The idle mind never rests: functional brain connectivity across the psychosis continuum

SOCIETAL RELEVANCE

Psychotic disorders are characterized by fundamental disturbances in cognition, perception, emotion and motivation, for which currently available treatment options at best reduce symptoms and suffering (i.e., there is no remedy). The exact mechanisms leading to psychotic phenomena are hitherto unresolved, hampering the development of novel therapeutic interventions. Although the prevalence rates are relatively low (ranging from 0.5%-1% for schizophrenia and from 2.3%-3.5% for the broader category of psychotic disorders) [1], the resulting social disabilities and costs to society are high. In addition to the direct burden, continuous stigmatization may result in a vicious cycle of discrimination leading to social isolation, unemployment, drug abuse or institutionalization, which further reduces the chances for recovery and reintegration [2]. Therefore, early diagnosis and intervention are needed to lower the burden on individuals with psychosis, their family members and society. A better understanding of neurobiological mechanisms contributing to the vulnerability for psychosis will help to reach that goal.

SCIENTIFIC PERSPECTIVES

The studies of this thesis have yielded new insights into the functional brain architecture of individuals with (increased risk for) psychotic disorder. Various functional connectivity (fc) alterations in resting-state (rs) networks (i.e., the default mode network, mescorticolimbic network and frontoparietal network) were identified in patients with psychotic disorder and non-affected siblings with respect to controls, suggesting a familial, possibly genetic, predisposition. In addition, there were also apparent organisational network alterations in the patient group, indicating reduced ability for specialized processing to occur within highly interconnected brain regions. The associations between the proxy genetic risk groups (patients and siblings) and functional brain alterations were not conditional on any of the environmental risk factors (exposure to cannabis, developmental trauma or urbanicity) that were examined.

It could be argued that using a proxy genetic risk factor is rather non-specific and may not capture specific fc connectivity alterations. Therefore, polygenic risk scores, which combine common genetic risk variants (i.e., single-nucleotide polymorphisms (SNPs)) [3,4], may help to unravel and further delineate state- and trait-related effects on brain connectivity in psychotic disorder in the near future. Eventually, enhanced knowledge of the impact of the genetic liability on brain functioning will provide clues with regard to specific components of the liability to the disorder, such as neurotransmitter systems that are involved and cognitive mechanisms that need further exploration [5]. In addition, combining rs-fMRI with other neurobiological domains (i.e., neurochemical and electrophysiological data) or other imaging modalities (e.g., diffusion tensor imaging) may be even more valuable for explaining neural mechanisms contributing to psychosis vulnerability [6].

Besides known methods (i.e., seed-based correlation analysis, graph theoretical analysis) to investigate functional brain organisation, a novel graph theory based method was, for the first time, applied to this research population. This novel analysis revealed disturbances in network organisation in patients with psychotic disorder, possibly indicating more dispersed network communication (i.e., higher levels of redundancy as a result of interactions between multiple network nodes). These results warrant replication. In addition, an important objective for future research will be the use of longitudinal designs following individuals as they transition from high-risk or prodromal states to the disorder. This is relevant for determining whether whole brain network models are useful in predicting clinical outcomes. Moreover, the study of disease-related brain changes around illness onset will be essential for understanding whether altered network organisation contributes to psychosis vulnerability in the sense that it represents a principal pathology of inter-regional connectivity, or rather that it begins in an isolated brain region and progressively spreads throughout the network [7].

TRANSLATION OF RESTING-STATE FUNCTIONAL IMAGING INTO THE CLINICAL REALM

Although rs-fMRI has proven successful as a research tool, little translation has been made to the clinical realm. In general, the rs-fMRI abnormalities seen in clinical research populations, such as psychotic disorder, have not translated into the capability to acquire valuable diagnostic or prognostic information in individual patients [8]. Despite progress in this area, the clinical usefulness of rs-fMRI has yet to be firmly established. Notwithstanding the fact that the identification of group differences has improved our knowledge of the basis of network alterations, determining whether single fMRI scans contain sufficient information to classify and make predictions about individuals remains a critical challenge. One possible approach to generate single-subject inferences from fMRI data is through machine learning classifiers [9]. This approach may provide a means to use neuroimaging as a clinical diagnostic or prognostic tool, when proven useful [10]. In order to achieve definite conclusions about brain alterations associated with psychotic disorder, one should replicate and combine results from different rs-studies. While distinct labs will always vary in their analytical approach, there are certain standards or guidelines that may help improve reproducibility and strengthen the conclusions that can be made [8].

From the present thesis it can be concluded that rs-fMRI contributes to enhanced insight in functional cerebral network alterations associated with the vulnerability for psychotic disorder, which eventually may help pave the way to novel diagnostic and therapeutic interventions. Nevertheless, much work is needed before rs-fMRI can be used routinely in the clinical setting. Advances in, and direct comparisons of, the various analysis methods are warranted to further test their efficacy in detecting disease/vulnerability states at the group level and especially at the level of the individual.

KNOWLEDGE DISSEMINATION

Given the stage of resting-state fMRI research in patients with psychotic disorder and the fact that the abovementioned innovative approaches warrant replication before clinical applications/directions can be pursued, the current focus is on knowledge transfer within and outside the scientific community. Within the scientific community, knowledge dissemination involves publications in peer-reviewed journals and presentations at (inter)national research conferences, such as the Schizophrenia International Research Society (SIRS) conference. In this way, research results and methodological developments can be discussed with other scientists, driving international collaboration and consensus on analytic approaches.

Additionally, scientific results should be made public at more clinically oriented conferences (such as the yearly conference of the *Nederlandse Vereniging voor Psychiatrie (NVvP)*) and/or other conferences/symposia that are accessible to the general public (including patients and their families). It is the responsibility of the scientific community to not only inform/educate stakeholders without a necessary scientific background, but also to search for feedback and support from these parties, and to explore collaborative efforts (e.g., in order to establish research directions or to increase accessibility of research information through magazines and websites managed by patient organisations). Adequate dissemination of knowledge will help to reduce stigmatisation, not only at the level of the general public, but also at the level of professionals and patients.

REFERENCES

1. van Os J, Kapur S (2009) Schizophrenia. Lancet 374: 635-645.
2. Rossler W, Salize HJ, van Os J, Riecher-Rossler A (2005) Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 15: 399-409.
3. International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, et al. (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460: 748-752.
4. Iyegbe C, Campbell D, Butler A, Ajnakina O, Sham P (2014) The emerging molecular architecture of schizophrenia, polygenic risk scores and the clinical implications for GxE research. Soc Psychiatry Psychiatr Epidemiol 49: 169-182.
5. MacDonald AW, 3rd, Thermenos HW, Barch DM, Seidman LJ (2009) Imaging genetic liability to schizophrenia: systematic review of FMRI studies of patients' nonpsychotic relatives. Schizophr Bull 35: 1142-1162.
6. Price GW, Michie PT, Johnston J, Innes-Brown H, Kent A, et al. (2006) A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian family study of schizophrenia. Biol Psychiatry 60: 1-10.
7. Fornito A, Zalesky A, Pantelis C, Bullmore ET (2012) Schizophrenia, neuroimaging and connectomics. Neuroimage 62: 2296-2314.
8. Fox MD, Greicius M (2010) Clinical applications of resting state functional connectivity. Front Syst Neurosci 4: 19.
9. Huf W, Kalcher K, Boubela RN, Rath G, Vecsei A, et al. (2014) On the generalizability of resting-state fMRI machine learning classifiers. Front Hum Neurosci 8:502.
10. Iwabuchi SJ, Liddle PF, Palaniyappan L (2013) Clinical utility of machine-learning approaches in schizophrenia: improving diagnostic confidence for translational neuroimaging. Front Psychiatry 4: 95.