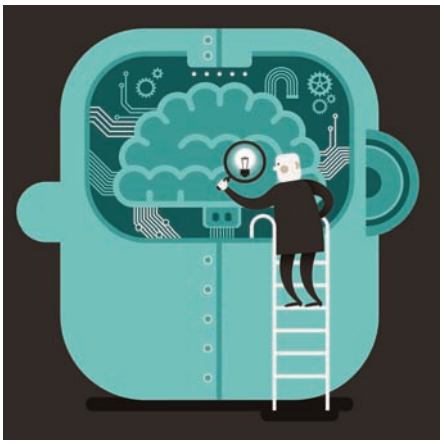

Anosognosia in Schizophrenia: Hidden in Plain Sight

by DOUGLAS S. LEHRER, MD, and JENNIFER LORENZ, MD

Dr. Lehrer is from Wright State University Boonshoft School of Medicine, Department of Psychiatry, Dayton, Ohio, and Summit Behavioral Healthcare, Cincinnati, Ohio; Dr. Lorenz is from Wright State University Boonshoft School of Medicine, Department of Psychiatry, Dayton, Ohio, and USAF Medical Center, Wright-Patterson Air Force Base, Department of Mental Health, Ohio.

Innov Clin Neurosci. 2014;11(5–6):10–17

SECTION EDITOR: Paulette Gillig, MD, PhD, Professor of Psychiatry, Wright State University, Boonshoft School of Medicine, Department of Psychiatry, Dayton Ohio

FUNDING: No funding was received for the development of this article.

FINANCIAL DISCLOSURES: The authors have no conflicts of interest relevant to the content of this article.

ADDRESS CORRESPONDENCE TO: Douglas Lehrer, MD, Chief Clinical Officer, Summit Behavioral Healthcare, 1101 Summit Road, Cincinnati, OH 45237; Phone: (513) 948-3909; Fax: (513) 948-8631; E-mail: Douglas.Lehrer@wright.edu

KEY WORDS: Schizophrenia, psychosis, insight, anosognosia, cognition

ABSTRACT

Objective: Poor insight is a cardinal symptom of schizophrenia that, while not universally and uniformly expressed in all patients, is among the most common of its manifestations. Available neurobiological and neurocognitive evidence linking the phenomenon to core pathophysiology of schizophrenia justifies extension of the anosognosia construct to schizophrenia-related insight deficits. Poor insight is a core attribute of schizophrenia, occurring in 57 to 98 percent of patients. Insight is an important outcome predictor, associated with treatment adherence, relapse frequency, symptom remission, psychosocial functioning, vocational attainment, and risk of violence toward self or others. Combined findings lend urgency to the importance of reducing psychotic relapse. This can only be achieved in the majority of patients with consistent medication adherence—something that is often exceedingly difficult in patients lacking belief in the fact of their illness. This article examines whether anosognosia, the unawareness of deficit or illness, should apply to our understanding of insight deficits in patients with schizophrenia. Although research in the field is limited at this time, there is hope that anosognosia as a symptom of schizophrenia will become a focus of further research and a critically important therapeutic target amenable to treatment.

Design: This article is a literature review and conceptualization.

Conclusion: Limited research in the field gives cause for hope that anosognosia as a symptom of schizophrenia will become a critically important therapeutic target that is amendable to treatment.

INTRODUCTION

"I don't need medicine—there is nothing wrong with me. I just came here for a check-up."

The arrival of chlorpromazine more than six decades ago brought an almost jubilant sense of optimism in the treatment of patients with psychosis. Though controversies exist regarding whether, in fact, the neuroleptic era has actually resulted in better long-term outcomes,[1-3] no practicing psychiatrist could possibly deny that rejection of antipsychotic medications is a key factor in poor prognosis. While patients may stop taking their medication for cogent reasons (e.g., side effects, inability to negotiate logistics of scheduling doctor visits, loss of prescription benefits), a lack of insight into the fact of psychosis often lies at the heart the problem. Recent neuroscientific inquiry into the nature of the insight deficit has reconceptualized and linked the phenomenon of lack of insight to brain-based pathology, and is the subject of this review.

INSIGHT DEFICITS

Poor insight is a core attribute of schizophrenia that is highly prevalent, occurring in 57 to 98 percent of patients with schizophrenia.[4] A widely accepted definition of insight incorporates the following conceptual elements: awareness of having an illness, recognizing the signs and symptoms of the illness, attributing consequences and deficits to the illness, and understanding the need for treatment of the illness. Insight is thus best understood as a multidimensional construct rather than an "all or none" phenomenon.[5] Several theories attempt to explain poor insight in psychotic patients. The "clinical model" postulates that insight is a primary symptom attributable to the psychotic process. The "psychological denial model" views poor insight as a coping mechanism to preserve emotional well-being by protecting against distress. The "neuropsychological model" contends that poor insight is caused by inadequate neurocognition caused by brain deficits.[6]

Investigation of insight deficits requires not only a carefully operationalized definition of insight, but also a systematic means of measuring and quantifying the phenomenon. This challenge has been approached in a variety of ways, resulting in several scales used in research. Some investigators have utilized specific insight-related items on broader psychiatric rating scales, particularly when primary study aims were not directly related to insight. For example, the General Symptoms item 12 (G12) of the 30-item Positive and Negative Syndrome Scale (PANSS)[7] rates "impaired insight and judgment" from 1 (no impairment) to 7 (severe impairment). Investigators with more focused interests in the phenomenology and effects of insight deficits have developed dedicated, multidimensional insight scales. While a thorough review of these various tools is beyond the scope of this paper, we will cite a few illustrative examples.

The Insight and Treatment Attitudes Questionnaire (ITAQ)[8] is an 11-item semi-structured interview that measures awareness of illness and attitudes regarding treatment, and was probably the first scale developed specifically to measure insight in psychiatric subjects. McEvoy et al designed the ITAQ for a study of 52 patients with schizophrenia who were examined acutely and longitudinally for 2.5 to 3.5 years.[8] They observed a trend toward significance (p=0.53) in the positive relationship between initial ITAQ scores and quality of outcomes, and observed that insight was not consistently related to the magnitude of acute psychopathology.[8]

Most widely used in research primarily concerned with insight in psychotic patients is the Scale to Assess Unawareness of Mental Disorder (SUMD), developed by Amador et al,[9] who considered insight a multidimensional concept that occurs on a continuum. The SUMD distinguishes the processes of awareness and attribution, defining the former as "recognition of signs or symptoms of an illness" and the latter as "explanations about the cause or source of these signs or symptoms." It also prompts current and retrospective assessments of signs and symptoms. The scale was designed for use in schizophrenia as well as other mental disorders. Ratings are provided on the basis of direct patient interview. Amador et al[10] used the SUMD during their field trials to investigate the severity of self-awareness deficits across several psychosis-prone disorders. They compared insight deficits in subjects with schizophrenia and schizoaffective disorders to those with psychotic and nonpsychotic mood disorders. They assessed patients' awareness of the efficacy of pharmacotherapy, the social consequences of having a mental disorder, and six common symptoms of schizophrenia: hallucinations, delusions, anhedonia, asociality, thought disorder, and blunt affect. They found that schizophrenia groups had the greatest incidence of self-awareness deficits on multiple items relative to other groups that included patients with schizoaffective disorder, psychotic depression, or bipolar mania.

There are self-administered, validated tools as well, such as the Beck Cognitive Insight Scale (BCIS),[11] which is based on a separation of the concepts of "cognitive insight" and "clinical insight." Clinical insight is described as the awareness of mental illness requiring treatment, while cognitive insight encompasses the patient's ability to evaluate, reappraise, and modify distorted beliefs or misperceptions. These interpretations are regulated at a "higher level" of cognition, also called metacognition, allowing clinicians to assess self-regulating and self-monitoring functions of thought processes. The BCIS assesses a patient's objectivity about delusional thinking, previous errors, reattribution of false explanations, and ability to receive corrective information from others. It includes self-reflectiveness and self-certainty subscales in order to measure willingness and capacity to entertain alternate explanations and over-confidence in validity of beliefs.

SIGNIFICANCE OF INSIGHT DEFICITS IN SCHIZOPHRENIA

Insight is an important outcome predictor associated with treatment adherence, relapse frequency, symptom remission, psychosocial functioning, vocational attainment, and risk of violence toward self or others.[4] Diminished insight increases the likelihood of involuntary hospitalizations and utilization of emergency services.[12] Lacro et al[13] reviewed two decades of literature concerning risk factors for nonadherence with antipsychotic drug regimens in patients with schizophrenia and

reported poor insight as most consistently implicated. Whether a patient chooses to take medications or not may have a marked effect on his prognosis. Leucht et al[14] recently published a broad and extensive meta-analysis of 50 years of antipsychotic therapy in people with schizophrenia. They reported that patients who took antipsychotic drugs were less likely to relapse, need re-hospitalization, or engage in aggression, and also enjoyed a better quality of life. Relapse, in turn, increases the economic burden of treatment and contributes to the stigma of mental illness.[15]

The manner in which an individual who is undergoing the initial onset of illness understands his or her situation may also have implications for long-term outcomes. Many patients with mental illness are afflicted with symptoms for years before receiving adequate treatment, including physician consultation, correct diagnosis, and initiation of pharmacologic treatment. Early recognition of the pathological nature of evolving psychosis could prompt the person to confide in loved ones and seek immediate help, thereby reducing the duration of untreated psychosis (DUP).[16] Poor insight, avolition, and social isolation predicts longer DUP, which is then associated with more severe symptoms at hospital admission or outpatient intake, poor prognosis, decreased response to neuroleptic medications, elevated suicide risk, more severe cognitive and negative symptoms, and more frequent relapses and hospitalizations.[17,18] DUP is of particular interest when addressing negative symptoms. DUP lasting less than nine months predicts improvement of negative symptoms, while DUP lasting longer than nine months is associated with high incidence of persistent negative symptoms. Consequences of negative symptoms include cognitive deficits, poor functional outcome, social impairment, and poor quality of life. There is currently no established treatment other than prevention to address primary negative symptoms, and pharmacologic treatments have a limited impact on symptoms.[19] It is important to identify patients in the early stages of psychosis or who are at high risk for developing psychosis in order to reduce DUP. Effective antipsychotic pharmacotherapy early in the disorder could have a positive impact on prognosis, reducing long-term morbidity possibly through the putative neuroprotective role of these medications.[20]

Reduction of time spent in a state of psychosis is important because active psychosis may indicate a period of disease progression. Psychotic relapse may cause positive symptoms to become increasingly refractory to antipsychotic medications, with failure to return to previous levels of functioning.[15] Lieberman et al[21] noted in their landmark early-1990s, first-episode studies that recovery times subsequent to resumption of treatment following relapse became increasingly prolonged with each successive relapse. Cahn et al[22] explored the neuroanatomical correlates of this phenomenon using magnetic resonance imaging (MRI) in which 48 patients during the first five years of schizophrenia underwent serial structural MRI to measure brain volume. Longer cumulative duration of active psychosis was associated with greater decreases in gray matter volume and increase in lateral and third ventricle volumes. Andreasen et al[23] similarly performed semiannual MRI examinations over an average period of seven years in 202 patients enrolled in the Iowa Longitudinal Study. Andreasen reported that "duration of relapse is closely related to loss of brain tissue over time in multiple brain regions, including indicators of generalized tissue loss (total cerebral volume) and loss in subregions, particularly the frontal lobes. Simply counting the number of relapses (exclusive of duration), on the other hand, has no predictive value." Andreasen postulated a "three-hit hypothesis" to explain the mechanism of brain tissue loss during relapse: 1) developing neural pathways undergo premorbid dyplasia, 2) peri-onset excessive elimination of synapses results in glutamatergic and dopaminergic dysfunction, and, 3) relapse leads to neuronal loss via excitotoxicity caused by glutamatergic and dopaminergic dysregulation and related oxidative stress. Christensen, Holcomb, and Garver[24] offered an alternative hypothesis of relapse-related neurotoxicity based upon their observation of white matter changes in serial MRIs of relapsing/remitting subjects with schizophrenia. Noting that myelin-containing oligodendrocytes comprise cerebral white matter and that oligodendrocytes are sensitive to glutamate-induced excitotoxicity, the authors concluded that "swelling of myelin and of white matter, associated interference with the speed of neurotransmission through myelinated axons, and dyssynchrony of information processing by subcortical and cortical networks may be associated with psychosis exacerbation."

In any case, these combined findings lend urgency to the importance of reducing psychotic relapse. At the present time, this can only be achieved in the majority of patients with consistent medication adherence-something that is often exceedingly difficult in patients lacking belief in the fact of their illness. On the other hand, Andreasen cautioned, it is important to use the lowest possible dosage to control symptoms since overly aggressive intensive treatment with (especially first-generation) antipsychotic medications that are currently available has paradoxically been implicated in tissue loss.

ANOSOGNOSIA: A NEUROLOGICAL CONSTRUCT FOR INSIGHT DEFICITS

The term *anosognosia* (a=without, noso=disease,

gnosia=knowledge) was coined by French neurologist Joseph Babinksi in 1914 to describe the unawareness of deficit or illness, specifically referring to cases of left hemiplegia. Babinski believed the lesions were cortically based and likely located in the right hemisphere. He noted that patients were often oblivious to deficits (anosognosia) or unconcerned with the severity of disability (anosodiaphorie).[25] His contemporary, Gabriel Anton, described the failure to recognize visual loss in cortical blindness patients, a phenomenon now known as the Anton-Babinski syndrome. The term *anosognosia* now more broadly refers to a neurologically based denial of illness and unawareness of disability, not limited to patients with hemiplegia.

Should this construct be applied to our understanding of insight deficits in schizophrenia? To do so, there should be sufficient evidence that pathophysiological changes associated with schizophrenia bear meaningful relationships with insight impairments. This does appear to be the case.

PREFRONTAL CORTEX

The prefrontal cortex (PFC) has been an area of intense investigation in schizophrenia since the days of Kraepelin and Alzheimer. In fact, we now consider prefrontal neuropil loss, gray matter volume reduction, functional "hypofrontality," and executive cognitive dysfunction to be signature pathophysiologies of schizophrenia. Therefore, the PFC is an appropriate brain region in which to probe for any statistical relationships with insight deficits in these patients.

Shad, Muddasani, and Keshavan[26] measured MRI-derived volumes in the dorsolateral and orbitofrontal regions of the PFC (DLPFC and OFC, respectively) in 14 medication-naïve, first-episode schizophrenia patients and 21 healthy controls. The investigators utilized the SUMD to quantify insight function in the patients in order to explore the potential correlation between insight and prefrontal subregional volume. They found an inverse relationship between right DLPFC volume and awareness of symptoms and a positive correlation between right OFC volume and attribution of symptoms. These findings were asserted to be consistent with an understanding of the differential functions of the prefrontal subregions. That is, the DLFPC is critical to self-monitoring and organization; therefore a decrease in DLFPC volume might lead to impaired symptom awareness. In contrast, the OFC exerts executive modulation over limbic processing, likely playing a critical role in attribution of significance of events. The authors explained the OFC findings in light of Kapur's "motivational salience" model of psychosis,[27] suggesting that increased OFC function (assumed from increased volume) caused subjects to experience percepts with aberrantly elevated salience, leading to misattribution of symptoms.

Neurocognitive tests of prefrontal and executive functioning have also probed the relationship between insight and regional PFC function. Aleman et al[28] performed a meta-analysis of 35 studies published between 1980 and 2004. The studies that were included used measures of IQ and/or prefrontal and executive function, the latter most often represented by the Wisconsin Card Sorting Test (WCST), which is generally considered to be a highly sensitive and valid neurocognitive measure of prefrontal function. Notably, the studies included those focusing on schizophrenia in particular as well as those more broadly concerned with psychosis. While the relationship between IQ and insight was weak, the relationship between WCST scores and insight was consistent and robust. Moreover, the WCST-insight relationship was strongest in people with schizophrenia, per se, rather than being equally observed in those with psychotic disorders in general.

Shad et al[29] also published a review of 34 English-language studies that investigated the relationship between frontal lobe function as measured by neurocognitive tests, and insight deficits in subjects with schizophrenia. As with the above meta-analysis, they found that the most consistently replicated findings were of positive correlations between Wisconsin Card Sorting Test scores and indicators of intact insight. The authors suggested that insight deficits might result from impaired prefrontal mediation of conceptual organization and flexibility in abstract thinking. They also offered an "insight-anosognosia model" that probably involves parietal structures and bears underlying similarities with that suffered by neurological patients.

Orfei et al[30] used the BCIS along with structural and diffusion tensor MRI neuroimaging techniques (latter to inspect white matter architectural organization) to study the neuroanatomy of cognitive insight in schizophrenia, comparing 45 patients with schizophrenia to 45 healthy control subjects. The results showed a correlation between insight as measured by the BCIS self-reflectiveness index and lower gray matter volume in the right ventrolateral prefrontal cortex (VLPFC). The VLPFC is involved in working memory and decision making. The findings suggest that a reduced VLPFC volume corresponds with a diminished capacity to entertain alternative explanations about one's misperceptions leading to impairment in awareness of illness.

INSULAR CORTEX AND ERROR AWARENESS

The insula modulates awareness of interoceptive stimuli—that is, awareness and appraisal of internal states. As such, it is critically involved in sensory and emotional processing and sense of self. Among

the many insular functions (and as a broad generalization), the anterior insula is involved in emotional processing while the posterior insula is critical to multimodal sensory processing particularly somatosensory but also auditory and visceral modes.[31,32] Moreover, the insula has multiple and complex connections to other brain areas, including those implicated in the pathophysiology of schizophrenia, such as the PFC (OFC and anterior cingulate cortex [ACC]), limbic system, thalamus (mediodorsal and ventroposterolateral nuclei), and the specific sensory cortices.

Multiple investigators have found insular abnormalities in people with schizophrenia, and using a wide range of experimental methods including in-vivo imaging and post-mortem inspection. Glahn et al[33] completed a meta-analysis (31 peer-reviewed articles, 1,195 patients and 1,262 healthy control subjects) to examine regional gray matter changes in schizophrenia. The bilateral insular cortices stood out as showing the greatest effect size of gray matter volume reductions in patients versus controls. Jakob and Beckmann[34] described cytoarchitectural abnormalities in post-mortem brains of some but not all studied decedents who had schizophrenia. Various investigators using functional MRI during facial emotion or vocal prosody recognition activation paradigms identified the insula as a key region of interest distinguishing persons with schizophrenia versus healthy subjects.[31] Farrer et al[35] measured regional cerebral blood flow (rCBF) using H2O15 positron emission tomography (PET) to determine the neuroanatomy of attribution of agency. Eight subjects with schizophrenia and eight healthy control subjects underwent scanning during a task in which they attempted to control the motion of a virtual hand using a joystick. At times, the "hand" was actually under the subject's control while at other times it was not; the distinction was ambiguous, thus challenging the subject's ability to attribute agency to the perceived action. While normal control subjects showed increased rCBF in the right insular cortex and right angular (parietal) cortex during periods of actual control, subjects with schizophrenia failed to show this hemodynamic activation response to the changing conditions.

Palaniyappan et al[36] explicitly linked insular abnormalities with insight deficits in subjects with schizophrenia. They measured bilateral insular cortical surface area and white matter volume using MRI in 57 relatively stable (average Global Assessment of Function [GAF] score=63) subjects with schizophrenia, and statistically measured correlations with a single-item insight score derived from the Signs and Symptoms of Psychotic Illness scale (SSPI). They found significant relationships in the right but not left insular with moderate effect sizes (Spearman's r=-0.041 and -0.35 for area and white matter volume, respectively).

Klein, Ullsperger, and Danielmeier[37] postulated a neuroanatomic model of insular function in which the anterior insula is involved in conscious error detection ("error awareness") and the detection of unexpected outcomes and salient stimuli, while the posterior insula is more involved in integrating somatosensory input. Extrapolating from their model, we might predict that ideas of reference might be associated anteriorally, while hallucinatory phenomena and "Schneiderian" delusions of external bodily control could involve posterior insular involvement.

DEFAULT MODE NETWORK

Marcus Raichle et al[38] postulated in 2001 the existence of an organized default mode of brain function that is activated during periods of wakeful rest and deactivated during focused activity. Subsequent research, principally reliant on functional neuroimaging modalities, described an anatomically identifiable "default mode network" (DMN). This distributed brain network includes the medial prefrontal cortex, lateral parietal cortex, anterior cingulate cortex, posterior cingulate cortex, and precuneus. The DMN is involved with processes of self-reflection, social cognition, and mind-wandering. Hyperconnectivity has been noted in the DMN of individuals at high risk for developing schizophrenia.

Whitfield-Gabrieli et al[39] studied patients with schizophrenia; young, at-risk, first-degree relatives; and unaffected controls using fMRI during alternating conditions of wakeful rest and a focused working memory task. While the unaffected controls showed predictable deactivation of DMN during active task, the patients and relatives showed diminished deactivation, as well as greater activity in right DLPFC. This finding has essentially been replicated twice by two other research groups.

Liemburg et al[40] studied connectivity within the DMN and hypothesized that poor-insight patients (n=19) would show greater connectivity impairment than their good-insight peers (n=25). Insight grouping was assigned on the basis of the PANSS insight item (G12). All subjects underwent resting fMRI. Results showed that "schizophrenia patients with relatively preserved insight showed stronger connectivity than patients with poor insight in the anterior cingulate cortex and precuneus, both key regions in self-reflective processing. These findings tentatively support the hypothesis that poor insight may be related to impaired self-related processing." In other words, poor insight was associated with a relative breakdown of DMN connectivity and operations.

TREATMENT CONSIDERATIONS

In 2003, the World Health Organization (WHO) stated that "the need to develop strategies to

improve adherence is an essential element in reducing the global burden of disease." In no field of healthcare is this statement more valid than in schizophrenia. Treatment aimed at improving insight could have a tremendous impact on outcomes of schizophrenia. Insight is rarely specifically measured in treatment studies, despite research suggesting its independence from other psychotic symptoms. Regrettably, but not surprisingly, no medication specifically targets insight.

A recent meta-analysis[41] reviewed the impact of various treatments on insight. The review was limited by small effect size and scarceness of studies specifically measuring insight. Cognitive behavioral therapy, adherence therapy, and psychoeducation were found to have small-to-moderate effects on insight, though not statistically significant. Social skills training and video self-observation may be beneficial in treating insight; however, more evidence is needed to evaluate the efficancy of these treatments. Comprehensive treatments involving multiple treatment modalities have also shown promising results.

A limited literature concerning novel somatic interventions is of interest. Gerretsen et al[42] described a treatment-resistant 39-year-old man with schizophrenia who showed brief illness awareness following a dose of bilaterally applied electroconvulsive therapy (ECT). Levine et al[43] similarly demonstrated a short-lived insight improvement following left-ear, cold-water, caloric vestibular nerve stimulation (CVS) first in a patient with psychotic mania and then with two patients with schizophrenia. Finally, Kim et al[44] reported beneficial effects from repetitive transcranial magnetic stimulation (rTMS) on visuospatial neglect in a cohort of 27 patients acutely recovering from stroke. Treatment was delivered at rapid rate (10 cycles/second) during 10 sessions over the lesioned posterior parietal cortex. Though this last study population was quite distinct from patients with schizophrenia, it may well be that commonalities in underlying neural abnormalities associated with anosognosia (of which visuospatial neglect is a form) make rTMS trials in poor-insight schizophrenia worthwhile. Moreover, the increasing availability of rTMS labs in research and clinical settings makes this a viable proposition. While these reports may not immediately translate into current clinical practice, they suggest that insight deficits may represent an ultimate therapeutic target for localized cortical modulation.

In the relative absence of controlled trials focusing on improving insight, per se, clinical principles must apply. Proper therapeutic sequencing would seem essential to improving insight and treatment adherence. For instance, applying psychoeducational and cognitive-behavioral interventions during the window of time when a patient is showing meaningful response to pharmacotherapy (in the latter half of a hospitalization, for instance) and is in his or her most lucid condition may permit a greater engagement in ongoing care. Similarly, continuing these efforts during periods of highest nonadherence risk, for example during the first year after discharge, when many patients choose to stop treatment, may also have greatest benefit. Recognizing the need for indefinite reinforcement of insight-building dialogues should inform how members of the patient's treatment team interact with the patient, providing structure to case manager visits, and the "15-minute medication check." Treating professionals should promote and participate in the family's efforts to sustain their loved one's limited insights and treatment adherence, inviting family members into the treatment and psychoeducational process. By extension, professionals should assist and support those who also help families, NAMI for instance.

CONCLUSION

Poor insight is a cardinal symptom of schizophrenia that, while not universally and uniformly expressed in all patients, is among the most common of its manifestations. Available neurobiological and neurocognitive evidence linking the phenomenon to core pathophysiology of schizophrenia justifies extension of the anosognosia construct to schizophrenia-related insight deficits. The myriad negative consequences of illness denial, whether mediated by treatment nonadherence or otherwise, mandates that clinicians and researchers make insight-enhancement a high-priority focus of professional attention, innovation, and resource allocation. Limited research in the field gives cause for hope that schizophrenic anosognosia will become a critically important therapeutic target amendable to treatment.

The problem of anosognosia is inextricably linked with the failed hopes of the 60+ year-long neuroleptic era. Effective approaches to this problem will allow patients, families, and care providers to engage in a collaborative paradigm rather than the antagonistic tug-of-war that characterizes relationships with illness-denying individuals and often tragically concludes with losses of those relationships altogether. Successful efforts should permit early disease recognition, aggressive and sustained treatment, and prevention of chronicity and social disability.

REFERENCES

1. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: A meta-analysis of the outcome literature. *Am J Psychiatry.* 1994;151(10):1409–1416.
2. Harrison G, Hopper K, Craig T, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry.* 2001;178:506–517.
3. Zipursky RB, Reilly TJ, Murray RM. The myth of schizophrenia as a progressive brain disease. *Schizophr Bull.* 2013;39(6):1363–1372.
4. Buckley PF, Wirshing DA, Bhushan

P, et al. Lack of insight in schizophrenia: impact on treatment adherence. *CNS Drugs*. 2007;21(2):129–141.
5. David AS. Insight and psychosis. *Br J Psychiatry*. 1990;156:798–808.
6. Cooke MA, Peters ER, Kuipers E, Kumari V. Disease, deficit, or denial? Models of poor insight in psychosis. *Acta Psychiatrica Scandinavica*. 2005;112(1):4–17.
7. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
8. McEvoy JP, Freter S, Everett G, et al. Insight and the clinical outcome of schizophrenic patients. *J Nerv Ment Dis*. 1989;177(1):48–51.
9. Amador XF, Strauss DH, Yale SA, et al. Assessment of insight in psychosis. *Amer J Psychiatry*. 1993;150:873–879.
10. Amador XF, Flaum M, Andreasen NC, et al. Awareness of illness in schizophrenia and schizoaffective and mood disorders. *Arch Gen Psychiatry*. 1994;51(10):826–836.
11. Beck AT, Baruch E, Balter JM, et al. A new instrument for measuring insight: the Beck Cognitive Insight Scale. *Schizophr Res*. 2004;68(2-3):319–329.
12. Shad MU, Keshavan MS, Tamminga CA, et al. Neurobiological underpinnings of insight deficits in schizophrenia. *Int Rev Psychiatry*. 2007;19(4):437–446.
13. Lacro JP, Dunn LB, Dolder CR, et al. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of the literature. *J Clin Psychiatry*. 2002;60(10):892–909.
14. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379(9831):2063–2071.
15. Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. *Schizophr Res.* 2013;148(1-3):117–121.
16. Loebel AD, Lieberman JA, Alvir JM, et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry.* 1992;149(9):1183–1188.
17. Drake RJ, Haley CJ, Akhtar S, Lewis SW. Cause and consequences of duration of untreated psychosis in schizophrenia. *Br J Psychiatry*. 2000;177:511–515.
18. Dell'Osso B, Glick ID, Baldwin DS, Altamura AC. Can long-term outcomes be improved by shortening the duration of untreated illness in psychiatric disorders? A conceptual framework. *Psychopathology*. 2013;46(1):14–21.
19. Boonstra N, Klaassen R, Sytema S, et al. Duration of untreated psychosis and negative symptoms – a systematic review and meta-analysis of individual patient data. *Schizophr Res.* 2012;142(1-3):12–19.
20. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. *Schizophr Bull.* 1991;17(2):325–351.
21. Lieberman JA, Alvir KM, Koreen A, et al. Psychobiologic correlates of treatment response in schizophrenia. *Neuropsychopharmacology*. 1996;14(3 Suppl):13S–21S.
22. Cahn W, Rais M, Stigter FP, et al Psychosis and brain volume changes during first five years of psychosis. *Eur Neuropsychopharmacol*. 2009;19(2):147–151.
23. Andreasen NC, Liu D, Ziebell S, et al. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am J Psychiatry.* 2013;170(6):609–615.
24. Christensen J, Holcomb J, Garver DL. State-related changes in cerebral white matter may underlie psychosis exacerbation. *Psychiatry Res.* 2004;130(1):71–78.
25. Langer KG. Babinski's anosognosia for hemiplegia in early twentieth-century French neurology. *J Hist Neurosci.* 2009;18(4):387–405.
26. Shad MU, Muddasani S, Keshavan MS. Prefrontal subregions and dimension of insight in first-episode schizophrenia: a pilot study. *Psychiatry Res*. 2006;146(1):35–42.
27. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160(1):13–23.
28. Aleman A, Agrawal N, Morgan KD, David AS. Insight in psychosis and neuropsychological function: meta-analysis. *Br J Psychiatry.* 2006;189:204–212.
29. Shad MU, Tamminga CA, Cullum M, et al. Insight and cortical function in schizophrenia: a review. *Schizophr Res.* 2006;86(1–3):54–70.
30. Orfei DM, Piras F, Macci E, et al. The neuroanatomical correlates of cognitive insight in schizophrenia. *Soc Cog Affect Neurosci*. 2013;8(4):418–423.
31. Wylie KP, Tregellas JR. The role of the insula in schizophrenia. *Schizophr Res*. 2010;123(2–3):93–104.
32. Craig AD. How do you feel – now? The anterior insula and human awareness. *Nat Rev Neurosci.* 2009;10(1):59–70.
33. Glahn DC, Laird AR, Ellison-Wright I, et al. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biol Psychiatry.* 2008;64(9):774–781.
34. Jakob H, Beckmann H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. *J Neural Transm.* 1986;65(3–4):303–326.
35. Palaniyappan L, Mallikarjun P, Joseph V, Liddle PF. Appreciating symptoms and deficits in schizophrenia: right posterior insula and poor insight. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(2):523–527.
36. Farrer C, Franck N, Frith CD, et al. Neural correlates of action attribution in schizophrenia. *Psychiatry Res.*

2004;131(1):31–44.
37. Klein TA, Ullsperger M, Danielmeier C. Error awareness and the insula: Links to neurological and psychiatric diseases. *Front Hum Neurosci.* 2013;7:14.
38. Raichle ME, MacLeod AM, Snyder AZ, et al. A default mode of brain operation. *Proc Natl Acad Sci USA*. 2001;98(2):676–682.
39. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci USA.* 2009;106(4):1279–1284.
40. Liemburg EJ, van der Meer L, Swart M, et al. Reduced connectivity in the self-processing network of schizophrenia patients with poor insight. *PLoS ONE*. 2012;7(8):e42707.
41. Pijnenborg GH, van Donkersgoed RJ, David AS, Aleman A. Changes in insight during treatment for psychotic disorders: A meta-analysis. *Schizophr Res.* 2013;144(1–3):109–117.
42. Gerretsen P, Diaz P, Mamo D, et al. Transient insight induction with electroconvulsive therapy in a patient with refractory schizophrenia: A case report and systematic literature review. *J ECT*. 2011;27(3):247–250.
43. Levine J, Toder D, Geller V, et al. Beneficial effects of caloric vestibular stimulation on denial of illness and manic delusions in schizoaffective disorder: a case report. *Brain Stimul.* 2012;5(3):267–73.
44. Kim BR, Chun MH, Kim DY, Lee SJ. Effect of high- and low-frequency repetitive transcranial magnetic stimulation on visuospatial neglect in patients with acute stroke: a double-blind, sham-controlled trial. *Arch Phys Med Rehabil.* 2013;94(5):803–7.