Highlights from the 2012 Schizophrenia International Research Society Conference, April 14–18, 2012

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Abstract

The 2012 Schizophrenia International Research Society (SIRS) Conference, held in Florence, Italy, attracted more than 1,600 attendees from 53 countries to the stately Firenze Fiera Conference Center from April 14–18, 2012. Providing four major plenary sessions, thirty-five symposia sessions and six workshops, this 3rd Biennial SIRS Conference was jointly sponsored by Vanderbilt University School of Medicine, Department of Psychiatry and SIRS. In conjunction with the Schizophrenia Research Forum, a Web project of the Brain and Behavior Research Foundation, and with our thanks to the SIRS organizers and staff, we bring you the following report on the meeting's discussions concerning drug therapy development for schizophrenia, psychological and social treatment for schizophrenia, and the challenges of predicting psychosis with brain imaging.

Schizophrenia Drug Development: Does the Pipeline have a Pulse?

The final day of the SIRS meeting in Florence began with a session on new drug development, chaired by Wolfgang Fleischhacker of the Medical University of Innsbruck, in Austria.

Donald Goff of Harvard University, Cambridge, Massachusetts, USA, opened with an overview of some of the factors that have led to stagnation in the development of new drugs for schizophrenia, including some that are well known: animal models that fail to predict effects in humans, the heterogeneity of the disorder, and poor assay sensitivity in clinical trials. He suggested that current animal models may suffer largely from the fact that they do not recapitulate any parts of what appear to be a neurodevelopmental disorder or vulnerability. Thus, the pairing of neurodevelopmental animal models with a better understanding of the prodrome and the brain antecedents of the first episode may prove more fertile ground for finding new drug targets. He also suggested that in the short term, pharmacogenomics may advance to the point that it will allow researchers to look for stronger signals in subpopulations of the very heterogeneous subject pools that populate clinical trials.

John Kane, of the North Shore-Long Island Jewish Healthcare System, New York, USA, followed with a look at the problems that face drugs able to make it through the discovery phase to clinical trials. He presented this in the framework of a series of open questions that the community needs to address, the first being whether researchers are really studying homogeneous samples of patients experiencing acute exacerbation of symptoms, as opposed to mixed samples that also include patients who are chronically symp-

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tomatic. These patients may experience improvement over baseline, but that does not really count as remission, he argued, and researchers must find a way to reliably identify patients having an acute exacerbation.

Assessing relapse prevention also presents problems: only a third of patients who relapse in trials are hospitalized, he said, and we don't have a good way to know how informative hospitalization is as a measure of relapse. Few relapse prevention trials monitor real recovery, or adherence, Kane said.

Kane also mentioned the recent rise in failed trials (note: a failed trial is one in which a proven marketed drug does not separate from placebo, as opposed to a negative trial, where the test drug does not separate from placebo). The issue is not specific to trials of antipsychotic medications; indeed, it is even more of a problem for antidepressants. But when combined with a dearth of new molecular targets, the end result is that several major drug companies have dropped out of psychiatric drug development. There does not appear to be any one reason for this—among the candidates are excessive delays before treatment, too many inappropriate subjects, lack of inter-rater reliability and reliable informants (see also Kinon et al., 2011)—and, thus, any single solution is unlikely to resolve the problem.

The basic list of questions that Kane left the audience with was: How do we establish true drug efficacy? Can we confirm the presence of an acute exacerbation? How can we establish a stable baseline and minimize placebo response in studies involving negative or residual positive symptoms? Are there better ways to assess long-acting antipsychotics? In the Q&A session, the difficulties posed by heterogeneous and sometimes inappropriate subject populations were echoed. One drug company researcher in the audience mentioned that the industry, which spends about $2.5 billion to bring a drug to market, gives a counterproductive incentive to contract research organizations: get us many patients quickly.

News from the Front

The overview talks were followed by updates from drug companies on their development efforts, and here we summarize some of these. Presenting on behalf of Forest Laboratories and Gedeon Richter, Anjana Bose of Forest, New York, USA, discussed cariprazine, a dopamine D3/D2 partial agonist, which has high selectivity for D3 compared to other antipsychotic drugs (APDs) and very low potency at other neurotransmitter receptors. In a Phase 3 trial, cariprazine was significantly more effective than placebo and aripiprazole, a standard APD. Although weight gain appears to be low with this drug, there was evidence for increased extrapyramidal symptoms. The drug also has been shown to separate from placebo in bipolar mania trials.

Robert Conley of Eli Lilly, Indianapolis, Indiana, USA, provided new data on one of Lilly's metabotropic glutamate 2/3 receptor agonists. The data he showed indicated comparable efficacy to standard APDs, but without the weight gain. It also appears that the drug can be used safely with some of these standard APDs. Lilly has also looked at weight gain separately, and found that it may be mediated by c-Fos in orexin (hypocretin)-containing cells. The high weight-gain drugs appear to have highest c-Fos in these cells.

The next speaker was Gerhard Gross of Abbot Laboratories in Ludwigshafen, Germany, which does not currently have a compound in clinical trials. Though their selective D3 antagonist failed to show therapeutic effects in a recent trial, Gross discussed preclinical data that keep the drug in active development. For example, there is some evidence that the drug ameliorates the behavioral effects of NMDA receptor antagonists in animals, and this parallels some positive results seen on cognitive tests in the human clinical trial.

David Hosford of Targacept, Inc., Winston-Salem, North Carolina, USA, provided an update on the α7 nicotinic cholinergic receptor partial agonist TC-5619. Looking to make sense of conflicting earlier data regarding differential effects on tobacco users versus non-users, Targacept has conducted new studies that indicate that TC-5619's positive results on cognition and negative symptoms were driven by the smokers in the study.

In a post hoc analysis of their work showing negative symptom improvement with a glycine reuptake inhibitor, F. Hoffmann-La Roche, Ltd., in Basel, Switzerland, did a factor analysis to determine which aspects of negative symptomatology drove the signal. Daniel Umbricht reported that factors mapping onto the domain of avolition, as opposed to those considered to contribute to blunted affect/expressive deficits, were mainly improved. This is encouraging if indeed, as has recently been argued, avolition is the core problem in negative symptom schizophrenia (see, e.g., Foussias and Remington, 2008).— Hakon Heimer

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Psychological and Social Treatment for Schizophrenia

Dawn Velligan of the Texas Health Science Center, San Antonio, and Shitij Kapur of the Institute of Psychiatry, London, UK, chaired the April 15th opening plenary session. The speakers reviewed the research on some of the nonpharmacologic treatments aimed at improving cognitive and social function in people with schizophrenia.

The first speaker, Christos Pantelis of the University of Melbourne, Australia, focused on imaging studies of cogni-

tive remediation techniques. He noted long-standing data indicating that cognitive function is already compromised at disease onset and remains relatively stable through the ups and downs of psychosis. However, given the studies in the last several years reporting brain changes around the time of disease onset, some researchers wonder whether this is associated with loss of cognitive function.

Pantelis said that people with schizophrenia show more severe deficits in cognitive function than do even frontal lobe injury patients, yet it appears that not all of these deficits are present in the first episode. Pantelis stated that cognitive remediation shows some consistent evidence for changing brain structure, though surprisingly not in the dorsolateral prefrontal cortex, but rather in medial and temporal cortical areas that subserve social cognition (e.g., the anterior cingulate cortex). He noted that these seem to be the areas that change early in illness.

Pantelis hypothesizes that some aspects of cognition are normal at disease onset, or mature normally but then deteriorate, and these might be the most amenable to improvement with cognitive remediation techniques. However, he also believes that cognitive remediation may need to happen during early to late adolescence to have this effect. Conversely, he suggests other cognitive functions never fully mature in schizophrenia, but could be addressed with cognitive adaptation methods, i.e., setting up "workarounds" in a person's environment. The latter may be the more valuable for patients with severe deficits.

Steffen Moritz of the University Medical Centre Hamburg-Eppendorf, Germany, discussed data on "meta-cognitive training," a method he developed with Todd Woodward of the University of British Columbia, Canada, to address delusional thinking in schizophrenia. He defined meta-cognition as "one's knowledge concerning one's own cognitive processes or anything related to them," or, more colloquially, "thinking about thinking."

The computer-based training method (available for free in a number of languages) is intended to reduce jumping to conclusions from minimal data and also to decrease distortions in the perceptions of people with schizophrenia. Moritz reported that, in comparison to the cognitive remediation product COGPACK, the meta-cognitive training does produce significant results on these measures, and also reduces positive symptoms. In fact, he said, a single session significantly reduced jumping to conclusions and conviction of beliefs. More recently, the researchers have added a cognitive behavioral therapy (CBT) component, and preliminary data from a randomized controlled trial suggest superiority over COGPACK on a number of measures.

In the Q&A session, one audience member wondered whether the training, though targeting high-level cognition, such as beliefs, might not also be exerting beneficial effects by improving working memory or speed of processing. Moritz said that they would not expect this to be the case, and had not found evidence for such effects.

The next speaker, Douglas Turkington of the University of Newcastle, UK, discussed the effectiveness of CBT for positive and negative symptoms in schizophrenia. In his estimation, the evidence base from recent prospective studies shows that there is a long-term benefit of CBT, above and beyond the befriending of the patient by a professional. He notes that CBT and cognitive remediation appear to have comparable results, suggesting that there should be studies including both modalities.

However, these studies were all administered by experts, Turkington noted. What about mental health workers with less training? He presented new, unpublished data indicating that community nurses or case workers, trained and supervised regularly, could achieve lasting improvement in symptomatology and indicators of relapse. Turkington added the heartening possibility that CBT might benefit patients who refuse antipsychotic drugs for their positive symptoms. He reported data that indicated surprising benefits, not only on positive, but also negative symptoms. He interprets this as a function of people actively choosing a course of therapy and benefiting from something that resonates. These patients were not more likely to start to take antipsychotic drugs after the CBT.

Turkington believes that researchers will have to start thinking about which modalities fit best for different patients; for example, those with a strong delusional framework without hallucinations versus those who hear multiple voices but lack prominent delusions.

The final speaker, Michael Green of the University of California, Los Angeles, discussed social cognitive training for people with schizophrenia. He reviewed a large body of data indicating that social cognition, more than non-social cognition, is a major determinant of community functioning for people with schizophrenia. Empathy research, in particular, is an emerging focus in this area. Green made a distinction between lower-level emotional empathy ("I feel your pain") and higher-level, cognitive empathy ("I understand what you're experiencing"). Empathic accuracy depends on both, he said, and is valuable for patients.

In the clinic, Green and his collaborators have developed an intervention called Social Cognitive Skills Training (SCST) that targets emotional processing, social perception, attributional bias, and mental state attribution (or Theory of Mind). In a recent pilot trial, they found that the training significantly improves emotional processing, including facial affect perception and emotion management.

Following Green's lecture, the Chairs and the audience had a lively discussion concerning the difficulties of choosing between methods. Harking back to Turkington's lecture,

one discussant suggested that it would depend on the patients and their current states. Chair Kapur wondered how it will be possible to implement proven, effective treatments on a large scale, and Green suggested that standardization may be a barrier both to research and clinical deployment. Turkington said that the key to broad implementation may be to make the methods more widely available for free. An audience member commented that there will be hard work ahead to convince psychologists in the community, who will be the main implementers, of the effectiveness of given therapies, since a significant portion of them, at least in the United States, believes that the patient-therapist relationship is more important to recovery of function than the particular specialized therapy. She suggested that, if a body like the American Psychological Association evaluated and vetted treatments, it might aid in implementation.— Hakon Heimer

The Challenge of Predicting Psychosis with Brain Imaging

Although the first psychotic episode in schizophrenia may seem to come on suddenly, it typically reflects the culmination of subtle shifts in behavior, called the "prodrome." A cadre of brain imagers at the 2012 SIRS presented their work on detecting the brain changes behind psychosis onset, with a focus on people at high risk for developing psychosis. Of people showing attenuated psychotic symptoms or a brief, yet quickly resolved episode of psychosis, about a third develop full-blown psychosis within three years, according to a recent analysis (Fusar-Poli et al., 2012). Studying a population enriched for imminent psychosis offers researchers a chance to capture valuable before-and-after snapshots of the brain, and to discern differences between those who transition to psychosis and those who don't. What's more, extracting accurate predictors of psychosis would guide early treatment decisions, which are currently complicated by the high number of high-risk people who do not ever develop psychosis.

The challenge lies in the large amount of variability in any single measure of brain scan data. Combining different measures in a multimodal approach might offer greater accuracy, and several researchers tried to pull together structural neuroanatomy, brain activity, neurochemistry, and connectivity findings. The multimodal approach poses a tremendous burden of time and cost, however, so it may still be a while before psychiatry sees a clinical application of imaging.

Signs of Psychosis in Dopamine

In an April 15th symposium, Oliver Howes of Imperial College, London, UK, reviewed his work on signs of enhanced dopamine levels in schizophrenia and in high-risk patients. His new meta-analysis of 50 positron-emission tomography (PET) or single-photon emission computed tomography (SPECT) studies on the subject finds that presynaptic increases in dopamine distinguish schizophrenia from controls, but not measures of dopamine receptor or transporter availability. Elevated dopamine also marks high-risk subjects, who show increased dopamine synthesis capacity in the striatum compared to controls (Howes et al., 2009), and Howes said that this has recently been replicated in a second cohort. Intriguingly, higher dopamine levels also distinguish those who later transition to psychosis, suggesting that overactive dopamine synthesis or release precedes illness. This measure shows some specificity for psychotic illness, because healthy people who have hallucinations without any functional downsides show dopamine levels similar to controls (Howes et al., 2012).

Stefan Borgwardt of the University of Basel, Switzerland, followed with a review of other measures that distinguish high-risk subjects from controls, including brain volume reductions (Mechelli et al., 2011); similar to the pattern with dopamine, people who later develop psychosis show even more pronounced reductions. He suggested that following brain changes, rather than abnormalities, was important, and integrating the relationships between different brain measures rather than focusing on a single measure may increase predictive power.

A Multimodal Look at the Prodromal Brain

Getting an integrative look at the brain to better define a high-risk state with better accuracy for transition to psychosis was the focus of a symposium on April 16th. Paolo Fusar-Poli of King's College, London, UK, described his efforts to put together how brain activity varies with neurochemistry, specifically glutamate. Last year he reported that in a group of high-risk patients, glutamate levels in the thalamus (measured with magnetic resonance spectroscopy, or MRS) were inversely correlated with fMRI signals in the dorsolateral prefrontal cortex or the orbitofrontal cortex evoked during a verbal fluency task in which subjects generated a word beginning with a given letter; the corresponding correlations in the controls were in the opposite direction (Fusar-Poli et al., 2011). Extending this kind of analysis to dopamine, Fusar-Poli reported new results showing a direct correlation between striatal levels of dopamine and activation of the inferior frontal gyrus.

Another method in the multimodal genre is to consider all structural changes in the brain using voxel-based morphometry analysis (VBMA), which gives an unbiased view of all the voxels in a brain scan, rather than a priori choos-

ing some region of interest. In a VBMA published last year, Fusar-Poli found that those who later developed psychosis showed—at baseline—reductions in the inferior frontal gyrus and the superior temporal gyrus. He is now working to integrate these structural findings with fMRI results in people imaged at the time of their first episode of psychosis. In this same multimodal symposium, Stefan Borgwardt presented other data highlighting the insula, which VBMA found to have a smaller volume in people designated with a high-clinical-risk mental state for only three months (and so had a higher transition-to-psychosis probability) compared to those in that category for five years (with a lower chance of transition).

Christopher Chaddock of King's College, London, UK, continued with the dopamine theme, but this time in the context of prediction errors. Dopamine neurons produce a teaching signal by firing when experience differs from what is expected. Abnormalities in prediction error signaling have been proposed to underlie psychosis, such that dopamine would inappropriately tag innocuous stimuli as salient, and psychosis would emerge as a cognitive explanation for these abnormally learned associations (Kapur, 2003).

Abnormal prediction error signaling has been found in people with schizophrenia, and Chaddock asked whether this emerges even earlier in the prodrome. While undergoing fMRI, 15 high-risk and 18 control subjects learned to choose a stimulus that predicted a money reward. Controls showed increased fMRI activity in the striatum (a recipient of dopamine inputs) during unexpected reward trials, and decreased activity during unexpected neutral, non-rewarded trials. The inverse was observed in the high-risk group, however, with striatal activity suppressed during unexpected reward trials, and boosted during unexpected neutral ones. The magnitude of the abnormal reward signal correlated with severity of psychotic symptoms, and was highest for those who had transitioned to full-blown psychosis. Adding a PET scanning dimension, Chaddock also reported that those with the highest levels of presynaptic dopamine exhibited the greatest abnormal response-to-reward prediction errors.

Machines at Work

While group differences between those who transition and those who don't are helpful for understanding psychosis onset, it doesn't mean they'll be able to predict an individual's fate. To move toward something more predictive, Nikos Koutsouleris of the University of Pennsylvania, Philadelphia, discussed the application of machine learning to pull patterns from brain imaging data that foretell psychosis. This means thinking of disease as a disturbance of relationships, rather than discrete abnormalities, he said.

Koutsouleris has had some success in training pattern recognition algorithms to discriminate between those who develop psychosis and those who don't using neuroanatomical features and cognitive features (Koutsouleris et al., 2011). He presented preliminary evidence showing no additional benefit from combining these measures, however. In a sample of 31 high-risk subjects, with 14 transitioning to psychosis, he reported that the classifier could recognize those who transitioned based solely on neuroanatomical features with 64% accuracy, and based only on cognitive features with 80% accuracy. Combining the two resulted in accuracy of 76%, correctly identifying 71% of those who transitioned (an increase in sensitivity compared to cognitive alone) and 81% of those who didn't (a decrease in specificity compared to cognitive alone). Koutsouleris said that his classifiers did not do so well in distinguishing controls from those with chronic schizophrenia, suggesting that the brain state in chronic schizophrenia is much more heterogeneous than in the prodrome, perhaps reflecting the different disease courses, lifestyles, and medication histories that emerge with chronic disease.

Making Connections

Stephen Lawrie of the University of Edinburgh, UK, focused on relating morphological features—cortical folding, in particular—to functional data in a different kind of high-risk cohort consisting of people at genetic risk who have two or more first- or second-degree relatives with schizophrenia. Prompted by the increase in gyrification index (the ratio of the length of the inner fold over that of the outer fold) in prefrontal cortex found in genetic high-risk subjects who developed schizophrenia (Harris et al., 2007), Lawrie proposed that this reflected an abnormally high degree of local connectivity. To test this, he studied the relationship between gyrification index and functional connectivity, measured via fMRI during an executive function task. Prefrontal gyrification (folding) correlated positively with local connectivity between medial and lateral regions of the prefrontal cortex, but correlated negatively with long-range connectivity between prefrontal cortex and thalamus; these correlations were not seen in controls (Dauvermann et al., 2012). Lawrie suggested that in schizophrenia, local connections are increased at the expense of long-range connections.

Lawrie also described an effort to infer direction of the signals flowing through the brain in these high-risk subjects, using dynamic causal modeling. This approach pulled out a role for signals originating in the thalamus and moving to inferior frontal gyrus (IFG), and high-risk individuals with psychotic symptoms or who had transitioned to schizophrenia showed greater connection strength between thalamus and IFG than did high-risk people without symptoms or

healthy controls. Finally, using a graph theory to get a global view of the brain's network of connections, Lawrie reported similar network structures in both high-risk individuals and controls, but that those who transition exhibited a higher degree of connectivity and clustering of regions.—Michele Solis

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