptual disturbance phase yet dissipates later in the prodrome as the experiences become delusional. As would be expected, the average age of these subjects at the time of first diagnosis was mid-20s (25 ± 9.5 years); however, no age differences were reported between the “insight” and “no insight” groups.

First-episode schizophrenia—Longitudinal studies tracking insight into illness in patients with first-episode psychosis report that insight into illness improves at follow-up visits (Fennig *et al*., 1996; Mintz *et al*., 2004; Sim *et al*., 2006; Saeedi *et al*., 2007; Parellada *et al*., 2009; Saravanan *et al*., 2010; Segarra *et al*., 2012; Capdevielle *et al*., 2013). A 5-year longitudinal study reported continuous improvement in insight into illness measurements at 6months, 1 year, and 5 years (Johnson *et al*., 2012). In another longitudinal study, insight into illness improved at 1-year follow-up yet failed to further improve during the subsequent year (Parellada *et al*., 2011), suggesting greatest improvement during the acute phase of treatment and hospitalization.

Midlife chronic phase of schizophrenia—During the chronic phase in midlife, individuals with schizophrenia appear to have greater insight into illness than during the first episode of psychosis. Studies that have compared multiple-episode versus first-episode patients have reported more awareness of having a mental illness in the multiple-episode

group (Thompson *et al*., 2001; Schennach *et al*., 2012; Koren *et al*., 2013). Explanations for this difference included the following: acceptance of illness by chronic patients (psychological model); greater psychological defensiveness by the first-episode patients (psychological model); lack of education or knowledge about schizophrenia during the first episode of psychosis (psychoeducation model); and a longer time undergoing treatment (clinical/psychopathological model). In one study, although the multi-episode group had greater insight into illness at the time of admission, first-episode patients had significantly greater improvement in insight during the acute phase of treatment and at the time of discharge (Schennach *et al*., 2012), which suggests that first-episode patients (and possibly younger patients) may have a greater capacity for developing insight into illness than those in later phases of schizophrenia. This idea is supported by another study, in which younger patients experienced greater changes in insight into illness during a psychotic episode (Chen *et al*., 2001).

A number of cross-sectional studies whose samples consisted primarily of subjects during the chronic phase of schizophrenia have reported a modest-to-moderate association between age and insight into illness (Mohamed *et al*., 2009; Braw *et al*., 2012), while others have failed to find such a relationship (Amador *et al*., 1993; David *et al*., 1995; Gerretsen *et al*., 2013b). These mixed findings among cross-sectional studies are confounded within this phase of illness by heterogeneous sampling, possibly including first-episode and late-life patients, schizoaffective disorder patients, and combining hospitalized (institutionalized) and community-dwelling patients.

Late-life schizophrenia—There exists a paucity of literature that tracks insight into illness in late life. Of the aforementioned studies, few included subjects greater than 60 years, thus failing to adequately assess the effects of aging on insight into illness in late life. One cross-sectional study included patients up to 84 years and separated subjects into four age groups (Wiffen *et al*., 2010a). The greatest insight impairment was found in the >56 years group, followed by the 18–28 years group. Insight into illness was significantly better in the two intermediate groups. These findings, although preliminary, suggest that insight impairment is severe with the onset of psychosis, modestly improves over midlife, and worsens again in late life.

The decline in insight into illness in late life may be a function of the premature aging observed in schizophrenia. Although age-related cognitive decline occurs at a similar rate between patients with schizophrenia and healthy controls, functional impairment tends to occur earlier because of lower cognitive reserve (Rajji and Mulsant, 2008; Rajji *et al*., 2013).

Proposed trajectory of insight into illness

Based on the literature outlined in the previous sections, we propose that the course of insight impairment follows a U-shape trajectory (Figure 1). During adolescence and early adulthood, when prodromal and first episode of psychosis phases typically occur, insight impairment progresses with the emergence of psychosis (Mintz *et al*., 2004; Bota *et al*., 2006; Saeedi *et al*., 2007; Parellada *et al*., 2009, 2011). During hospitalization and treatment

with antipsychotic medication, insight into illness tends to improve during the recovery period (Weiler *et al*., 2000; Johnson *et al*., 2012; Schennach *et al*., 2012; Segarra *et al*., 2012).

With the exception of episodic worsening during recurrent psychotic episodes, there is a modest improvement in insight into illness throughout midlife, during the chronic phase of schizophrenia (Thompson *et al*., 2001; Schennach *et al*., 2012; Koren *et al*., 2013). Possible explanations for this improvement include the following: a longer duration of treatment; amelioration of psychotic symptoms; acceptance of one's condition; acquisition of knowledge about the illness; and improved coping techniques (Koren *et al*., 2013).

The trajectory of insight into illness into late life remains unclear, although limited evidence suggests that it may decline during this phase. This may be due to a longer duration of illness (Wiffen *et al*., 2010b); however, if this were the case, one would expect a decline in midlife rather than the observed improvement in insight into illness. We propose that worsening insight impairment in late life may, in part, be explained by the cognitive decline associated with premature aging (Figure 2). Although cognitive decline in patients with schizophrenia appears to progress at a similar rate in comparison with healthy individuals, patients with schizophrenia have less cognitive reserve and accompanying neuroanatomical alterations (e.g. cerebral atrophy and decreased neuroreceptor density) that may lead to premature aging (Rajji *et al*., 2013). Insight impairment in late life may also be influenced by the sample studied, as the severity of psychopathology and illness trajectory are worse in institutionalized versus community-dwelling patients with schizophrenia (Rajji and Mulsant, 2008). Longitudinal studies that include participants with late-life schizophrenia are required to test this hypothesis.

Conclusion and future directions

Impaired insight into illness is a common feature of schizophrenia, which negatively influences treatment adherence and clinical outcomes. Our systematic review of the literature suggests that insight impairment is associated with illness severity, duration of untreated psychosis, lower premorbid intellectual function (i.e. IQ), executive dysfunction, and memory deficits. The course of insight impairment appears to follow a U-shaped curve (Figure 1), where insight impairment increases with the first episode of psychosis, decreases over midlife, and increases again in late life. Insight impairment also tends to fluctuate with each episode of psychosis, likely in relation to worsening positive symptoms that improve with antipsychotic treatment. Preliminary evidence suggests that the relationship between impaired insight and measures of cognitive dysfunction appears to attenuate with age, while the relationship with premorbid intellectual function is preserved. The association between impaired insight and negative symptoms is unclear.

This review has a number of limitations: First, many relevant articles may have been omitted from our Medline® search. For most studies, although they may comment on the relationship between aging and insight impairment, the effects of aging were not their primary aim. Second, lack of longitudinal studies that track insight impairment over a significant period of time renders it challenging to make generalizations about the effects of

aging. Third, the negligible representation of older adults with schizophrenia in the insight literature serves as a barrier to truly understanding the effects of aging on insight into illness in late life.

Insight into illness is recognized as a multidimensional construct that usually consists of awareness of having a mental disorder, its symptoms, its implications, and need for treatment; however, little-to-nothing is known about the effects of aging on these core domains, which may follow different courses over the lifespan. We suggest a longitudinal study to track insight into illness and its core domains in relation to other clinical features (e.g. positive, negative, and cognitive symptoms; treatment adherence; and functional outcomes) from early to late life in patients with schizophrenia. Naturally, the impracticality of such a study poses difficulties. As such, a more pragmatic approach would be to utilize a cross-sectional methodology, including samples from across the lifespan from prodromal phase to late life. A greater understanding of the course and correlates of insight at each phase of illness across the lifespan may help us better understand a complex phenomenon with significant implications for treatment adherence and treatment outcomes. The ultimate clinical application of gaining insight into illness is developing the capacity to consent to treatment. Future research may demonstrate that different strategies at different phases of illness may yield better clinical results. For example, psychoeducation and CBT for psychosis may be of greater benefit in younger patients to improve insight into illness, while neurostimulation and cognitive remediation strategies may be indicated for those in later life.

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Key points

- Impaired insight into illness appears to follow a U-shaped trajectory, where insight impairment is severe during the first episode, modestly improves over mid-life, and declines again in late-life.
- Insight impairment fluctuates during each episode of psychosis, likely in accordance with positive symptoms.
- The association between insight impairment and cognitive dysfunction attenuates with age, while the relationship with premorbid intellectual function is preserved.
- Future studies are required to investigate the trajectory of insight into illness and its core domains across the lifespan from prodromal phase to late life.

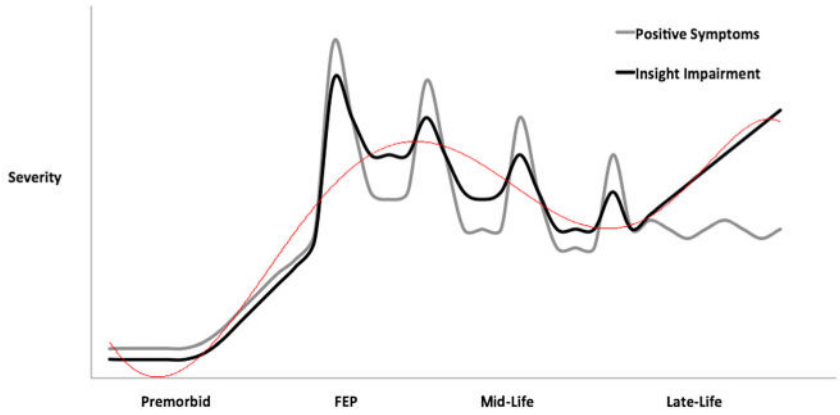

Figure 1.

Theoretical trajectory of insight impairment and positive symptom severity across the course of schizophrenia (red line—insight impairment trend line).

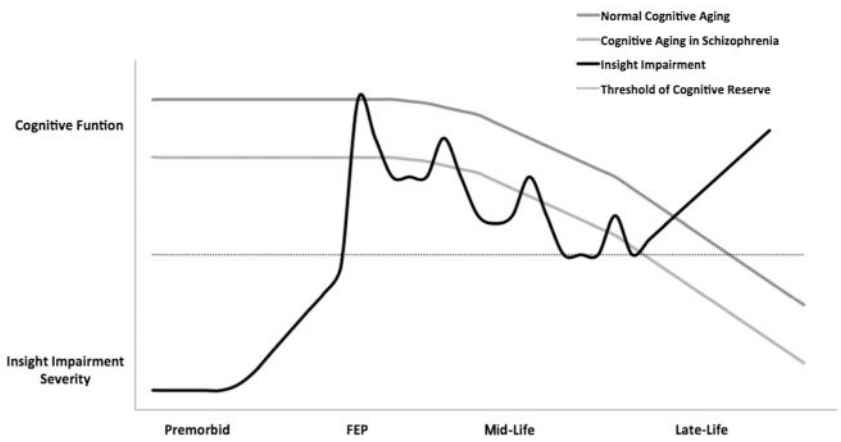

Figure 2.

Theoretical trajectory of insight impairment in relation to cognition across the course of schizophrenia.

Table 1

Relationship between age and insight into illness in schizophrenia spectrum disorders

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
Gerretsen *et al*., 2013a, Hum Brain Mapp	52	2	41.5 (14.5), 23–77	U	PANSS G12	r = 0.12, p = 0.395, n.s.	N	N/A	N/A	–	
Gerretsen *et al*., 2013b, Schizophr Res	50	1	65.2 (5.5), 60–79	U	PANSS G12, BIS	PANSS G12, r = 0.05, p = 0.729, n.s.; BIS, r=−0.23,p = 0.117, n.s.	N	N/A	N/A	–	
Mingrone *et al*., 2013, Compr Psychiatry	158	2	40.1 (10.8), ?	O	SUMD items 1–3	SUMD 1,r=0.08, n.s.; SUMD 2, r=0.03, n.s.; SUMD 3, r=0.01, n.s.	N	N/A	N/A	–	
Braw *et al*., 2012, Eur Psychiatry	66	3	SZ, 26.8 (8.4), <60; bipolar, 43.9 (12.4), <60	O	SUMD items and subscales, PANSS G12	SUMD 1, r=−0.36, p< 0.01; SUMD 2, n.s.; SUMD 3, r= −0.30, p< 0.05; SUMD awareness of anhedonia asociality, r= −0.64, p< 0.001; PANSS G12, r= −0.32, p< 0.01	Y	N/A	N/A	–	Differences in insight between bipolar and schizophrenia patients disappeared when age was used as a covariate.
Schennach *et al*., 2012, Eur Psychiatry	399	3	35.4 (11.1), <65	H	PANSS G12	r= −0.01, p = 0.77	N	Mean 64.7 days (SD = 46.5)	*F*-test, p = 0.88, n.s.	N	Age was not associated with changes in insight from admission to discharge among those characterized as “improved,” “worsened,” “unchanged,” or “no lack of insight.”
Xiang *et al*., 2012, Compr Psychiatry	139	2	33.4 (9.8), <50	O	ITAQ	r=−0.01, n.s.	N	N/A	N/A	–	
Ayesa-Arriola *et al*., 2011, Early Interv Psychiatry	164	4, 1	27.3 (7.8), <60	B	SUMD items 1–3	*t*-test, n.s.	N	N/A	N/A	–	No difference in age between “good” and “poor” (>1) insight groups.
Gilleen *et al*., 2011, Schizophr Bull	31	2	38.3 (10.4), 21–62	B	SAI-E, SUMD item 1	Weak association between age and SAI informant-rated treatment compliance	Y	N/A	N/A	–	
Lysaker *et al*., 2011, Compr Psychiatry	65	1	46.3 (8.9), ?	O	SUMD items 1–3	n.s.	N	N/A	N/A	–	
Parellada *et al*., 2011, Schizophr Bull	53	4, 1	15.43 (1.95), <17	B	SUMD items and subscales	N/A	–	2 years	Baseline age and insight at 2 years: SUMD 1, r=−0.49, p< 0.01; SUMD 2,	Y	

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
									r= −0.33, p< 0.05; SUMD 3, < 0.05; SUMD 3, r= −0.46, p<0.01; symp. awareness, r= −0.39, n.s.; symp. attribution, r= −0.17, n.s.		
Buchy *et al*., 2010, Early Interv Psychiatry	165	4, 3	22.5 (4.0), 14–30	B	SUMD item 1	F= 0.76, p = 0.56, n.s.	N	N/A	N/A	–	Five insight groups did not significantly differ in age.
Nakamae *et al*., 2010, Psychiatry Clin Neurosci	47	2	53.0 (13.0), ?	H	SUMD general items	R^2 n.s.	N	N/A	N/A	–	Age did not predict insight into illness.
Wiffen *et al*., 2010, Schizophr Res	303	1	Median 30.6, 18–62	U	SAI-E	F= 2.31, p = 0.08, n.s.	N	6 months	F = 2.77, p = 0.04	Y	Age predicted insight improvement.
Wiffen *et al*., 2010, Clin Schizophr Relat Psychoses	670	1	42 (14.0), 18–84	U	PANSS G12	F= 8.26, p< 0.0001	Y	N/A	N/A	–	Oldest and youngest groups had less insight than midlife groups.
De hert *et al*., 2009, Eur Psychiatry	1213	1	35.5 (11.9), 16–83	H	PECC	Impaired insight into illness (AMI), r= 0.06, p = 0.042; impaired insight into symptom attribution (ASAMI), r= 0.08, p = 0.004; AMI parameter est. = 0.03, p = 0.263; ASAMI parameter est. = 0.004, p = 0.137	Y	N/A	N/A	–	
Mohamed *et al*., 2009, Schizophr Bull	1432	2	40.5 (11.1), 18–67	B	ITAQ	r= 0.07, p< 0.01	Y	N/A	N/A	–	
Parellada *et al*., 2009, Psychol Med	110	4, 3	15.5 (?), 9–17	B	SUMD items and subscales	n.s.	N	N/A	N/A	–	
Raffard *et al*., 2009, Psychiatry Res	60	1	33.4 (9.5), 18–56	O	SUMD items and subscales	SUMD 1, r= 0.00, n.s; SUMD 2, r= −0.14, n.s.; SUMD 3, r= −0.03, n.s.; symptom awareness, r=0.00, n.s.; symptom attribution, r= −0.06, n.s.	N	N/A	N/A	–	
Stefanopoulou *et al*., 2009, Psychiatr Q	36	2	34.9 (9.8), 20–52	H	ITAQ	n.s.	N	N/A	N/A	–	
Karow *et al*., 2008, Eur Arch Psychiatry Clin Neurosci	59	1	34.7 (13.0), ?	H	BIS, SUMD, PANSS G12	r=−0.17 to 0.08, n.s.	N	N/A	N/A	–	

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
Bassitt *et al*., 2007, Eur Arch Psychiatry Clin Neurosci	50	2	31.7 (7.1), 18–50	O	SUMD symptom awareness + symptom attribution	r= 0.05, p = 0.75, n.s.	N	N/A	N/A	–	
Sapara *et al*., 2007 Schizophr Res	28	2	39.0 (10.5), 19–60	O	SAI-E, BIS	r (controlling for duration of illness) = 0.25–0.23, p>0.20, n.s.	N	N/A	N/A	–	
Tirupati *et al*., 2007, Compr Psychiatry	183 treated; 143 never treated	2	Treated patients, 44.4 (13.6), ?; never-treated patients, 46.9 (16.3), ?	O	PANSS G12	Treated, r=0.37, p < 0.01; never treated, r= −0.05, n.s.	Y	N/A	N/A	–	
Haddock *et al*., 2006, Br J Psychiatry	304	4, 3	<22 years, 19.6 (1.6), ?; >21 years, 32.9 (9.9), ?	B	BIS	*t*-test, n.s.	N	18 months	F = 3.88, p = 0.023	Y	No difference in <22-year and >21-year groups in insight at baseline. There was an interaction between insight, age, and treatment at 18 months.
Lysaker *et al*., 2006, J Neuropsychiatry Clin Neurosci	53	1	47.5 (9.1), ?	O	SUMD items 1–3	n.s.	N	N/A	N/A	–	
McEvoy *et al*., 2006, Psychol Med	251	4, 3	23.9 (4.7), 16–40	B	ITAQ	r=0.16, p = 0.016	Y	N/A	N/A	–	
Shad *et al*., 2006, Psychiatry Res	14	4, 3 (antipsychotic naive)	26.23 (7.5), ?	H	SUMD	Symptom awareness, β = 0.08; p = 0.78, n.s.; symptom attribution, β = 0.004; p = 0.99, n.s.	N	N/A	N/A	–	
Simon *et al*., 2006, Cogn Neuropsychiatry	38	2	24 (7), 16–38	H	SUMD items and subscales factor analysis	n.s.	N	N/A	N/A	–	
Donohoe *et al*., 2005, J Nerv Ment Dis	30	2	? (?), <55	O	BIS	*t*-test, n.s.	N	N/A	N/A	–	No difference in age between “poor” and “good” (>9) insight groups
Keshevan *et al*., 2004 Schizophr Res	535	4, 1	16–45	U	PANSS G12	F = 0.10, p = 0.75, n.s.	N	N/A	N/A		No difference in insight impairment between age groups
Nakano *et al*., 2004, Psychiatry Res	37	2	53 (10), 33–75	H	SAI-Japanese	SAI-J total, r= −0.21, n.s.; SAI 1 (treatment acceptance), r= −0.40, p< 0.05; SAI 2 (illness awareness), r = −0.11, n.s.; SAI 3 (symptom awareness/ attribution), r= −0.17, n.s.	Y	N/A	N/A	–	

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
Shad *et al*., 2004, Neuroimage	35	4, 1	Good insight, 25.4 (7.8), N/A; poor insight, 26.1 (6.7), N/A	H	HDRS insight item	$t = -0.31$, $p = 0.75$, n.s.	N	N/A	N/A	–	
Arduini *et al*., 2003, Can J Psychiatry	42 SZ; 22 bipolar	3	SZ, 37.4 (12.2), ?; bipolar, 36.7 (11.8), ?	H	SUMD items 1–3	n.s.	N	N/A	N/A	–	
Rossell *et al*., 2003, Psychol Med	78	2	33.7 (8.50), <55	B	SAI-E	n.s.	N	N/A	N/A	–	
Yen *et al*., 2002, J Nerv Ment Dis	44 SZ; 33 psychotic bipolar; 32 nonpsychotic bipolar	3	SZ, 33.8 (9.9), 19–61; psychotic bipolar, 33.5 (12.4), 16–64; nonpsychotic bipolar, 41.2 (11.1), 21–71	O	SAI-E total	β=0.02, n.s.	N	N/A	N/A	–	Age did not predict insight into illness.
Goldberg *et al*., 2001, J Nerv Ment Dis	211	3	41 (8.6), 21–69	B	PANSS G12	β=−0.01, n.s.	N	N/A	N/A	–	
Pyne *et al*., 2001, J Nerv Ment Dis	177	2	34.5 (8.7), 18–54	B	Awareness of mental illness Likert scale	OR = 2.98, $p< 0.05$ for illness denial if <30 years	Y	N/A	N/A	–	
Flashman *et al*., 2000, A J Psychiatry	30	1	Aware, 36.4 (14.9), ?; unaware, 33.9 (9.9), ?	B	SUMD	$t = 0.55$, $p = 0.59$, n.s.	N	N/A	N/A	–	
Laroi *et al*., 2000, Psychiatry Research	21	1	36 (10.2), <60	B	SUMD items and subscale total	n.s.	N	N/A	N/A	–	
Marks *et al*., 1995, Schizophr Res	59	2	42.7 (10.8), ?	O	SAIQ	SAIQ tot, n.s.; worry, n.s.; need for treatment, $r = 0.32$, $p<0.05$; illness presence/ outcome, $r= 0.31$, $p< 0.05$. Neither significant after controlling for length of illness	Y	N/A	N/A	–	
Weiler *et al*., 2000, Schizophr Res	81 SZ; 14SA	1	SZ, 37.3 (8.4); SA, 35.6 (14.5)	H	ITAQ	n.s.	N	N/A	N/A	–	
Carroll *et al*., 1999 Schizophr Res	110	2	35.6 (10.9), <64	B	ITAQ	r=0.05, n.s.	N	N/A	N/A	–	
Schwartz *et al*., 1998, Compr Psychiatry	66	2	42.0 (6.7), 21–53	O	SUMD items 1–3	R^2 n.s.	N	N/A	N/A	–	Age did not predict nsight into illness.
Collins *et al*., 1997, Schizophr Res	58	2	34.1 (8.0), ?	O	SAI	r=0.32, $p = 0.01$; β= 0.19, $p = 0.091$, n.s.	N	N/A	N/A	–	
Dickerson *et al*., 1997, Psychiatr Serv	87	1	39.4 (9.9), <65	O	PANSS G12	n.s.	N	N/A	N/A	–	
Kim *et al*., 1997, Compr Psychiat	63	2	38.2 (13.3), 20–61	B	SAI	SAI-J total, $r= -0.21$, n.s.; SAI 1 (treatment acceptance), $r= -0.28$, $p = 0.060$; SAI 2 (illness awareness), $r= -0.23$, $p =$	Y	N/A	N/A	–	

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
						0.113; SAI 3 (symptom awareness/attribution), 0.113; SAI 3 (symptom awareness/attribution), −0.37, $p = 0.010$					
Schwartz *et al*., 1997, Compr Psychiatry	23	2	40.1 (8.1), 20–52	H	Modified total SUMD score	r= 0.07, n.s.	N	N/A	N/A	–	
Almeida *et al*., 1996, Int J Geriatr Psychiatry	40	Late paraphrenia	? (?), >55 years	B	SAI	n.s.	N	N/A	N/A	–	
Cuffel *et al*., 1996, J Nerv Merit Dis	89	2	38.9 (7.1), <55	O	Awareness of illness interview	r= 0.08, n.s.	N	N/A	N/A	–	
Fennig *et al*., 1995, Schizophr Res	309	3	? (?), <60, 52.4% under 29 years old.	H	HDRS insight item	n.s.	N	N/A	N/A	–	
Macpherson *et al*., 1996, Br J Psychiatry	64	2	?	H	SAI	r= −0.19, $p = 0.14$	N	N/A	N/A	–	
Aga *et al*., 1995, Indian J. Psychiatry	59	2	35.4 (10.5), 18–55	H	SAI	*t*-test, n.s.	N	N/A	N/A	–	No difference in impaired insight between “low” (<66% max score) and “high” insight groups.
Cuesta *et al*., 1995, Am J Psychiatry	52	3	30.8 (7.9), 19–45	H	Lack of insight index (3 items from AMDP)	n.s.	N	N/A	N/A	–	
David *et al*., 1995. Br J Psychiatry	150	3	26.4 (6.5), 16–50	B	PSE	β= 0.12, $p = 0.2$, n.s.	N	N/A	N/A	–	Age did not predict insight into illness.
Kemp and Lambert, 1995, Schizophr Res	29	2	28.4 (7.0), 16–45	H	Modified SUMD symptom awareness and attribution	N/A	–	3–6 weeks	n.s.	N	Age did not correlate with improvements in insight.
Lysaker and Bell, 1995, J Nerv Ment Dis	44	1	45 (10), ?	B	PANSS G12	N/A	–	26 weeks	n.s.	N	Age did not correlate with changes in insight.
Amador *et al*., 1994, Arch Gen Psychiatry	221 SZ; 49 SA	1	SZ, 34.4 (11.2), ?; SA, 33.6 (12.1), ?	U	SUMD items and subscales	n.s.	N	N/A	N/A	–	
Cuesta and Peralta, 1994, Schizophr Bull	40	2	27.7 (7.5), 17–46	H	Lack of insight index (3 items from AMDP)	n.s.	N	N/A	N/A	–	
Amador *et al*., 1993, Am J Psychiatry	43	1	31.2 (8.8), ?	H	SUMD items and subscales	n.s. (no statistics provided)	N	N/A	N/A	–	
Young *et al*., 1993, Schizophr Res	31	2	38.4 (7.3), 25–53	B	SUMD symptom awareness	*t*-test, n.s.	N	N/A	N/A		No difference in age between “low” and “high” insight groups

Authors, year, journal	*N*	Dx[a]	Mean age (SD), range[b]	Status[c]	Measure of insight into illness	Cross-sectional association	Significant (Y/N)	Longitudinal follow-up	Longitudinal association	Significant (Y/N)	Comments
David *et al.*, 2007b, Br J Psychiatry	91	3	31.4 (9.8), <65	B	PSE	r<0.15, n.s.	N	N/A	N/A	–	

Dx, diagnosis; PANSS, Positive and Negative Syndrome Scale; BIS, Birchwood Insight Scale; SUMD, Scale to Assess Unawareness of Mental Disorder; ITAQ, Insight and Treatment Attitudes Questionnaire; SAI-E, Schedule for the Assessment of Insight—Expanded version; PECC, Psychosis Evaluation Tool for Common Use by Caregivers; HDRS, Hamilton Rating Scale for Depression; SAIQ, Self-Appraisal of Illness Questionnaire; PSE, Present State Examination.

[a] 1 = schizophrenia (SZ), schizoaffective (SA), and/or schizophreniform; 2 = schizophrenia only; 3 = unspecified/mixed psychoses; and 4 = first-episode psychosis.

[b] ?, indicates data not specified.

[c] Hospitalized (H), out-patient (O), both (B), or unspecified (U).