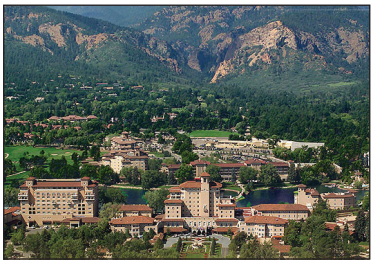

Highlights from the Biennial International Congress on Schizophrenia Research (ICOSR), March 28–April 1, 2015

Matej Markota [1], Urvakhsh Mehta [2], Michele Solis [3]

Abstract

The 2015 International Congress on Schizophrenia Research, held in Colorado Springs, Colorado, attracted over 1,000 attendees from March 28–April 1, 2015. With the gracious assistance of Congress directors Carol Tamminga and Chuck Schulz, as well as meeting staff Dorothy Denton and Cristan Tamminga, we bring you the following reports on various Congress sessions concerning approaches to prevention in schizophrenia and social cognition.

Approaches to Prevention in Schizophrenia

A number of presentations at the 2015 ICOSR addressed potential strategies for prevention in schizophrenia. These ranged from prenatal supplements to what constitutes an optimal maintenance therapy in schizophrenia.

One of the most hotly debated sessions at the conference centered on whether patients with schizophrenia need maintenance antipsychotic treatment. Wolfgang Fleischhacker from Medical School Innsbruck in Austria argued that, although it is unclear which antipsychotics are most effective for maintenance treatment after the first episode of psychosis, it has been consistently shown that in the short term antipsychotic use is associated with significantly reduced relapse rates. Robin Emsley from Stellenbosch University in South Africa showed that discontinuation of antipsychotic maintenance results in treatment failure of the next relapse in one out of six patients. However, the overwhelming majority of studies exploring the effectiveness of antipsychotic maintenance treatment are relatively short, with limited data available beyond three years after the first episode of psychosis.

Lex Wunderink from Friesland Mental Health Services in the Netherlands presented the results of a first randomized clinical trial with a seven-year follow-up. Patients were randomly assigned to early antipsychotic dose reduction/discontinuation or to standard maintenance treatment groups. Wunderink's findings suggest that relapse rates were initially higher in the dose reduction/discontinuation group but leveled at three years. At seven years of follow-up, patients in the dose reduction/discontinuation arm of the study showed a significantly better recovery rate and functional remission compared to patients in the maintenance treatment group (Wunderink et al., 2013). This study underscores the importance of using longer follow-up periods in clinical trials of maintenance treatment and of including functional status, in addition to relapse rate, as an outcome evaluation. Although the findings of this study strongly indicate that guided dose reduction and, if possible, discontinuation may be a feasible strategy leading to better long-term functional outcome, Wunderink pointed out that additional studies are needed before such a strategy can become a general guideline in treating patients with first-episode psychosis.

[1]Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN
[2]National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India
[3]Schizophrenia Research Forum (SRF), Seattle, WA

Address for correspondence: Hakon Heimer, Schizophrenia Research Forum, Brain and Behavior Research Foundation, 470 Lloyd Avenue, Providence, RI 02906 Fax: 401-273-6035; E-mail: hakon@schizophreniaforum.org

Accepted: June 3, 2015

A message from the ICOSR co-founders …

We are delighted that Matej Markota, Urvakhsh Mehta, and Michele Solis have provided readers of *Clinical Schizophrenia & Related Psychoses* this detailed synthesis of key sessions from the Fifteenth Biennial International Congress on Schizophrenia Research recently held in Colorado Springs, Colorado, March 28–April 1, 2015. Scientists representing the broad range of disciplines involved with discovery in schizophrenia gathered at the Congress to exchange data, techniques and ideas. Their cutting-edge experimental work stimulated lively discussion and open exchange of ideas toward a better understanding of the neurobiology and treatment of schizophrenia. We were particularly pleased that the Congress also provided a special opportunity for introducing young investigators to the colleagueship of the schizophrenia scientific community.

Understanding schizophrenia is a leading challenge for medical research today. We are delighted that the Congress plays a formative role in advancing new knowledge concerning this disabling condition. As you read this excellent report, we hope that you share the same excitement that we have concerning our field's development.

Carol Tamminga, MD and Charles Schulz, MD
Co-Founders and Co-Organizers
International Congress on Schizophrenia Research

Intervening Before Psychosis

A number of presenters had investigated the effect of dietary supplementation on the risk of developing schizophrenia. Perhaps the most anticipated was an attempted replication of a 2010 study which found that omega-3 polyunsaturated fatty acids reduce the risk of transition to psychosis in ultra-high risk subjects (Amminger et al., 2010). Patrick McGorry from the University of Melbourne presented results from an ongoing multicenter, international randomized controlled trial on a larger cohort, which found no significant effect of omega-3 polyunsaturated fatty acids on transition rate of ultra-high risk subjects at a 12-month follow-up. McGorry pointed out that there was a trend for dimensional measures of symptoms and functioning to favor the omega-3-treated group at six months, and that further analyses looking at the subgroup with good adherence to the omega-3s may reveal beneficial effects. A two-year follow-up study is underway to determine whether a delayed effect of omega-3 polyunsaturated fatty acids can be identified. A potentially important difference between the original study by Amminger at al. and the replication is that the psychosocial interventions in the latter were more substantial and may have enabled the placebo-treated group to reach the same low level of transition to psychosis. In a similar study, Emsley tested the effectiveness of omega-3 polyunsaturated fatty acids plus antioxidants on relapse prevention in subjects with schizophrenia and found no significant effect (Emsley et al., 2014).

Randy Ross of the University of Colorado in Aurora found that infants of healthy mothers who received prenatal supplementation with phosphatidylcholine have improved cerebral inhibition, a mechanism postulated to be deficient in schizophrenia (Ross et al., 2013). While these early findings are intriguing, it is currently unknown if a prenatal phosphatidylcholine-rich diet and/or supplementation can decrease the risk of developing schizophrenia in offspring.

Alan Brown of Columbia University in New York City conducted a study with potentially important implications for primary prevention of schizophrenia. Based on the data from a Finnish national birth cohort, Brown's team found that pregnancy levels of maternal cotinine, a nicotine metabolite and a reliable measure of maternal smoking, are associated with higher risk of schizophrenia in offspring. The association between maternal cotinine levels and schizophrenia in offspring remained significant after adjusting for parental history of psychiatric disorders, maternal age, and birth provenance. The offspring included in the study were between 15 and 26 years old, with an additional follow-up study planned in the future to test this effect in older offspring. While the observed correlation between maternal smoking and schizophrenia does not necessarily imply causation, these findings are interesting in light of strategies aimed at prevention of schizophrenia.

In a similar study, Emsley tested the effectiveness of omega-3 polyunsaturated fatty acids plus antioxidants on relapse prevention in subjects with schizophrenia and found no significant effect …

There is robust evidence that cognitive impairments precede the onset of psychosis by many years (Woodberry et al., 2008). Larry Seidman from Harvard University in Cambridge, Massachusetts, presented results from a pilot study showing that computer-based, targeted cognitive training significantly improves processing speed and role functioning in clinically high-risk individuals (Hooker et al., 2014). It is currently unclear, however, if cognitive training can prevent or delay the onset of schizophrenia.

References

Wunderink L, Nieboer RM, Wiersma D, Sytema S, Nienhuis FJ. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 2013;70(9):913-920.

Amminger GP, Schafer MR, Papegeorgiou K, Klier CM, Cotton SM, Harrigan SM, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry 2010;67(2):146-154.

Emsley R, Chiliza B, Asmal L, du Plessis S, Phahladira L, van Niekerk E, et al. A randomized, controlled trial of omega-3 fatty acids plus an antioxidant for relapse prevention after antipsychotic discontinuation in first-episode schizophrenia. Res 2014;158(1-3):230-235.

Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. Am J Psychiatry 2013;170(3):290-298.

Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. Am J Psychiatry 2008;165(5):579-587.

Hooker CI, Carol EE, Eisenstein TJ, Yin H, Lincoln SH, Tully LM, et al. A pilot study of cognitive training in clinical high risk for psychosis: initial evidence of cognitive benefit. Schizophr Res 2014;157(1-3):314-316.

Animal Modeling

A number of animal models used to test strategies for preventing the behaviors and phenotypes associated with schizophrenia was also a focus of this year's ICOSR. Patricio O'Donnell, formerly of the University of Maryland in Baltimore and now with Pfizer, used a rodent neonatal ventral hippocampal lesion model of schizophrenia to test the effect of antioxidant treatment on development of schizophrenia-associated phenotypes. Using this model, he and his collaborators found that antioxidant treatment during juvenile periods prevents the loss of perineuronal nets and parvalbumin neurons, both repeatedly shown to be decreased in schizophrenia (Zhang and Reynolds, 2002; Pantazopoulos et al., 2010; Pantazopoulos et al., 2015; Lewis et al., 2012; Mauney et al., 2013; Berretta et al., 2015). Juvenile or adolescent antioxidant treatment also prevented the development of behavioral and electrophysiological abnormalities in adult animals in this model (Cabungcal et al., 2014). O'Donnell, however, warns that manipulating redox balance in patients carries significant risks, and reliable markers of oxidative stress should be developed before such interventions can be safely used in subjects at risk for schizophrenia.

Tony Grace from the University of Pittsburgh in Pennsylvania asserted that converging evidence shows that children hyper-responsive to stress have a higher chance of later conversion to schizophrenia. Offspring of mitotoxin methylazoxymethanol acetate (MAM)-treated pregnant rats show hyper-responsivity to stress in the prepubertal period and in adulthood, together with other behavioral, histological, and electrophysiological alterations reminiscent of schizophrenia. Grace found that peripubertal diazepam administration prevents electrophysiological and behavioral alterations in adult offspring of MAM-treated animals. While peripubertal anxiety and stress reduction with diazepam in humans would not be appropriate, Grace pointed out that these results do indicate a potential role for psychosocial interventions aimed at reducing stress and anxiety in individuals at high risk of schizophrenia.

O'Donnell, however, warns that manipulating redox balance in patients carries significant risks, and reliable markers of oxidative stress should be developed before such interventions can be safely used in subjects at risk for schizophrenia.

Many pressing questions on prevention in schizophrenia were addressed at the 2015 ICOSR. While important steps have been made in the past several years, more needs to be learned before safe and effective strategies for prevention can be developed.—Matej Markota.

References

Zhang ZJ, Reynolds GP. A selective decrease in the relative density of parvalbumin-immunoreactive neurons in the hippocampus in schizophrenia. Schizophr Res 2002;55(1-2):1-10.

Pantazopoulos H, Woo TU, Lim MP, Lange N, Berretta S. Extracellular matrix-glial abnormalities in the amygdala and entorhinal cortex of subjects diagnosed with schizophrenia. Arch Gen Psychiatry 2010;67(2):155-166.

Pantazopoulos H, Markota M, Jaquet F, Ghosh D, Wallin A, Santos A, et al. Aggrecan and chondroitin-6-sulfate abnormalities in schizophrenia and bipolar disorder: a postmortem study on the amygdala. Transl Psychiatry 2015;20:5.

Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci 2012;35(1):57-67.

Mauney SA, Athanas KM, Pantazopoulos H, Shaskan N, Passeri E, Berretta S, et al. Developmental pattern of perineuronal nets in the human prefrontal cortex and their deficit in schizophrenia. Biol Psychiatry 2013;74(6):427-435.

Berretta S, Pantazopoulos H, Markota M, Brown C, Batzianouli ET. Losing the sugar coating: Potential impact of perineuronal net abnormalities on interneurons in schizophrenia. Schizophr Res 2015 Jan 16. doi: 10.1016/j.schres.2014.12.040.

Cabungcal JH, Counotte DS, Lewis EM, Tejeda HA, Piantadosi P, Pollock C, et al. Juvenile antioxidant treatment prevents adult deficits in a developmental model of schizophrenia. Neuron 2014;83(5):1073-1084.

Social Cognition in Schizophrenia

Among the symptoms of schizophrenia, impairments in social cognition—that special set of skills that helps us interact with others—may cause the most disability and loss of quality of life. In this meeting report on the topic from the ICOSR, we combine a plenary talk summary from ICOSR Young Investigator travel awardee Urvakhsh Mehta of the National Institute of Mental Health and Neurosciences in Bangalore, India, with a related symposium report from Schizophrenia Research Forum reporter Michele Solis.

The Systems That Make Us Social

In his Sunday, March 29, plenary talk, Michael Green of the University of California, Los Angeles, provided a synthesis of the last decade in social neuroscience research, which has arrived at four possible neural subsystems within the social brain that drive a range of social cognitive processes. He discussed various empirical studies employing neuroimaging and electroencephalography techniques that support the existence of these neural systems and also highlighted emerging evidence of their disruption in schizophrenia. He also deliberated on potential implications of studying these social brain neural systems in other brain disorders and translating this information to develop novel treatment strategies targeting social cognition deficits.

The social cue identification system subserves the processing of biological motion, facial emotions, affective prosody, and gestures. Neural regions include the fusiform gyrus (face identification), amygdala (emotional valence), and the posterior superior temporal sulcus (biological motion). Green presented fairly robust evidence of dysfunctional task-related brain activation in these regions in patients with schizophrenia. The experience sharing system comprises shared neural circuits that are active while observing as well as engaging in social situations. These include the motor resonance system (mirror neuron regions of the premotor cortex and inferior parietal lobule) and the affect sharing system (dorsal cingulate and anterior insula). Given the limited number of studies exploring these systems, it was noted that even though there was evidence indicating a dysfunction in these neural regions in schizophrenia, the data were inconsistent.

The mentalizing system, which plays a role in reflective thinking, involves the medial prefrontal cortex, temporoparietal junction, precuneus, and temporal pole—regions that clearly overlap with the default-mode network seen on resting-state functional brain imaging. Studies in schizophrenia have demonstrated either reduced or delayed activations in these networks during theory of mind tasks. The emotion regulation system influences expression of emotions within appropriate social contexts and includes brain regions that overlap with the amygdala and the ventral and dorsal lateral prefrontal cortices. Dysfunctional neural activity in these brain regions has regularly been demonstrated in schizophrenia.

Lastly, the potential translational applications of utilizing these social brain systems as targets for novel treatment strategies were discussed. These go beyond conventional cognitive remediation strategies, to include intranasal oxytocin, novel pharmacotherapy, and neuromodulatory strategies.

A synchronized functioning of these four systems is considered to be necessary for empathic and adaptive prosocial behaviors, according to Green. He then discussed newer tasks to tap into coordinated functioning of these neural systems (e.g., the empathic accuracy task by Zaki and colleagues; Zaki et al., 2009) and their application in schizophrenia (Harvey et al., 2013). Social brain aberrations in varying degrees have been described in other disorders such as bipolar disorder, autism, frontotemporal dementia, personality disorders, and even traumatic brain injury and post-traumatic stress disorder. This overarching dimensional strategy not only provides an organizational framework to support future studies in schizophrenia, but also lends itself to a transdiagnostic Research Domain Criteria (RDoC)-like investigational approach. Lastly, the potential translational applications of utilizing these social brain systems as targets for novel treatment strategies were discussed. These go beyond conventional cognitive remediation strategies, to include intranasal oxytocin, novel pharmacotherapy, and neuromodulatory strategies.—Urvakhsh Mehta.

References

Zaki J, Weber J, Bolger N, Ochsner K. The neural bases of empathic accuracy. Proc Natl Acad Sci U S A 2009;106(27):11382-11387.

Harvey PO, Zaki J, Lee J, Ochsner K, Green MF. Neural substrates of empathic accuracy in people with schizophrenia. Schizophr Bull 2013;39(3):617-628.

Targeting Social Cognition Deficits

Deficits in social cognition currently go largely untreated, and an afternoon symposium on Tuesday, March 31, was devoted to finding ways to boost social cognition. Stephen Marder of UCLA began with his recent results showing how combining social cognition training with a dose of oxytocin, a hormone that boosts affiliative feelings, leads to lasting gains in empathic accuracy, meaning how well a person

gauges how another person feels, compared to training with placebo (Davis et al., 2014). Marder also presented new data suggesting that oxytocin influences specific neural systems, which gives some insight into how it works. For example, while watching biological motion, oxytocin led to more mu suppression, which is an EEG measure of the engagement of the mirror neuron system thought to mediate empathy. Oxytocin also led to less pupil dilation while viewing fearful images, suggesting that the hormone affected attention-allocating brain systems.

Mercedes Perez-Rodriguez of the Icahn School of Medicine at Mount Sinai, New York City, also found evidence for drug-induced facilitation of cognitive remediation training for mentalizing, which refers to deciphering the mental states of others. Missing social cues and focusing on the literal aspects of a conversation, people with schizophrenia and the milder schizotypal personality disorder (SPD) are impaired at mentalizing. Focusing on people with SPD because their social cognition impairments are not mixed up with effects of antipsychotic medications or negative symptoms, Perez-Rodriguez reported that the alpha2-adrenergic receptor agonist guanfacine combined with cognitive remediation training led to greater gains in mentalizing, as measured by their reactions to the Movie for the Assessment of Social Cognition (MASC), than those who had received a placebo plus training. Perez-Rodriguez also suggested that mentalizing could be taken too far—that distorted over-interpretations of another person's behavior could be just as impairing to social cognition and may affect those with borderline personality disorder. She is currently testing oxytocin to see if it may help normalize both surfeits and deficits in mentalizing.

Training up neural systems for social cognition may also help those at risk of psychosis, according to a presentation by Christine Hooker of Harvard University, Cambridge, Massachusetts. Building on previous work in schizophrenia (Hooker et al., 2013), Hooker showed that a 40-hour regimen of computerized training of both cognitive and social skills over four to eight weeks improved these skills in people at risk of developing psychosis. Brain scanning revealed discrete changes in the brain network subserving emotion recognition, including decreased activity in the amygdala and superior temporal sulcus (STS). This was accompanied by increases in correlated activity between the STS and the anterior cingulate cortex and medial prefrontal cortex—a measure of functional connectivity. An intervention's effect on functional connectivity may ultimately matter the most, she suggested, based on results from another study designed to train a person's ability to understand the mental states of others (Theory of Mind). This resulted in enhanced functional connectivity between the amygdala and other cortical regions, indicating that non-pharmacological interventions can rework brain circuits important for social cognition.

Dawn Velligan of the University of Texas Health and Science Center at San Antonio, Texas, presented results from a pilot study of a negative symptom intervention called MOtiVation Enhancement (MOVE) treatment. This is a home-based therapy designed to comprehensively address every aspect of negative symptoms. For example, therapists cued behavior at a person's home by using alarms or other reminders; reminded people of the pleasure they had at an outing; practiced skills in the neighborhood, such as going to a store; role played to practice social interactions; and delivered cognitive behavior therapy to address self-defeatist thinking. "We wanted to throw the kitchen sink at these negative symptoms to see if we would get some kind of effect," Velligan said. They did, but it took nine months: among people with persistent negative symptoms (who were, maybe not surprisingly, difficult to recruit), consisting of 26 receiving MOVE and 25 treatment as usual, those receiving MOVE showed a small improvement in motivation and social engagement. Velligan called it a small effect for a lot of effort and suggested that something such as oxytocin may prime the brain for larger improvements. —Michele Solis.

References

Davis MC, Green MF, Lee J, Horan WP, Senturk D, Clarke AD, et al. Oxytocin-augmented social cognitive skills training in schizophrenia. Neuropsychopharmacology 2014;39(9):2070-2077.

Hooker CI, Bruce L, Fisher M, Verosky SC, Miyakawa A, D'Esposito M, et al. The influence of combined cognitive plus social-cognitive training on amygdala response during face emotion recognition in schizophrenia. Psychiatry Res 2013;213(2):99-107.