Highlights from the 2016 Schizophrenia International Research Society Conference, April 2–6, 2016

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Abstract

The 2016 Schizophrenia International Research Society (SIRS) Conference, held in Florence, Italy, attracted approximately 1,800 attendees from over 54 countries to the stately Firenze Fiera Conference Center from April 2–6, 2016. Providing plenary sessions, special sessions, symposia, workshops, oral presentations and poster presentations, this 5th Biennial SIRS Conference focused on "Deconstructing Schizophrenia towards Targeted Treatment." 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 selected highlights.

Of Vitamin D, Critical Periods, and Clinical Trials

In a SIRS plenary talk on Tuesday, April 5, ***CS*** Board Member John McGrath of Queensland Brain Institute in Brisbane, Australia, deftly bridged the gap between epidemiology and neuroscience. McGrath first identified vitamin D as a risk factor for schizophrenia (McGrath et al., 2010), and he showed that the relationship between low levels of vitamin D at birth and risk for schizophrenia could be replicated in a larger sample. Delving into the actions of vitamin D, a steroid, he showed that it could induce a calcium signal in some but not all neurons. McGrath suggested that calcium signaling, which has also been highlighted by genetics studies, could shape brain development, and a dearth of vitamin D might delay brain maturation. This might be remedied in public health campaigns that screen babies for low vitamin D and then supplement as necessary.

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Takao Hensch of Harvard University in Cambridge, Massachusetts, filled his plenary talk with the molecular mediators of critical periods—the time windows during which the brain is particularly open to being changed by experience. Using the visual cortex and its malleability by visual experience as the venue, Hensch described the central role that inhibitory neurons play in critical period timing, which he suggested is disrupted in the run-up to mental disorders. On the flipside, neuronal stability provides a way to consolidate changes wrought during critical periods. Therapeutically, finding ways to reopen critical periods may be helpful for brain injuries, or to boost effects of training.

Clinical Trials Update

An evening session devoted to some of the latest clinical trials of drugs for schizophrenia offered a smattering of good news. Though current antipsychotic drugs attenuate the hallucinations and delusions of psychosis, researchers have been stymied in finding something to treat the paralyzing lack of motivation and expression comprising schizophrenia's so-called negative symptoms. ***CS*** Board Member Wolfgang Fleischhacker of the Medical University of Innsbruck in Austria described a Phase 3 trial of cariprazine in people with predominantly negative symptoms. Cariprazine

is unusual in its preferential but not selective activation of D3 dopamine receptors. The randomized, controlled study found that six months of cariprazine treatment decreased negative symptoms and increased social performance more so than risperidone did; importantly, positive symptoms did not worsen.

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Patrick McGorry of Orygen Youth Health and the University of Melbourne in Australia presented results from the Neuro-ProE study, a ten-site, randomized, controlled study designed to replicate an earlier trial suggesting that omega-3 fatty acids (in fish oil capsules) could prevent transition to psychosis among young people deemed at high risk (Amminger et al., 2010). After six months of treatment with either fish oil or placebo, McGorry reported no difference in transition rates between the two in nearly 1,000 people, either at six or twelve months. This lack of replication is complicated by the fact that those on fish oil did not reliably take their capsules. Transition rates were also lower than in earlier studies (11% vs. 25%), suggesting that it may be necessary to follow participants for a longer time; this follow-up is currently underway.

Clinicians will often keep a patient on an antipsychotic for a month or two before deciding whether it is effective or not. According to a study presented by Stephen Heres of the Technical University of Munich in Germany, clinicians can make the call much earlier, in just two weeks. In a randomized, double-blind study, called the SWITCH trial, patients were given olanzapine or amisulpride for two weeks. If at two weeks they had gained a 25% improvement in their total PANSS score, they were maintained on that drug. If they did not reach this level, they were either switched to the other drug or maintained on the same drug. Six weeks later, the switchers had reached the same rates of remission as the initial responders had; the non-switchers, however, only achieved a little over half that rate.

Kimberly Vanover of Intra-Cellular Therapies presented another round of positive results from a Phase 3 trial for its drug called ITI-007. The drug has multiple targets, including serotonin, dopamine, and glutamate systems, which are engaged in a step-like fashion as the dose is increased. Following a positive Phase 2 trial (Lieberman et al., 2015), the new in-patient study found that a daily 60-mg dose of ITI-007 induced a significant decrease in PANSS total score at Day 28 compared to placebo, with good control of symptoms in as quickly as one week. They also documented improvements in illness severity, and personal and social performance. The drug was as safe and tolerable as placebo. Side effects included mild sedation and fatigue, which Vanover suggested might be mitigated by taking the drug at bedtime.

In the search for treatments for negative symptoms, repetitive transcranial magnetic stimulation (rTMS) has offered some hope, with meta-analyses finding moderate effects that exceed those of antipsychotic drugs. Alkomiet Hasan of Ludwig-Maximilians-Universitat in Munich, Germany, shared recently published work from a multicenter trial of rTMS over the dorsolateral prefrontal cortex (DLPFC) for negative symptoms (Wobrock et al., 2015). Taking eight years in all to complete, the trial randomly assigned 175 patients with predominately negative symptoms either into rTMS or sham stimulation groups. After three weeks of treatment sessions each workday, Hasan reported no difference between the rTMS and sham groups. He did, however, hold out a new thread of hope: brain scanning revealed that when rTMS resulted in volume changes of hippocampal regions, the extent of this change correlated with negative symptom reductions. This suggests that measures of how well rTMS engages the relevant brain circuitry will be important in evaluating rTMS as a treatment.

Philip McGuire of King's College London rounded out the session with a trial of cannabidiol (CBD), the second-most abundant compound in cannabis. Animal and human studies have suggested CBD has some antipsychotic effects not mediated by D2 receptor blockade (Leweke et al., 2012), making it a possible add-on therapy to usual antipsychotics. The trial randomized 88 patients who responded to antipsychotic drugs but who remained symptomatic to take either placebo or CBD in addition to their usual antipsychotic. Six weeks later, the CBD group had greater improvements in their positive symptoms than those with placebo, and had twice as many subjects with at least a 20% change in total PANSS score. Because patients who use cannabis run a greater risk of relapse, McGuire suggested that replacing cannabis with CBD might avoid the psychosis-inducing effects of the predominant cannabinoid, tetrahydrocannabinol (THC).—Michele Solis.

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A New Day for Dopamine?

The study of dopamine dysfunction, once the dominant theme in schizophrenia research, has faded a bit in recent years. But a Sunday afternoon, April 3, SIRS symposium promised "Exciting New Findings about Dopamine." This report summarizes that session, along with two other relevant talks.

Dopamine-containing cells lie in the midbrain, sending connections far and wide throughout the brain. Too much dopamine marks the striatum in schizophrenia, and this surfeit engages the D2 subtype of dopamine receptors, driving psychosis. In contrast, in the cortex, a deficit of dopamine has been suspected, but detecting this has been stymied by the lack of a good tracer molecule that could give a signal among the fewer D2 receptors found there. Anissa Abi-Dargham of Columbia University in New York City has rectified the situation with a new radioactive tracer, FLB457, which binds D2/D3 receptors. Using positron emission tomography (PET) to image FLB457 binding before and after dopamine release induced by amphetamine, she reported, blunted dopamine release in schizophrenia subjects relative to healthy controls in the dorsal lateral prefrontal cortex (DLPFC) (Slifstein et al., 2015). This also correlated with DLPFC activity during a working memory task, suggesting that dopamine helps to mobilize this region when needed.

Though excessive dopamine swamps the striatum, particularly the associative striatum, in schizophrenia, exactly why this might be has been unclear. For example, postmortem studies examining tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis, have been mixed. Tertia Purves-Tyson of Neuroscience Research Australia took a comprehensive look at the ecosystem of molecules involved in regulating dopamine levels in fifty postmortem brain samples from people with schizophrenia and fifty from controls. Zeroing in on the substantia nigra, she confirmed the lack of a difference in TH in mRNA and protein levels; however, she did find a 35% increase in mRNA of aromatic acid decarboxylase (AADC), the enzyme that converts L-DOPA to dopamine, in schizophrenia patients relative to controls. If this difference pans out in AADC protein, it could help explain the dopamine excess, as could other changes she detected among D2 receptors and transporters.

Cecillia Flores of McGill University in Montreal, Canada, explored the development of dopamine projections in mice. These projections, it turns out, take their time in getting established: though they reach the striatum early in life, they do not fully innervate the cortex until adulthood. How this process unfolds in adolescence, she finds, has repercussions for adult brain organization. Flores has focused on netrin, an axon guidance molecule, and its receptor DCC. DCC signaling within dopamine-containing neurons influences cortical innervation (Manitt et al., 2011), and newer data with techniques to selectively disrupt DCC in dopamine-containing neurons in adolescence confirmed this, resulting in a significant increase in dopamine axons in the prefrontal cortex, though these were reduced in length and the number of synapses. This suggests that the dopamine network is particularly vulnerable during adolescence.

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Dopamine signals can be brief or sustained, yet the mechanics of how these different signaling regimes come about has been unclear. Bita Moghaddam of the University of Pittsburgh in Pennsylvania addressed this by looking at the consequences of dopamine neuron stimulation in rats. Stimulating ventral tegmental area (VTA) neurons, which include dopamine neurons, led to long-lasting dopamine release measured by microdialysis in multiple brain regions, lasting for more than forty minutes. The sustained release was actively maintained by neural activity and promoted by internalization of transporters that usually clear it from extracellular space. Small animal fMRI showed that VTA stimulation resulted in robust activation of dorsal striatum—a surprise, given there is no direct connection between the two, though consistent with fMRI signals found there in schizophrenia. Moghaddam proposed that VTA stimulation activates two separate pathways that converge on dorsal striatum.

In his comments about the talks, ***CS*** Board member Anthony Grace of the University of Pittsburgh noted that Abi-Dargham's work supported the notion that problems with salience and cognition are linked to dopamine dysregulation in the striatum, and problems with working memory to dopamine in the cortex. He also noted that Moghaddam's data exhibited the multiple levels of regulation of the dopamine system, which is controlled through its own activity.

Clinical Insights

On Monday afternoon, April 4, an imaging symposium featured two talks relevant to dopamine, both of which proposed clinical uses of imaging. Imaging can help interpret failed drug trials, noted Anissa Abi-Dargham while referring to newly published work on a D1 receptor agonist, called DAR-0100A. Based on work finding that trace levels of D1 receptor agonists could improve cognition in monkeys with haloperidol-induced impairments (Aleman et al., 2000), Abi-Dargham and colleagues embarked on a proof-of-concept trial of DAR-0100A in people with schizophrenia (Girgis et al., 2016). Low doses of DAR-0100A did not improve working memory, and brain imaging revealed that it did not even activate working memory circuitry. This suggests that the drug didn't work because it did not engage the relevant circuitry, thus keeping alive the idea of D1 receptor activation as a pro-cognitive therapy.

Anil Malhotra of Zucker Hillside Hospital in Glen Oaks, New York, presented recently published work in which brain imaging can help predict treatment response. Based on resting-state fMRI, which detects a default pattern of brain activity when a person is not engaged in a task, he found that the pattern of connections between the striatum and ninety-one different regions in the brain can predict whether someone will respond to antipsychotic medicines (Sarpal et al., 2016). He also noted that variations in the gene encoding the D2 receptor (DRD2), the target of antipsychotic drugs, can matter. A new analysis of the DRD2 variant pinpointed by the PGC's genome-wide association study (GWAS) of schizophrenia showed that the risk allele was associated with a slightly better response to antipsychotic drugs, consistent with Malhotra's earlier work of a different DRD2 variant (Zhang et al., 2010).

The discussant of the session, Shitij Kapur of King's College London, lamented that imaging had not yet reworked clinical practice in ways that his younger self had imagined twenty years ago. He outlined what he saw as the current obstacles: the need for longitudinal studies to really identify the operative changes; an uncertainty about what appropriate outcomes should be; a requirement for an assay to be simple enough to be included in a busy clinical practice; and cost.—Michele Solis.

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