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Seeing the bigger picture: multimodal neuroimaging to investigate neuropsychiatric illnesses

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After several decades of moderate pessimism about the enterprise of developing novel therapeutic interventions for neuropsychiatric disorders, there has been recent progress toward the use of new treatment methods. For example, there is good reason to be optimistic given the efficacy of ketamine administration and brain stimulation techniques in the context of patients with depression for whom the right treatment has yet to be identified.¹⁻⁴ However, despite this progress, there is still a long way to go, and our group posits that the use of magnetic resonance imaging (MRI) techniques may play an important role in the continuing development and refinement of therapeutic strategies.

Though this has been a popular notion for some time, MRI-based techniques that index measures of brain structure and function have often been criticized for their inability to be used as a clinically relevant biomarker for diagnosis, treatment design, or the evaluation of treatment efficacy. At present, the nosology across all neuropsychiatric illness subtypes is typically not defined by biomarker-based criteria, but rather by clinical observations that are then used to create clinical definitions (e.g., patients with schizophrenia for whom the right treatment has yet to be identified). While it is tempting to search for a HbA_{1c}-like biomarker (used to diagnose diabetes) for the clinical staging, prognostication and prediction of illness onset for neuropsychiatric illnesses, it is noteworthy that neurobiological features may interact across indices describing genetics and brain circuits. In keeping with this ideology, most neuroimaging work can be characterized as single-modality studies: studies that investigate a single neuroimaging modality (e.g., structural MRI only) in a given sample at a single time point, despite possibly collecting multiple contrasts. While these works are undoubtedly useful and help to build a picture of illness pathophysiology, multimodal studies, which assess multiple neuroimaging modalities in the same population, have the potential to provide more comprehensive data that may be analyzed to identify biomarkers.

Notably, previous research has shown how both structural and functional MRI can be used as a means to refine brain

stimulation approaches.^{5,6} Also, there is emerging consensus that neuropsychiatric disorders affect brain circuits and networks.^{7,8} Importantly, many of these discoveries have enabled the development of the therapeutic treatments described above. The purpose of this editorial is to argue that, increasingly, we need to move away from single-modality studies and move toward the integration of multiple modalities in the context of neuroimaging studies if we are to develop robust signatures of brain function and dysfunction that are indicative of neuropsychiatric illness and its underlying complexity.

The case for multimodal neuroimaging studies

Typically, for any particular neuropsychiatric illness, there are few widely accepted models that fully capture their neural complexity. Nonetheless, tell-tale disease signatures exist, such as hippocampal volume decrease in Alzheimer disease,⁹ decreased cortical thickness in associative cortices in schizophrenia,¹⁰ and altered functional connectivity of the subgenual cingulate in major depressive disorder.^{11,12} The important issue is that none of these well-established signatures currently rise to the level of being used as a clinical biomarker. Yet, of the existing models of disease progression that do exist, all incorporate a progressive change across multiple architectures of the human brain (which may be heterogeneous across individuals), leading to the onset of clinically detectable disordered behaviour and functioning. Among the most famous examples are the continually updated Jack curves,^{13,14} which suggest that the accumulation of Alzheimer disease-related pathology (i.e., amyloid- β plaques and tau tangles) lead to alterations in synaptic function, ultimately leading to disordered neuronal communication and cell death. In schizophrenia, mechanistic theories typically involve alterations in brain chemistry specific to dopaminergic^{15,16} and, to a lesser extent, glutamatergic pathways^{17,18} (among others). Notably, a subset of these theories then posit that this disordered brain chemistry may lead to accelerated synaptic pruning in late maturing areas.^{19,20} Theoretical models of altered brain architecture abound

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across major diagnostic categories of neuropsychiatric disorders (such as autism spectrum and major depressive disorders), although the experimental evidence has yet to catch up to these theories. In neuroimaging, the main reason for this lag is the specific emphasis on studies of single modalities or MRI contrasts. The underlying measures, in and of themselves, are typically sensitive to overall change but (with some exceptions) are not specific to dimensions of brain architecture (i.e., specific features related to cytoarchitecture, myeloarchitecture, or neuronal function).²¹ Thus, the experiments do not match the models of the diseases that we have built over time. The only meaningful way to test these models empirically will be through the integration of multiple neuroimaging modalities, which, in aggregate, may reveal specificity regarding dimensions of disordered brain architecture that the use of a single modality will not.

Opportunities for multimodal imaging studies

In the practical sense, performing multimodal neuroimaging research in the context of biological psychiatry is enabled by typical practices during the acquisition process, as laboratories will usually acquire more than a single MRI-based contrast during an imaging session (e.g., structural and resting-state functional MRI will often be acquired during the same session). A review article published in 2016 identified the existing multimodal neuroimaging studies that investigated patients with schizophrenia.²² The authors found 25 studies that fit this criterion, of which only 5 studies were published before 2010. Notably, there is substantial heterogeneity within this literature, as most studies include only 2 different modalities and have small sample sizes. This suggests that the evaluation of multimodal neuroimaging data using emerging multivariate analyses and computational techniques may be lacking in clinical populations and is highly warranted. Thus, from the analytical standpoint, a relevant question is how do we best integrate these data streams in order to achieve an interpretable finding?

A straightforward approach that examines the univariate relationship between neuroimaging measures across populations may be the simplest way to start discovering the interplay among these indices. For example, some members of our group were involved in a recent multimodal study that aimed to elucidate the role of glutamate-mediated excitotoxicity in antipsychotic-naïve patients with first-episode psychosis by examining the relationship between proton magnetic resonance spectroscopy and structural neuroimaging measures.²³ Our results indicated a negative association between precommissural dorsal caudate glutamate + glutamine levels and precommissural caudate volume, providing support for a focal excitotoxic mechanism that may be related to structural deficits that occur in patients with schizophrenia.

While this is clearly an important step forward, the multivariate space for examining how to integrate measures is an important one. Seidlitz and colleagues²⁴ combined several morphometric parameters (up to 10) acquired using multimodal MRI. Their main findings provided evidence suggesting that cortical areas connected by edges in “morphometric

similarity networks” are cytoarchitecturally alike and associated with high co-expression of genes specialized for neuronal functions. Since these initial findings, the same group applied this technique to a sample of patients experiencing psychosis,²⁵ in whom they identified globally reduced morphometric similarity as well as reduced frontal and temporal and increased parietal morphometric similarity. Similarly, our group has shown that subtle variation in cognition can be captured by integrating MRI measures sensitive to myelin concentration (T_1/T_2) and other microstructural indices derived using diffusion MRI.²⁶ This required reparametrizing the hippocampus using non-negative matrix factorization (which provides improved interpretability of a set of components that can be best described by the influence of myelin content and fibre orientations). Importantly, by relating the components to performance on hippocampal-related tasks using partial least squares, we demonstrate a sensitivity to variation in human behaviour greater than that achievable by using a single modality or univariate measures. In another recent study, Baum and colleagues²⁷ used diffusion MRI and n-back fMRI to examine the cortical topography of structure–function coupling (i.e., the association between structural and functional connectivity) and how it evolves through adolescent development. They observed spatial differences in structure–function coupling that were related to cortical hierarchies of functional specialization as well as evolutionary expansion. Moreover, they identified structure–function coupling associations with age (i.e., hierarchy-dependent age effect in the transmodal cortex) and executive performance (i.e., rostralateral prefrontal cortex structure–function coupling associated with executive performance). These are critical steps forward, demonstrating that the advent of validated and novel techniques may be needed to properly identify how brain disorders may propagate across multiple architectures at the whole-brain level.

The potential way forward with multimodal neuroimaging studies

Importantly, there are several challenges in moving forward with these types of analyses. Here, we identify 3 critical challenges. As we move into more sophisticated analyses that require the understanding of both supervised and unsupervised machine learning techniques and multivariate statistics, it is critical that analytical scientists (computer and data scientists, statisticians and neuroinformaticians) be an integral part of study design as a means of performing meaningful evidence-based science. Too often, these individuals are included as an afterthought in neuroscientific and neuroimaging investigation once the data are collected. Second, it is important to acknowledge the increased time, accessibility, resources and expertise required for neuroimaging, additionally so for multimodal neuroimaging. However, our hope is that this investment provides a return that may ultimately enable an improved understanding of neuropsychiatric disorders. The third point refers back to the progressive nature of most neuropsychiatric disorders. The works cited here show how individuals can fall along a continuum defined

using multimodal neuroimaging data. However, the progressive nature of neuropsychiatric disorders has yet to be captured using these techniques, and this presents an area of opportunity moving forward. Ultimately, we believe that developing and using these techniques will be critical to basic neuroscientific study and to the development of biomarkers related to clinical phenotypes and treatment response. Notably, this editorial focused on MRI as a representative tool, but the same principle holds for other neuroimaging methods, such as positron emission tomography, magnetoencephalography and electroencephalography.

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