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Changes in insight over the first 24 months of treatment in schizophrenia spectrum disorders

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ABSTRACT

Background: While insight in schizophrenia improves with treatment, significant impairments often persist. The degree of persistence is not well characterised.
Aims: We assessed patient and clinician-rated changes in insight in acutely ill, minimally treated first-episode schizophrenia spectrum disorder patients over 24 months of standardised treatment with a depot antipsychotic.
Method: This single arm open label longitudinal cohort study included 105 participants with first-episode schizophrenia, schizophreniform or schizoaffective disorder. Insight was assessed at months 0, 6, 12 and 24 using the patient-rated Birchwood Insight Scale (BIS) and clinician-rated global insight item of the Positive and Negative Syndrome Scale (PANSS). Changes in insight over time were assessed using linear mixed-effect models for continuous repeated measures. Relationships between insight and psychopathology, functionality, cognition and quality of life were assessed with regression models.
Results: There was significant improvement over time for the PANSS insight item ($p < 0.0001$). However, the only significant improvement for the BIS was with the Need for Treatment subscale ($p = 0.01$). There were no significant improvements noted for the Symptom Attribution ($p = 0.7$) and Illness Awareness ($p = 0.2$) subscales, as well as the BIS Total score ($p = 0.6$). Apart from depressive symptoms at baseline, there were no significant predictors of patient-rated insight.
Conclusions: Clinicians should note that, even when treatment is assured and response is favourable, fundamental impairments in patient-rated insight persist.

1. Introduction

Impaired insight is a common and prominent feature of schizophrenia, with 50–80% of patients believing that they are not ill (Amador et al., 1994; Dam, 2006). The concept of insight has evolved over decades, with contemporary research recognising its multidimensional nature, including recognition of having a mental disorder, symptom attribution and awareness of need for treatment (Wiffen et al., 2010a, 2010b). The clinical importance of insight impairment lies in its association with poor treatment adherence (Velligan et al., 2017), heightened symptom severity and worse clinical outcomes (Lysaker et al., 2018). Although studies exploring insight have largely been cross-sectional, several longitudinal studies have been conducted. Prospective evidence suggests that insight is not a static phenomenon, and that there is improvement with treatment (Wiffen et al., 2010a, 2010b; Segarra et al., 2012; David et al., 1995; Cuesta et al., 2000; Mintz et al., 2004; Crumlish et al., 2005; Parellada et al., 2011; Pijnenborg et al., 2015; Gharabawi et al., 2006; Mohamed et al., 2009). This improvement is reportedly modest (Wiffen et al., 2010a, 2010b) and mostly occurs during in the early phase of treatment (Segarra et al., 2012; Mintz et al., 2004; Parellada et al., 2011). Impairments may persist in the stable phase of illness (Wiffen et al., 2010a, 2010b; Cuesta et al., 2000; Parellada et al., 2009). Consequently, insight is regarded as having both state and trait-like properties (Wiffen et al., 2010a, 2010b; Parellada et al., 2011). However, the degree to which insight impairment improves with treatment, and whether different components of insight are more amenable to treatment remains unclear.

The aim of the study was to assess changes in insight in acutely ill, minimally treated patients with a first-episode of schizophrenia spectrum disorder, over the first 24 months of flupenthixol decanoate depot treatment. Insight was assessed according to both patient and clinician-rated assessment instruments. We also investigated baseline and endpoint insight and its relationships to psychopathology,

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functionality, quality of life, neurological signs and cognitive status. We hypothesised that: 1) all measures of insight would improve with treatment; 2) substantial insight impairments would persist, and that 3) endpoint insight domains would have specific relationships with clinical, cognitive and neurological features of the illness. Previous studies did not necessarily take into account factors such as illness chronicity, prior medication exposure, level of psychotic symptoms and treatment adherence. Also, instruments to assess insight were not always optimal. In the present study we were able to address several of these potential confounds. By selecting a first-episode, minimally treated cohort we were able to assess the illness in its most symptomatic state and without effects of previous treatment and illness chronicity; the standardised treatment approach avoided possible differential effects of individual antipsychotics; and using depot antipsychotic removed the possible confound of covert non-adherence – of importance given that poor insight leads to a greater likelihood of patients rejecting medication (Lysaker et al., 2018).

2. Methodology

2.1. Study design

This was a single arm open label longitudinal study of a cohort of first episode psychosis patients investigating treatment outcome, its predictors and concomitants. Ethics approval was obtained from the Human Research Ethics Committee (HREC) of Stellenbosch University (SU) Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) (International Conference on Harmonization, 1996) and, although not a clinical trial assessing safety and tolerability of treatment, was registered at the South African National Clinical Trials Register (DOH-27-0710-1957; http://www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx).

2.2. Selection of study participants

In total, 105 patients were recruited between April 2007 and March 2011 from first hospital admissions and community clinics in the Greater Cape Town area. Written, informed consent was obtained from the patients. Where they were hospitalized involuntarily, or considered too ill to provide informed consent, assent was obtained together with consent from their legal guardian. Participant consent was then obtained once their condition had improved. Inclusion criteria were: men and women, inpatients or outpatients, aged 16–45 years, experiencing a first psychotic episode, and meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (American Psychiatric Association, 1994) diagnostic criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria included: lifetime exposure to a period > 4 weeks of antipsychotic medication, previous treatment with a long-acting depot antipsychotic, serious or unstable general medical condition, intellectual disability and overt substance abuse.

2.3. Treatment

We chose flupenthixol decanoate as the best tolerated depot that is freely available in the public health sector in South Africa. There was a one-week lead-in period of oral flupenthixol 1 to 3 mg/day followed by long acting flupenthixol decanoate injections every two weeks for the duration of the study. The initiation dose was 10 mg 2-weekly. Additional oral flupenthixol was prescribed at the discretion of the investigator. Permitted concomitant treatment included medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms and propranolol for akathisia. No benzodiazepines, propranolol or anticholinergics were permitted in the 12 h prior to assessments. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Clinical assessments

Diagnostic assessment was performed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Diagnoses were reviewed and revised by the investigators throughout the study. Insight was measured at baseline and after 6, 12 and 24 months using the Birchwood Insight Scale (BIS) (Birchwood et al., 1994). The BIS is a self-reported measure assessing clinical insight and comprises eight questions, each scored on a 4-point scale, with higher scores indicating better insight. The scale assesses three dimensions of insight: symptom attribution, illness awareness, and need for treatment, in addition to providing an overall total score. The G12 Insight item on the Positive and Negative Syndrome Scale (PANSS) was extracted. This item represents a clinician-rated assessment of global impairment of judgement and insight on a scale of 1 (no impairment) to 7 (extreme impairment). Psychopathology was assessed using the PANSS total score (Kay et al., 1987) and additional assessments included the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994), the Calgary Depression Scale for Schizophrenia (CDSS) total score (Addington and Addington, 1993), the World Health Organization Quality of Life Questionnaire-Brief Version (WHOQOL-BREF) domains for physical health, psychological, social relationships and environment (WHOQOL Group, 1998), the Neurological Evaluation Scale (NES) total score (Buchanan and Heinrichs, 1989), the Extrapyramidal Symptom Rating Scale (ESRS) total score (Chouinard and Margolese, 2005) and the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (MCCB) composite score (Nuechterlein and Green, 2006).

2.5. Statistical analyses

Analyses were conducted using Statistica 13 software (Dell). We assessed the distribution of the data by inspecting histograms and normal probability plots. Linear mixed-effect models for continuous repeated measures (MMRM) were constructed to assess the changes in BIS total and subscale scores and PANSS insight item over time, with age, gender and highest level of education as covariates. All of the variables were entered as fixed effects, except participant number which was entered as a random effect. Within analyses Fisher's Least Significant Difference (LSD) tests were used for multiple comparisons of post-hoc tests. Endpoint scores were calculated as last observation carried forward on all patients with at least one post-baseline BIS assessment ($n = 81$). All patients included in the endpoint analyses had therefore received at least 6 months of antipsychotic treatment during the study. Pearson correlation coefficients were used to assess relationships between insight and other symptoms at baseline and end-point. Correlations at the $p = 0.1$ level were used to select predictor variables for best subsets general regression models with BIS subscale and total scores and PANSS insight item as predictor variables and age, gender and level of education as covariates. Dependent variables were PANSS total score, CDSS total score, SOFAS, WHOQOL-BREF domains, NES Total score and MCCB Composite score. All tests were 2-tailed.

3. Results

The sample of 105 comprised 78 (74%) men and 27 (26%) women with a mean (s.d.) age of 24.5 (6.7) years. Eighty-one (77%) were of mixed ethnicity, 15 (14%) black and 9 (9%) white. DSM-IV diagnosis was schizophrenia ($n = 73$ [70%]), schizophreniform ($n = 31$ [29%]) and schizoaffective disorder ($n = 1$ [1%]). Mean duration of untreated psychosis was 37 (45) weeks. Thirty-three (31%) were hospitalized at the start of the study. Sixty-one (58%) patients were antipsychotic naïve and the other 44 (42%) had received antipsychotics for a mean

of 6 (7) days. Eighty-one (77%) participants completed at least 6 months of treatment, and 64 (61%) completed 24 months of treatment. Of the 24 patients excluded from the endpoint analyses, reasons for discontinuation were, respectively, poor efficacy 4 (4%), poor tolerability 7 (7%), consent withdrawal 2 (2%), relocation 2 (2%), lost to follow-up 7 (7%) and other 4 (4%). The excluded participants did not differ from the rest of the sample in terms of age, sex, baseline BIS total and subscale scores and PANSS insight item. Mean endpoint flupenthixol dose was 12.9 (7.4) mg 2-weekly. Table 1 provides baseline and endpoint scores for psychopathology, cognition, functionality, quality of life, neurological signs and insight scores. PANSS total scores indicate that the patients were moderately to markedly ill at baseline (92.6 [15]), and only mildly ill at endpoint (52.5 [17.6]). Similarly, measures of functionality, quality of life, neurological signs and cognition indicate pronounced impairments at baseline, and substantial improvements at endpoint.

Fig. 1 shows the least squares means and 95% confidence intervals (CIs) by MMRM over 24-months of treatment for the BIS total and subscale scores and the PANSS insight item. There was a significant time-effect for the PANSS insight item ($F(3, 309) = 57.9$, $p < 0.0001$) with LSD tests indicating significant improvement from baseline to month 6 [mean (CI) change −1.64, (1.30–1.98), $p = 0.0001$], but no further improvement thereafter. There was also a significant effect for time for the BIS Need for Treatment subscale ($F(3, 309) = 3.7$, $p = 0.01$), with LSD tests indicating significant improvement at month 12 [mean (0.46, (0.17–0.74), $p = 0.001$)]. There were no significant time effects for BIS Symptom Attribution ($F(3, 309) = 0.5$, $p = 0.7$) and Illness Awareness ($F(3, 309) = 1.4$, $p = 0.2$) subscales as well as the BIS Total score ($F(3, 309) = 0.6$, $p = 0.6$).

According to the recommended cut-off scores of ≤2 for the BIS subscale scores (Birchwood et al., 1994) the numbers (%) of patients classified as having poor insight at baseline and endpoint respectively, were: Symptom Attribution subscale 65 (62%) and 55 (68%); Illness Awareness subscale 78 (74%) and 62 (77%); Need for Treatment subscale 64 (61%) and 44 (54%). The numbers (%) of patients with baseline and endpoint BIS total scores of ≤6 were, respectively, 62 (59%) and 44 (54%), and PANSS Insight item scores ≥4 (moderate impairment) were 96 (91%) and 22 (27%).The BIS total score was significantly correlated with the PANSS insight item at baseline ($r = -0.35$, $p = 0.0001$) but not at endpoint ($r = -0.20$, $p = 0.08$).

The correlations between the insight scores and clinical, functional, quality of life, cognitive and neurological scores at endpoint are provided in Table 2. The general regression models identified the following independent baseline and endpoint predictors of the insight measures: CDSS score [$\beta = 0.26$ (CI = 0.69–0.44), $p = 0.008$] predicted BIS total at baseline ($R^2 = 0.11$, $p = 0.008$); there were no significant predictors of BIS endpoint score ($R^2 = 0.007$, $p = 0.4$). PANSS total score [$\beta = 0.37$ (CI = 0.19–0.56), $p = 0.0001$], CDSS score [$\beta = -0.29$ (CI = 10.46–0.12), $p = 0.0009$] and WHOQOL-BREF social relationships [$\beta = 0.28$ (CI = 0.11–0.46), $p = 0.001$] predicted PANSS insight item at baseline ($R^2 = 0.30$, $p = 0.0001$); and PANSS total [$\beta = 0.57$ (CI = 0.33–0.81), $p = 0.0001$], WHOQOL-BREF environment [$\beta = 0.27$ (CI = 0.07–0.47), $p = 0.009$] and NES total [$\beta = 0.22$ (CI = 0.05–0.40), $p = 0.008$] predicted PANSS insight item at endpoint ($R^2 = 0.53$, $p < 0.0001$).

Finally, we assessed post-hoc whether emergent extrapyramidal symptoms influenced patients' perception of the need for treatment. We found no significant associations between BIS Need for Treatment subscale scores and anticholinergic use (ANOVA $F = 2.1$, $p = 0.15$) or endpoint ESRS total scores ($r = -0.02$, $p = 0.8$).

Table 1
Baseline and endpoint scores for psychopathology, functionality, cognition, quality of life, neurological signs and insight scores.

Variable	Baseline Mean (s.d.)	Endpoint Mean (s.d.)	T-value[a]	p[a]
PANSS (Total)	92.6 (15.0)	52.5 (17.6)	17.7	<0.0001
CDSS	2.9 (3.8)	1.1 (2.1)	4.3	<0.0001
SOFAS	44.6 (11.6)	63.7 (12.8)	−10.7	<0.0001
MCCB composite scores	22.0 (14.6)	28.5 (16.6)	−1.9	0.05
WHOQOL-BREF				
Physical health	12.0 (2.4)	12.2 (2.6)	−0.74	0.5
Psychological	13.0 (2.7)	13.4 (2.6)	−1.2	0.2
Social relationships	11.9 (4.2)	13.1 (4.2)	−2.0	0.05
Environment	11.6 (3.4)	12.1 (3.3)	−2.8	0.005
NES (Total)	14.1 (7.6)	6.6 (6.1)	7.4	<0.0001
BIS (Total)	5.8 (2.1)	6.2 (2.1)	−1.4	0.2
PANSS insight item	4.8 (1.1)	3.0 (1.1)	11.1	<0.0001

BIS, Birchwood Insight Scale; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functional Assessment Scale; MCCB, MATRICS Consensus Cognitive Battery; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief Version; NES, Neurological Evaluation Scale.
[a] *t*-Test for independent samples.

4. Discussion

This study investigated changes in patient-rated and clinician-rated insight from the acute, floridly psychotic state through the first 24 months of flupenthixol decanoate treatment in patients with a first-episode of schizophrenia spectrum disorder. The most striking finding was that there were minimal improvements in patient-rated insight, while clinicians rated highly significant improvements in global insight. At endpoint, poor self-rated insight persisted in the majority of patients. This occurred despite the fact that medication adherence was assured and the clinical response was generally favourable, with improvements noted for measures of psychopathology, functionality, quality of life, neurological signs and cognition.

At first glance, our findings appear to differ from previous longitudinal studies which reported improvements in insight over the course of treatment (Wiffen et al., 2010a, 2010b; Segarra et al., 2012; David et al., 1995; Cuesta et al., 2000; Mintz et al., 2004; Crumlish et al., 2005; Parellada et al., 2011; Pijnenborg et al., 2015; Gharabawi et al., 2006; Mohamed et al., 2009). However, those studies reported only modest improvements, and substantial insight impairments persisted in the stable phase of illness (Wiffen et al., 2010a, 2010b, Segarra et al., 2012, Parellada et al., 2009). A further possible explanation for our discrepant findings is the role of adherence. We used a depot formulation which provided assured adherence, while in other studies patients with poor insight who were treated with oral antipsychotics may have been less adherent and consequently responded less well to treatment. However, counting against this possibility is that another longitudinal study using long-acting injectable risperidone reported small but significant improvements in insight over six months (Wiffen et al., 2010a, 2010b).

Finally, differences in the diagnostic composition of patient samples across studies might explain our apparently discrepant findings. For example, Parellada et al. (2011) included a more diverse group of psychotic disorders including bipolar disorder, depressive disorder with psychotic symptoms, schizoaffective disorder and brief psychotic disorder. In the subset of patients with schizophrenia and schizophreniform disorder ($n = 57$), the authors found that insight was poorer than in the other psychotic patients, and actually worsened at year two. Similarly, the Wiffen et al. (2010a, 2010b) study, in which 30% of the sample had a diagnosis of schizoaffective disorder reported a positive association between good insight and diagnosis of schizoaffective disorder. Our study included only one patient with schizoaffective disorder, while schizophrenia and schizophreniform disorder made up the rest of the sample. Taken together, these findings suggest that patients with schizophrenia and schizophreniform disorder show little, if any, improvement in insight with treatment, whereas those with an affective component to their illness (mood disorders and schizoaffective disorder) have a greater chance of insight improvement with treatment. Our findings are therefore consistent with the observation that half of persons with schizophrenia do not recognise that they have an illness,

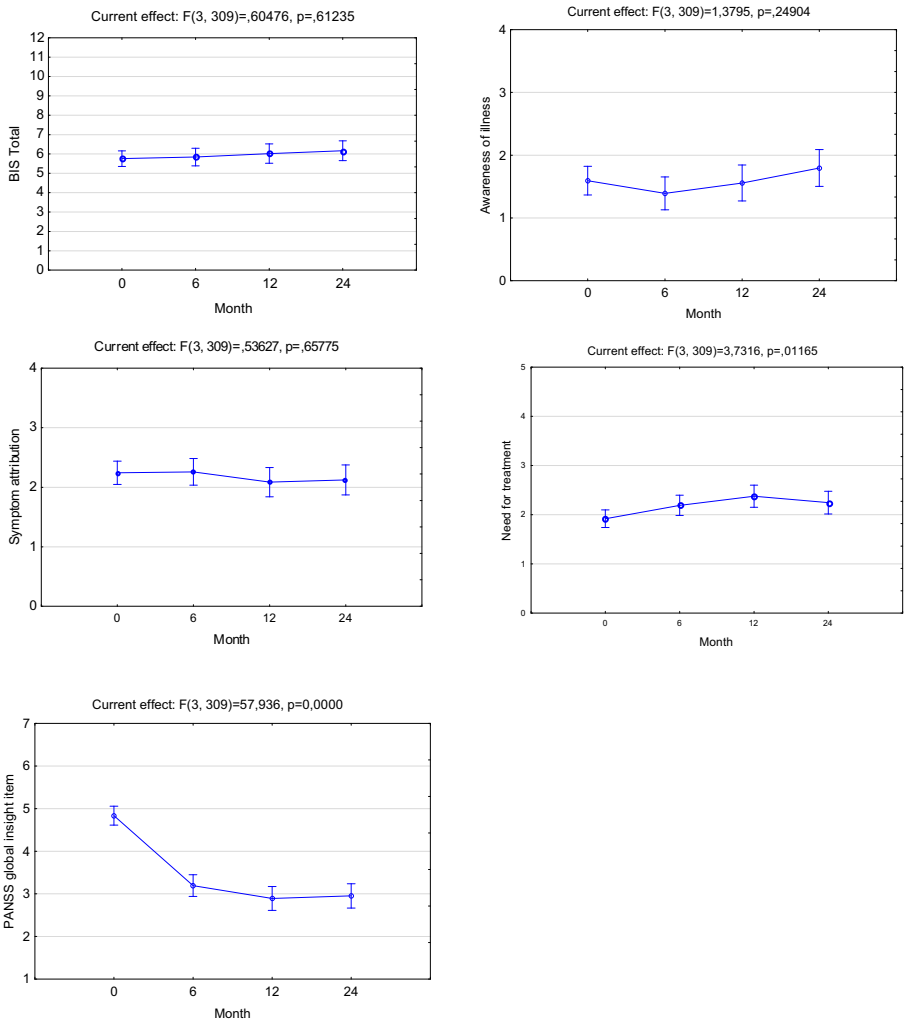

Fig. 1. Linear mixed effects (LS means and 0.95 confidence intervals) for the patient- and clinician-rated insight measures over time.

and this unawareness typically does not improve with treatment (Arango and Amador, 2011).

The failure of patient-rated insight to improve significantly with treatment, and the fact that this occurred despite the generally favourable response in other domains, is consistent with a phenomenologically orientated hypothesis in which insight impairment in schizophrenia is considered a long-standing disorder of the self, from which the psychotic symptoms emerge. While psychotic symptoms respond to treatment, the anomalous self-experiences persist and are considered to be trait-like features (Henriksen and Parnas, 2014). Our findings argue for a large trait-related component to insight in schizophrenia and schizophreniform disorder, perhaps more so than with many of the other clinical manifestations of the illness. Our findings therefore support and extend the proposal that a substantial component of insight impairment is trait-related (Wiffen et al., 2010a, 2010b) and are consistent with reports of specific neurobiological underpinnings of insight impairment (Shad et al., 2007). Indeed, in two neuroimaging studies that we conducted in the present study cohort, we found an association between symptom misattribution and frontal cortical thinning (Asmal et al., 2016) as well as between global insight impairment and white matter connectivity deficits involving a widespread network of tracts with a predilection for cortical midline structures (Asmal et al., 2017).

Our findings are of clinical relevance. They suggest that, even when patients with schizophrenia respond favourably to treatment, fundamental insight impairments persist. This has implications for shared decision making models regarding treatment choice, treatment engagement and medication adherence. Given the high rates of non-adherence in schizophrenia and the risks associated with relapse (Emsley et al., 2013) the most effective psychosocial and pharmacological ways of ensuring continuous treatment in individuals with

Table 2
Pearson correlation coefficients for the insight scores and clinical, functionality and cognitive scores at endpoints.

Variable	BIS Total endpoint		PANSS G12 endpoint	
	r	p-Value	r	p-Value
PANSS	−0.11	0.3	**0.63**	**0.0001**
CDSS	0.09	0.4	−0.05	0.6
SOFAS	0.08	0.5	**−0.40**	**0.0001**
WHOQOL-BREF				
Physical health	0.01	0.9	0.04	0.7
Psychological	−0.17	0.09	**0.23**	**0.02**
Social relationships	0.02	0.8	0.15	0.14
Environment	0.01	0.9	0.18	0.18
MCCB (composite scores)	0.15	0.34	−0.30	0.5
NES	−0.05	0.67	**0.43**	**0.0001**

BIS, Birchwood Insight Scale; PANSS, Positive and Negative Syndrome Scale; CDSS, Calgary Depression Scale for Schizophrenia; SOFAS, Social and Occupational Functional Assessment Scale; MCCB, MATRICS Consensus Cognitive Battery; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief Version; NES, Neurological Evaluation Scale.
Bold values indicates statistically significance at 0.05.

persistent deficits in illness awareness and recognition of the need for treatment should be considered.

In our study, the only predictor of patient-rated overall insight was depression score at baseline. Indeed, depression score also predicted clinician rated insight at baseline. This inverse relationship is in keeping with the well documented "insight paradox", which defines a relationship between better insight and higher depression levels in psychosis (Belvederi et al., 2016). However, the fact that that this was only apparent at baseline suggests that the relationship is only present in the acute psychotic state. Poorer insight according to the clinician global rating was predicted by higher psychopathology levels at baseline and endpoint, consistent with previous studies reporting significant associations between insight and other symptoms. However, similar to our study, effect sizes reported to date were small (Mintz et al., 2003). The association between insight impairment and poorer quality of life on some domains, is consistent with some previous reports (Wiffen et al., 2010a, 2010b; Dickerson et al., 1997; Lysaker et al., 1998; Roseman et al., 2008; Schwartz, 1998) although others found no association (Gharabawi et al., 2006) and others still reported an inverse relationship, i.e. between better insight and poorer quality of life. The relationship between insight impairment and more prominent neurological signs has been previously reported (Hill et al., 2012). The lack of an association between cognition and insight deserves consideration. A systematic review and meta-analysis including data from 72 studies and a total population of 5429 patients reported a small but significant relationship between clinical insight and cognition (Nair et al., 2014). However, evidence remains conflicting, likely due to methodological differences such as different patient samples (e.g. broadly or narrowly defined psychotic disorders, acute or chronic, symptomatic or clinically stable patients and the use of different instruments to assess both insight and cognitive functioning). Our findings are consistent with several longitudinal studies that did not find an association between insight and cognition (David et al., 1995; McEvoy et al., 1993; Kemp and David, 1996; Cuesta et al., 2006). The small effect sizes of the associations that were found with clinician rated global insight measures and other domains, together with the absence of associations with functionality and cognition, are consistent with other studies suggesting that insight is relatively independent of these other domains (Wiffen et al., 2010a, 2010b; Parellada et al., 2011). This appears to be particularly true for patient-rated insight, suggesting that this would be the best measure of trait-related insight.

4.1. Strengths and limitations

This study addressed several important methodological shortcomings of previous studies. First, by including minimally treated, first-episode patients we avoided effects of previous antipsychotic treatment and illness chronicity. Second, standardisation of treatment avoided possible differential effects of various antipsychotics, and use of a depot formulation removed the confounding effect of non- and partial adherence. While the association between poor insight and poor outcome could be explained by more severe symptoms causing poorer insight, it is equally possible that impaired insight causes non-adherence which in turn results in poorer treatment outcome (Lysaker et al., 2018). Third, the longitudinal nature of the study and relatively long follow-up period over 24 months, together with multiple assessment points, allowed us to track changes in insight over time. Finally, using the BIS allowed assessment of different components insight and together with the PANSS global insight item allowed comparison of both patient-rated and clinician-rated assessments of insight.

There are also limitations to consider. First, a possible explanation for the lack of improvement in patient-rated insight in our study is that cross-cultural factors may play a role. The clinical assessment of insight focuses largely on the biomedical model and may underestimate the role that cultural and social-environmental factors play in explanatory models that may fundamentally shape insight (Belvederi and Amore, 2018; Jacob, 2014). This means patients who may offer a culturally appropriate explanation for symptoms of illness may be scored lower than those who offer a biomedical explanation. Second, it is also possible that the limited educational status of our participants restricted their capacity to comprehend the statements in the BIS, and that consequently the clinician-rated assessment may more accurately reflect their true levels of insight. We consider this unlikely however, as our two study nurses took care to explain the meaning of each of the BIS questions and assisted participants in completing the scales, and in any event educational status did not correlate significantly with insight scores. Third, an alternative explanation is that patient-rated and clinician-rated instruments may not be measuring the same aspects of insight. While the clinician-rated PANSS insight item has been reported to strongly correlate with other, more comprehensive insight scale (Sanz et al., 1998) it not only rates insight but also "judgement" and is mono-dimensional. As such, it is subject to inter-rater bias and fails to capture the multidimensional nature of insight. Most importantly, it is possible that clinician assessments of insight may be influenced by overall impressions of illness improvement (Marks et al., 2000) and may not represent actual insight levels. This would be consistent with our finding of a significant correlation between patient-rated and clinician-rated insight at baseline but not at endpoint, as well as the significant associations of clinician-rated global insight with psychopathology and quality of life at both baseline and endpoint. Fourth, the narrow diagnostic inclusion criteria, while having the advantage of assessing insight in schizophrenia spectrum disorders specifically, means that results cannot be generalised to other diagnostic groups. Similarly, standardisation of treatment precludes generalisation of our findings to patients treated with other antipsychotics. Finally, our participants did not receive any formal psychological interventions aimed at improving insight. These interventions may improve insight, although a significant effect has not yet been demonstrated (Pijnenborg et al., 2013).

In conclusion, our findings suggest that insight as rated by patients is not responsive to antipsychotic treatment, and should be considered a trait feature of the illness. Future studies should take care to differentiate between patient and clinician rated assessments of insight.

Authors' contribution

Robin Emsley, Lebogang Phahladira, Laila Asmal and Bonginkosi Chiliza were responsible for the study conception and design. Sanja Killian, Freda Scheffler, Stefan Du Plessis and Hilmar Luckhoff were responsible for collection, extraction and coding of data included in the study. Robin Emsley provided the analysis and interpretation. Lebogang Phahladira and Robin Emsley drafted the manuscript, and all other authors provided critical comments.

All authors provided intellectual contribution and approved the final manuscript.

Declaration of interest

Bonga Chiliza has received speakers fees from Cipla, Lundbeck, and Sanofi. Robin Emsley has received speakers fees and participated in advisory boards from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

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References

Addington, D., Addington, J., 1993. Assessing depression in schizophrenia: the Calgary Depression Scale. Br. J. Psychiatry 163, S39–S44.

Amador, X.F., Flaum, M., Andreasen, N.C., Strauss, D.H., Yale, S.A., Clark, S.C., et al., 1994. Awareness of illness in schizophrenia and schizoaffective and mood disorders. Arch. Gen. Psychiatry 51 (10), 826–836 (Oct).

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (Washington, D.C.).
Arango, C., Amador, X., 2011. Lessons learned about poor insight. Schizophr. Bull. 37 (1), 27–28 (Jan).
Asmal, L., du Plessis, S., Vink, M., Chiliza, B., Kilian, S., Emsley, R., 2016. Symptom attribution and frontal cortical thickness in first-episode schizophrenia. Early Interv. Psychiatry 12 (4), 652–659 (Aug 29).
Asmal, L., du Plessis, S., Vink, M., Fouche, J.P., Chiliza, B., Emsley, R., 2017. Insight and white matter fractional anisotropy in first-episode schizophrenia. Schizophr. Res. 183, 88–94 (May).
Belvederi, M.M., Amore, M., 2018. The multiple dimensions of insight in schizophrenia-spectrum disorders. Schizophr. Bull. https://doi.org/10.1093/schbul/sby092 (Jun 23).
Belvederi, M.M., Amore, M., Calcagno, P., Respino, M., Marozzi, V., Masotti, M., et al., 2016. The "insight paradox" in schizophrenia: magnitude, moderators and mediators of the association between insight and depression. Schizophr. Bull. 42 (5), 1225–1233 (Sep).
Birchwood, M., Smith, J., Drury, V., Healy, J., Macmillan, F., Slade, M., 1994. A self-report Insight Scale for psychosis: reliability, validity and sensitivity to change. Acta Psychiatr. Scand. 89 (1), 62–67 (Jan).
Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res. 27 (3), 335–350 (Mar).
Chouinard, G., Margolese, H.C., 2005. Manual for the extrapyramidal symptom rating scale (ESRS). Schizophr. Res. 76, 247–265.
Crumlish, N., Whitty, P., Kamali, M., Clarke, M., Browne, S., McTigue, O., et al., 2005. Early insight predicts depression and attempted suicide after 4 years in first-episode schizophrenia and schizophreniform disorder. Acta Psychiatr. Scand. 112 (6), 449–455 (Dec).
Cuesta, M.J., Peralta, V., Zarzuela, A., 2000. Reappraising insight in psychosis. Multi-scale longitudinal study. Br. J. Psychiatry 177, 233–240 (Sep).
Cuesta, M.J., Peralta, V., Zarzuela, A., Zandio, M., 2006. Insight dimensions and cognitive function in psychosis: a longitudinal study. BMC Psychiatry 6, 26 (May 31).
Dam, J., 2006. Insight in schizophrenia: a review. Nord. J. Psychiatry 60 (2), 114–120.
David, A., van Os, J., Jones, P., Harvey, I., Foerster, A., Fahy, T., 1995. Insight and psychotic illness. Cross-sectional and longitudinal associations. Br. J. Psychiatry 167 (5), 621–628 (Nov).
Dickerson, F.B., Boronow, J.J., Ringel, N., Parente, F., 1997. Lack of insight among outpatients with schizophrenia. Psychiatr. Serv. 48 (2), 195–199 (Feb).
Emsley, R., Chiliza, B., Asmal, L., Harvey, B.H., 2013. The nature of relapse in schizophrenia. BMC Psychiatry 13, 50 (Feb 8).
First, M.B., Spitzer, R.L.G.M., Williams, L.B.W., 1994. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P). 2nd ed. New York State Psychiatric Institute, Biometrics Research, New York.
Gharabawi, G.M., Lasser, R.A., Bossie, C.A., Zhu, Y., Amador, X., 2006. Insight and its relationship to clinical outcomes in patients with schizophrenia or schizoaffective disorder receiving long-acting risperidone. Int. Clin. Psychopharmacol. 21 (4), 233–240 (Jul).
Henriksen, M.G., Parnas, J., 2014. Self-disorders and schizophrenia: a phenomenological reappraisal of poor insight and noncompliance. Schizophr. Bull. 40, 542–547.
Hill, M., Crumlish, N., Whitty, P., Clarke, M., Browne, S., Gervin, M., et al., 2012. The relationship between insight and neurological dysfunction in first-episode psychosis. Eur. Psychiatry 27 (3), 200–205 (Apr).
International Conference on Harmonization, 1996. ICH Harmonised Tripartite Guidelines for Good Clinical Practice. Brookwood Medical Publications Ltd, Surrey.
Jacob, K.S., 2014. Insight in psychosis: an independent predictor of outcome or an explanatory model of illness? Asian J. Psychiatr. 11, 65–71.
Kay, S.R., Fizbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–267.
Kemp, R., David, A., 1996. Psychological predictors of insight and compliance in psychotic patients. Br. J. Psychiatry 169 (4), 444–450 (Oct).
Lysaker, P.H., Bell, M.D., Bryson, G.J., Kaplan, E., 1998. Insight and interpersonal function in schizophrenia. J. Nerv. Ment. Dis. 186 (7), 432–436 (Jul).
Lysaker, P.H., Pattison, M.L., Leonhardt, B.L., Phelps, S., Vohs, J.L., 2018. Insight in schizophrenia spectrum disorders: relationship with behavior, mood and perceived quality of life, underlying causes and emerging treatments. World Psychiatry 17 (1), 12–23 (Feb).
Marks, K.A., Fastenau, P.S., Lysaker, P.H., Bond, G.R., 2000. Self-Appraisal of Illness Questionnaire (SAIQ): relationship to researcher-rated insight and neuropsychological function in schizophrenia. Schizophr. Res. 45 (3), 203–211 (Oct 27).
McEvoy, J.P., Freter, S., Merritt, M., Apperson, L.J., 1993. Insight about psychosis among outpatients with schizophrenia. Hosp. Community Psychiatry 44 (9), 883–884 (Sep).
Mintz, A.R., Dobson, K.S., Romney, D.M., 2003. Insight in schizophrenia: a meta-analysis. Schizophr. Res. 61 (1), 75–88 (May 1).
Mintz, A.R., Addington, J., Addington, D., 2004. Insight in early psychosis: a 1-year follow-up. Schizophr. Res. 67 (2–3), 213–217 (Apr 1).
Mohamed, S., Rosenheck, R., McEvoy, J., Swartz, M., Stroup, S., Lieberman, J.A., 2009. Cross-sectional and longitudinal relationships between insight and attitudes toward medication and clinical outcomes in chronic schizophrenia. Schizophr. Bull. 35 (2), 336–346 (Mar).
Nair, A., Palmer, E.C., Aleman, A., David, A.S., 2014. Relationship between cognition, clinical and cognitive insight in psychotic disorders: a review and meta-analysis. Schizophr. Res. 152 (1), 191–200 (Jan).
Nuechterlein, K.H., Green, M.F., 2006. MATRICS Consensus Battery Manual. MATRICS Assessment Inc., Los Angeles.
Parellada, M., Fraguas, D., Bombin, I., Otero, S., Castro-Fornieles, J., Baeza, I., et al., 2009. Insight correlates in child- and adolescent-onset first episodes of psychosis: results from the CAFEPS study. Psychol. Med. 39 (9), 1433–1445 (Sep).
Parellada, M., Boada, L., Fraguas, D., Reig, S., Castro-Fornieles, J., Moreno, D., et al., 2011. Trait and state attributes of insight in first episodes of early-onset schizophrenia and other psychoses: a 2-year longitudinal study. Schizophr. Bull. 37 (1), 38–51 (Jan).
Pijnenborg, G.H., van Donkersgoed, R.J., David, A.S., Aleman, A., 2013. Changes in insight during treatment for psychotic disorders: a meta-analysis. Schizophr. Res. 144 (1–3), 109–117 (Mar).
Pijnenborg, G.H., Timmerman, M.E., Derks, E.M., Fleischhacker, W.W., Kahn, R.S., Aleman, A., 2015. Differential effects of antipsychotic drugs on insight in first episode schizophrenia: data from the European First-Episode Schizophrenia Trial (EUFEST). Eur. Neuropsychopharmacol. 25 (6), 808–816 (Jun).
Roseman, A.S., Kasckow, J., Fellows, I., Osatuke, K., Patterson, T.L., Mohamed, S., et al., 2008. Insight, quality of life, and functional capacity in middle-aged and older adults with schizophrenia. Int. J. Geriatr. Psychiatry 23 (7), 760–765 (Jul).
Sanz, M., Constable, G., Lopez-Ibor, I., Kemp, R., David, A.S., 1998. A comparative study of insight scales and their relationship to psychopathological and clinical variables. Psychol. Med. 28 (2), 437–446 (Mar).
Schwartz, R.C., 1998. Insight and illness in chronic schizophrenia. Compr. Psychiatry 39 (5), 249–254 (Sep).
Segarra, R., Ojeda, N., Pena, J., Garcia, J., Rodriguez-Morales, A., Ruiz, I., et al., 2012. Longitudinal changes of insight in first episode psychosis and its relation to clinical symptoms, treatment adherence and global functioning: one-year follow-up from the Eiffel study. Eur. Psychiatry 27 (1), 43–49 (Jan).
Shad, M.U., Keshavan, M.S., Tamminga, C.A., Cullum, C.M., David, A., 2007. Neurobiological underpinnings of insight deficits in schizophrenia. Int. Rev. Psychiatry 19 (4), 437–446 (Aug).
The WHOQOL Group, 1998. Development of the World Health Organization WHOQOL-BREF quality of life assessment. Psychol. Med. 28 (3), 551–558.
Velligan, D.I., Sajatovic, M., Hatch, A., Kramata, P., Docherty, J.P., 2017. Why do psychiatric patients stop antipsychotic medication? A systematic review of reasons for nonadherence to medication in patients with serious mental illness. Patient Prefer Adherence 11, 449–468.
Wiffen, B.D., Rabinowitz, J., Fleischhacker, W.W., David, A.S., 2010a. Insight: demographic differences and associations with one-year outcome in schizophrenia and schizoaffective disorder. Clin. Schizophr. Relat. Psychoses 4 (3), 169–175 (Oct).
Wiffen, B.D., Rabinowitz, J., Lex, A., David, A.S., 2010b. Correlates, change and 'state or trait' properties of insight in schizophrenia. Schizophr. Res. 122 (1–3), 94–103 (Sep).