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Year-end review in Schizophrenia Research 2018

With each passing year, small but incremental advances continue to motivate schizophrenia researchers worldwide. As we begin 2019, it is essential to look back upon the year gone by, during which several diverse approaches to understanding the origins and management of schizophrenia, have best shaped and influenced other researchers. In contrast to previous such reviews (Mehta, 2018), the current review of the ten most cited manuscripts in recent issues of Schizophrenia Research (published between June 2017 – June 2018) has minor but noteworthy differences. First, more original research studies (eight) have received high citations as opposed to reviews and meta-analyses (two). Second, the most cited papers do not necessarily reflect the most talked about papers on social media like last year (figure-1). Lastly, the themes of individual papers are more diverse than overlapping, which was the case last year.

1. Tracking the shared neural circuitry of schizophrenia and bipolar disorder

In keeping with recent trends suggesting a genetic (Brainstorm Consortium et al., 2018) and cognitive (Clementz et al., 2016) overlap across schizophrenia and bipolar disorder that question the traditional dichotomy of psychotic disorders, a voxel-wise meta-analysis was performed on diffusion tensor imaging data from 47 case-control studies (Dong et al., 2017). Importantly, none of the white matter tracts had significantly different fractional anisotropy values between schizophrenia and bipolar groups. However, as compared to healthy subjects, two tracts demonstrated reduced fractional anisotropy – the corpus callosum genu and the left posterior cingulum fibers.

While these findings indeed emphasize the presence of shared rather than disorder-specific white matter microstructural abnormalities between these two disorders, it also leaves the door ajar to examine the more complex observations of how these shared neural circuitry aberrations relate to the shared genetic origins on the one hand, and the distinct clinical phenotypes on the other.

2. Improving predictions of quality of life in schizophrenia

The poor quality of life experienced by individuals with schizophrenia is a significant contributor to their extensive disability. It is well known that there is a multitude of factors that interact interdependently to predict the poor quality of life. In an effort to improve the modeling of such a complex outcome, Andrianariosa and colleagues, borrowing from previous work on the clinical relevance of childhood trauma (Hassan et al., 2016) in schizophrenia, incorporated this measure as an additional determinant of quality of life (Andrianarisoa et al., 2017).

Among 544 community-residing schizophrenia patients examined, 82% reported experiencing some form of childhood trauma on self-rated assessments, and 28% had a current major depressive episode. Among a broad array of factors examined, a current depressive episode was the strongest determinant of poor quality of life, followed by childhood trauma score, negative symptom score, and male gender. Despite potential sampling bias and a memory-recall bias – as a function of the subjective and retrospective nature of assessing trauma, the most important message from this study is that self-reported quality of life is associated with self-reported childhood trauma among other factors. This underlines the need to examine childhood trauma as a potential predictor of quality of life in longitudinal studies which implement advanced modeling techniques like path analyses. If consistently replicated, trauma-focused therapies can be used as a specific intervention to improve depression, negative symptoms, and quality of life in schizophrenia.

3. Mapping the shared cognitive phenotype between autism and schizophrenia

Schizophrenia and autism are both neurodevelopmental disorders that share common impairments in social behaviors, despite the stark difference in their respective ages of onset. Social cognition refers to our ability to apply cognitive processes during social interactions and is recognized as a critical determinant of both symptom, as well as, real-world outcomes in schizophrenia (Fett et al., 2011).

Movie for the Assessment of Social Cognition, a video-based assessment of theory of mind abilities was used to examine hyper- and hypomentalizing states between three groups – healthy subjects, autism and schizophrenia (Martinez et al., 2017). While both clinical groups demonstrated significant impairments on theory of mind, as compared to healthy subjects, the autism group had more significant impairments than the schizophrenia group. Interestingly, there were significant associations between theory of mind impairments and symptom severity in both groups. These findings of shared social cognition deficits between autism and schizophrenia complement the shared fronto-limbic and superior temporal sulcus aberrations during social cognition performance in these clinical groups (Sugranyes et al., 2011).

4. Disentangling the effects of smoking on risperidone pharmacokinetics

Smoking is known to alter the drug levels of many psychotropics by means of inducing cytochrome enzymes that metabolize most drugs. Nicotine dependence is also a fairly common comorbidity in patients with schizophrenia.

In a retrospective evaluation of a naturalistic drug database, plasma concentrations and dose adjusted plasma concentrations of risperidone, 9-hydroxyrisperidone and the active moiety were compared between smoking (n=401) and non-smoking (n=292)

groups of individuals with schizophrenia (Schoretsanitis et al., 2017). As expected, the smoking group received significantly higher doses of risperidone (by approximately 0.5mg/day) as compared to the non-smoking group. However, dose-adjusted plasma concentrations of 9-hydroxyrisperidone and the active moiety (risperidone + 9-hydroxyrisperidone), were significantly lower in the smoking as compared to the non-smoking group. Smoking habits (light versus heavy smoking) also had a differential effect on dose-adjusted plasma concentrations of the active moiety, with light smokers (and not heavy smokers) revealing lower dose-adjusted plasma concentrations, implying an accelerated metabolism of risperidone in this group. These findings highlight the complex mechanisms of effects of smoking on risperidone pharmacokinetics that are not only dose-dependent but also smoking habit dependent.

5. Continued efforts to improve social cognition – promises and challenges

It is now well established that social cognition deficits contribute to functional disability in schizophrenia. Subsequently, there have been several attempts at using different approaches to improve social cognition, especially since conventional medications have limited therapeutic effects (Kucharska-Pietura and Mortimer, 2013). Intranasal oxytocin is a promising intervention and Jarskog and colleagues reported one of the longest dosing trials of intranasal oxytocin (twice a day dosing for 12-weeks) in patients with schizophrenia and schizoaffective disorders (Jarskog et al., 2017).

Of the 68 patients who were randomized to receive oxytocin or placebo, 55 completed the trial. There was no significant benefit of oxytocin over placebo in the primary (social cognition) and minimal gains in secondary (social skills, symptoms and functioning) outcome variables. The treatment over a period of 12-weeks was generally well tolerated. Some interesting leads do emerge from this study (e.g., modest improvement in social skills, therapeutic effect in a subgroup of schizophrenia patients). However, these need to be cautiously interpreted and future studies may specifically examine their validity and replicability. Despite these negative results, future trials may examine different dosing schedules with more careful selection of patients and examine the additive effects of combining oxytocin with other cognitive therapies like cognitive training, neuromodulation and physical exercise.

6. Understanding historic time trends of mortality in schizophrenia

It is well known that individuals with schizophrenia have higher comorbid medical conditions and higher mortality rates as compared to those in healthy comparison subjects. Over the years, owing to a range of factors, mortality rates have declined. Lee and colleagues examined specifically, the standardized mortality rates in individuals with schizophrenia in longitudinal studies conducted during two specific time periods – pre-1970s and post-1970s (Lee et al., 2018). Here, the 1970s was chosen as a watershed decade that represented a distinct transition towards improved average life expectancy, especially in the developed countries.

However, in contrast to improving life expectancy and reducing mortality rates, this systematic review of eight mortality studies in schizophrenia found an increase in standardized mortality rates among individuals with schizophrenia from 2.2 in the pre-1970s period to 3 in the post-1970s – a net increase in standardized mortality by ~37%. These numbers are certainly concerning, primarily because of a rather positive time trend among the general population. The review also highlights the fact that natural causes of mortality (comorbid medical conditions) outnumbered unnatural causes of mortality (suicide and accidents), providing vital hints at directing targeted interventions. This widening longevity gap, as put by the authors, necessitates a thorough recalibration of services priorities, healthcare policies and patient awareness to initiate a much-needed course correction.

7. Identifying psychoses subtypes with good outcomes

There are increasing efforts at understanding predictors of treatment response to medications in patients with psychotic disorders. However, there is limited evidence to identify determinants of good outcomes in psychotic patients who choose not to be on any antipsychotic medications. While it is well documented that antipsychotic medications significantly reduce symptoms and improve functional disability (Thirthalli et al., 2010), it is also known that a small proportion of patients not on antipsychotic medications, also have good outcomes in the long run.

Using a retrospective file review method, 18-month treatment data from 584 patients with diverse psychotic disorders was examined (Conus et al., 2017). Among these, 108 (~18%) patients never took medications beyond three weeks and were categorized as non-adherent patients. While overall outcomes were poorer in this group as compared to the group who were adherent to medications, 41% and 33% of these non-adherent patients had good clinical and functional outcomes. Good premorbid functioning, shorter duration of prodrome, and milder symptom severity at presentation were predictors of good outcome in this subgroup of patients. These findings highlight the need to develop better investigations that can identify this category of patients who may be managed differently.

8. Pinning down the developmental origins of schizophrenia

Novel, high-throughput gene sequencing investigations suggest that rare, damaging variants across several thousand genes increase the risk of schizophrenia (Singh et al., 2017). However, it is not known how a multitude of genetic risk loci throughout the genome interact in driving the final common clinical phenotype of schizophrenia and related neurodevelopmental disorders. Narla and colleagues, in a series of experiments using neuronal cells derived from human induced pluripotent stem cells of four schizophrenia patients and four healthy control subjects (Brennand et al., 2011) examined if the multiplicity in genetic risks can be narrowed down to fewer final common ontogenic pathways (Narla et al., 2017), based on the.

This candidate pathway approach explored the pan-ontogenic Integrative Nuclear FGFR1 Signaling (INFS) pathway using RNA-Seq and specific ChIP-seq experiments in the neuronal committed cells. The authors identified an overactive INFS pathway that highlights a common maladaptive developmental process that gets triggered by the different schizophrenia-linked mutations, perhaps during early stages of embryogenesis. This is perhaps the crossroad at which most of the damaging genetic variants converge upon even before neuronal genesis and set in process a deviant developmental route leading to the clinical phenotype observed much later in life. The translational impact of these early findings lies in the ability to control the overactive INFS pathway, thus adaptively altering neurodevelopmental trajectories early during fetal development.

9. The importance of external validation of rating scales

The Clinical Assessment Interview for Negative Symptoms was developed for a more comprehensive assessment of negative symptoms, especially in treatment trials, that account for a multidimensional latent structure of negative symptoms (Kring et al., 2013). While the tool developers did demonstrate satisfactory psychometric properties of the new instrument, they attempted replication of the validation process (Blanchard et al., 2017) with the focus on examining its generalizability in diverse clinical settings across the world – referred to as population validity (McLeod, 2013).

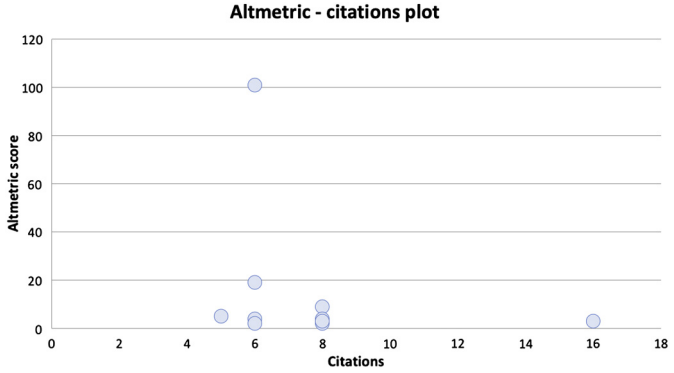
Data from over 500 individuals with a range of schizophrenia spectrum disorders recruited from 15 sites were analyzed. A two-factor structure was obtained on exploratory factor analysis, reflecting motivation and expression components, with good internal consistency. Convergent, discriminant, and ecological validity could also be demonstrated by examining the relationship with other scales of negative symptoms, positive symptoms, and real-world functioning respectively. Temporal stability of the scale was also satisfactory over a three-month follow-up period. Despite the limitations stemming from a naturalistic study design, the replication of satisfactory psychometric properties across broad clinical settings should certainly encourage greater use of this rating instrument in future studies.

10. Exome array exploration in multiplex families with schizophrenia

Exome arrays are intermediates between single nucleotide polymorphism based arrays and gene sequencing studies. This technique enables capture of rare-but-recurrent, likely deleterious, exonic variants. Data of 56,398 variants obtained from 99 multiplex families (total n = 341; cases = 118) participating in the Western Australian Family Study of Schizophrenia was compared to a much larger non-psychiatric sample of the UK-based Diabetes Genetics Replication and Meta-analysis) sample (McCarthy et al., 2017).

Exome chip variant burden was compared between cases and general population samples, and with unaffected relatives. This was supplemented with an agnostic pathway analysis. Despite the relatively small sample size of the multiplex families, cases had a significantly higher frequency of schizophrenia-related exome variants, compared to the general population sample. However, there were no variants with large effects that could be identified. The variant burden did not differ between cases and their relatives, as anticipated from earlier similar investigations (Loohuis et al., 2015). In addition, genes harboring variants in the cases were enriched for Extracellular Matrix receptor interaction pathway. These findings incrementally add to the nuanced understanding about the polygenic contributions to the origins of schizophrenia and related psychotic disorders.

Fig. 1: Scatter diagram depicting the relationship between citation index and Altmetric score (Melero, 2015) of the ten articles reviewed here



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