Functional neuroimaging in psychiatry and the case for failing better

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In Brief

The confluence of functional neuroimaging and cognitive neuroscience has revolutionised psychiatric research, yet clinical translation has been lacking. Nour et al. provide a critical perspective on this impasse and suggest how the field might fare better in the future.

SUMMARY

Psychiatric disorders encompass complex aberrations of cognition and affect, and are among the most debilitating and poorly understood of any medical condition. Current treatments rely primarily on interventions that target brain function (drugs) or learning processes (psychotherapy). A mechanistic understanding of how these interventions mediate their therapeutic effects remains elusive. From the early 1990s non-invasive functional neuroimaging, coupled with parallel developments in the cognitive neurosciences, seemed to signal a new era of neurobiologically-grounded diagnosis and treatment in psychiatry. Yet, despite three decades of intense neuroimaging research we still lack a neurobiological account for any psychiatric condition. Likewise, functional neuroimaging plays no role in clinical decision making. Here, we offer a critical commentary on this impasse and suggest how the field might fare better and deliver impactful neurobiological insights.

INTRODUCTION

"Try again. Fail again. Fail better."
Worstward Ho!, Samuel Beckett (1983)

The scale of investment in functional neuroimaging as a research tool in psychiatry dwarfs that of other recent innovations, with over 16,000 published articles over the past three decades (~1/3 in the last 5 years alone, according to PubMed). Yet, it is sobering to acknowledge that functional neuroimaging, in particular modalities such as functional magnetic resonance imaging (fMRI) and magneto/electroencephalography (M/EEG), play no role in clinical psychiatric decision making, nor have they defined a neurobiological basis for any psychiatric condition or symptom dimension. Thus, it remains difficult to refute a critique that psychiatry's most fundamental characteristic is its ignorance, that it cannot successfully define the object of its attentions, while its attempts to lay bare the aetiology of its disorders have been a litany of failures (Scull, 2021).

Psychiatry is surely in need of significant breakthroughs – both in conceptual understanding and treatment. Common neuropsychiatric conditions make up a sizeable fraction of global disease burden, with annual costs in Europe alone estimated at over €400bn, surpassing both cancer and cardiovascular disease (DiLuca and Olesen, 2014; Olesen et al., 2012). Yet, first-line pharmacotherapies still rely on putative molecular mechanisms of action that derive from serendipitous observations dating back to the 1950s (Braslow and Marder,

2019), and, despite some progress in development of novel therapies (Brannan et al., 2021; Brunoni et al., 2017; Carhart-Harris et al., 2021; Daly et al., 2019; Davis et al., 2021; Koblan et al., 2020; McClure-Begley and Roth, 2022; Mitchell et al., 2021; Popova et al., 2019), both pharmacological and psychological interventions remain ineffective for many patients (Malhi and Mann, 2018; McCutcheon et al., 2020; Simmonds-Buckley et al., 2021). It might be argued this attests to the unique complexity of psychiatric disorders, where causal pathways are assumed to reflect an interplay of psychological, socio-cultural, genetic, and other biological factors (Singh et al., 2022; Sterling and Platt, 2022; Trubetskoy et al., 2022). Despite this causal complexity, a core tenet of clinical cognitive neuroscience is that psychiatric symptoms are an expression of potentially identifiable altered neurophysiological function (a proximate cause), reflecting a multiplicity of upstream biopsychosocial causal factors (Deisseroth, 2021). Under this view, an ability to non-invasively measure brain activity in patient populations has held out a tantalising promise of triggering a new era of understanding and treatment.

Sophisticated modalities for examining human brain function, marked by a widespread adoption of fMRI in the early 1990s, catalyzed major advances in the cognitive neurosciences, and seemed to endow biological psychiatry with its ideal instrument (Dolan, 2008). A decade and a half ago, the current senior author articulated a widely held optimism that neuroimaging would "provide both a more principled classification of psychiatric disorders and a high level specification of aberrant cognitive processes" (Dolan, 2008), where this knowledge would in turn inform neuroscience-grounded clinical practice. The intervening years have seen an enormous expenditure of financial and human resources in this pursuit, and it is timely to reflect on what clinical advances of consequence have actually been delivered.

In this synoptic review, we focus on the application of non-invasive measures that reflect brain activity (i.e., fMRI and M/EEG). We include a historical perspective, considering key trends that have shaped the field, and highlighting a diversity in both study paradigms and analytic approaches. Although an overarching aim is to improve clinical outcomes, we consider it helpful to distinguish studies that pursue 'mechanistic' ('explanatory') questions regarding the neurobiology of symptoms (i.e., a 'theory-driven' approach), and more directly translational 'predictive' studies that use imaging data as input for diagnostic or prognostic machine learning models (i.e., a 'data-driven' approach) (Bennett et al., 2019; Huys et al., 2016; Maia et al., 2017). We examine the common and unique obstacles faced by these two avenues to clinical translation.

We conclude by considering the potential for translational impact. Here, we subscribe to a view of the brain as a computational organ, wherein psychiatric symptoms are construed

as reflecting alterations in key computational processes (Huys et al., 2021). Thus, understanding neural computation (both at the level of algorithmic processes and neural implementation (Marr, 1982)) is a necessary step towards advancing a deeper understanding of psychiatric conditions, and a likely prerequisite for clinical translation. To achieve this, we contend neuroimaging research in psychiatry, more than ever, needs to embrace theoretical frameworks derived from basic and computational neuroscience. This includes addressing how high-dimensional neural activity supports cognition, coupled with formulating testable predictions as to behavioural and symptomatic consequences of disruptions to these processes (Barack and Krakauer, 2021; Krakauer et al., 2017). Arguably an urgent necessity is to view symptoms through the lens of computational models of cognition, bridging a gap between knowledge articulated at different levels of investigation (from neural to behaviour) and species (Badre et al., 2015; Huys et al., 2016).

PSYCHIATRY'S EMBRACE OF FUNCTIONAL NEUROIMAGING

Functional localization

The non-invasive investigation of human brain activity dates to Hans Berger's landmark demonstration of modulation in EEG spectral properties as a function of behavioural state (Berger, 1929; Buzsáki, 2006). Later advances used positron emission tomography (PET) to measure baseline (resting) cerebral blood flow ([^{15}O]water PET) and metabolism ([^{18}F]fluorodeoxyglucose PET) as proxies for neural activity (Phelps et al., 1979; Raichle et al., 1983; Reivich et al., 1979). PET allowed a characterisation of changes in regional brain activity in response to cognitive engagement (Bench et al., 1993; Gusnard et al., 2001; Raichle, 1998; Raichle et al., 2001; Shulman et al., 1997). A major subsequent technological advance was measurement of neural activity using blood oxygenation level-dependent (BOLD) MRI contrast (i.e., BOLD fMRI) (Ogawa et al., 1990; Raichle, 1998; Raichle et al., 2001). BOLD fMRI was readily adopted as an investigational tool by human cognitive and systems neuroscientists, owing to advantages over PET that included improved spatiotemporal resolution and an absence of ionizing radiation exposure (Dolan, 2008).

Functional neuroimaging seemed to provide immediate advances in psychiatry by identifying apparent neuroanatomical loci for conditions and symptoms (Dolan et al., 1993; McGuire et al., 1994; Weinberger and Berman, 1988). For example, acute sadness,

antidepressant response, and treatment resistant depression were ascribed to hyperperfusion/hypermetabolism in subgenual cingulate cortex (sgACC), in addition to hypoperfusion in prefrontal, premotor and dorsal ACC (Mayberg et al., 1999, 2000, 2005). This motivated small open-label studies of deep brain stimulation (DBS) within sgACC in treatment resistant depression, where a therapeutic effect was linked to reductions in sgACC blood flow (Crowell et al., 2019; Kennedy et al., 2011; Mayberg et al., 2005). A similar rationale identified dorsolateral prefrontal cortex as a target for repetitive transcranial magnetic stimulation in depression, where efficacy in sham-controlled trials is thought to reflect a functional coupling between prefrontal cortex and sgACC (Baeken et al., 2017; Brunoni et al., 2017; Fox et al., 2012; George et al., 1995, 2010; O'Reardon et al., 2007; Senova et al., 2019; Valiengo et al., 2022; Weissman and Daskalakis, 2022). We note however that antidepressant efficacy of focal neuromodulation has not been demonstrated in all sham-controlled trials (Bergfeld et al., 2016; Croarkin et al., 2021; Dougherty et al., 2015; Holtzheimer et al., 2017; Yesavage et al., 2018).

Outcome variability in focal neuromodulation studies might reflect a host of factors including suboptimal stimulation targets, where functional neuroimaging (e.g., resting state fMRI) may yet play a role in assessing target selection and engagement in individual patients (Cash et al., 2021; Cole et al., 2020, 2022; Fitzgerald, 2021; Fox et al., 2012; Nord et al., 2019; Price et al., 2021; Siddiqi et al., 2021a; Weigand et al., 2018; Weissman and Daskalakis, 2022). Furthermore, neuroimaging-based techniques such as lesion network mapping show promise in identifying new anatomical targets that are causally implicated in therapeutic change (Joutsa et al., 2022; Siddiqi et al., 2020, 2021b, 2022). Nevertheless, it remains the case that mappings between neuroanatomical loci and psychiatric diagnoses or symptoms have remained elusive. Moreover, the future identification of any such mapping, while of clear clinical utility, would not necessarily constitute a neurobiological explanation of a condition.

Tasks, models, and neural correlates of cognition

Galvanized by advances in cognitive neuroscience, early functional neuroimaging studies in psychiatry increasingly focused on characterizing brain activity in the context of cognitive engagement, so-called 'task-based' studies. This approach assumes psychiatric symptoms and signs stem from how individuals process information about the world (from sensory input and/or memory). It also embodies a view that a deeper understanding of neural information processing will provide a mechanistic understanding of symptom generation. In

principle, this should accelerate development of new diagnostic, prognostic, and therapeutic tools in psychiatry (a perspective common to a broader 'theory-based' research programme (Huys et al., 2016, 2021; Maia et al., 2017)).

Task-based functional neuroimaging

Many task-based neuroimaging studies have exploited psychological constructs that seem relevant to psychiatric illness. For example, tasks that engage reward anticipation (e.g., monetary incentive delay task (Knutson et al., 2000)), working memory (e.g., n-back task (Owen et al., 2005)), and emotional processing (e.g., emotional faces task (Hariri et al., 2002; Morris et al., 1996)) (**Figure 1A**). Their deployment in small case-control studies often highlighted differential neural activation patterns between patient and control participants (e.g., a well-replicated blunted ventral striatal activation for reward anticipation in people with a diagnosis of schizophrenia (Radua et al., 2015)). However, a deeper explanatory insight was less obvious. One reason is that, although these investigations were conducted within a cognitive neuroscience framework, they have generally been divorced from formal, generative models of cognition. Such models seek to explain how task behaviour reflects (is generated by) latent computational processes by instantiating cognitive hypotheses in mathematically precise models (e.g., using reinforcement learning or Bayesian inference frameworks (Huys et al., 2016)). When combined with neural recordings, this computational approach offered an unprecedented window on task-related neural computations, for example those that underpin decision making (Dolan and Dayan, 2013).

One notable example is a series of landmark studies in awake monkeys, which revealed a correspondence between phasic activity of midbrain dopamine neurons and a reward prediction error (RPE) signal derived from a model-free temporal-difference reinforcement learning algorithm (Montague et al., 1996; Schultz, 1998; Schultz et al., 1997). Subsequently, a similar correspondence was shown in humans using fMRI (particularly in striatum), including demonstrating a relationship to dopamine using pharmacological manipulations and molecular neuroimaging (Deserno et al., 2015; O'Doherty, 2004; O'Doherty et al., 2003; Pessiglione et al., 2006; Schlagenhauf et al., 2013) (**Figure 1B**). More recently, fMRI studies have reported a correlation between mesostriatal BOLD activation and a diversity of prediction error (surprise) signals (Daw et al., 2011; Deserno et al., 2015; Hauser et al., 2017; Iglesias et al., 2013; Nour et al., 2018; Schwartenbeck et al., 2016), convergent with in vivo preclinical studies (Babayan et al., 2018; Bromberg-Martin et al., 2010; Chang et al., 2017; Sharpe et al., 2017; Starkweather et al., 2018; Takahashi et al., 2017).

A marriage of computationally-informed task designs, behavioural modelling, and neural recordings (i.e., model-based neuroimaging), thus enabled experimenters to make inferences about neural computation that go beyond information contained in behavioural data alone. Put simply, generative models of behaviour served as a bridge between neural and behavioural levels of description, and significantly augmented the explanatory potential of human cognitive neuroscience.

Computational psychiatry and the algorithmic basis of symptoms

The emergence of (theory-based) 'Computational Psychiatry' rests on an optimism that mechanistic insights, instantiated in generative computational models of behaviour, can accelerate neuroscience-inspired clinical translation in psychiatry (Adams et al., 2015; Bennett et al., 2019; Corlett and Fletcher, 2014; Gillan and Seow, 2020; Huys et al., 2011, 2016, 2021; Maia and Frank, 2017; Maia et al., 2017; Moutoussis et al., 2017; Petzschner et al., 2017; Stephan and Mathys, 2014). Computational psychiatry construes the brain as an information processing organ that builds parsimonious internal models of the world, with psychiatric symptoms stemming from alterations in these computations (which might occur even in the absence of aberrant neurobiological functioning). Putative alterations can be identified by fitting models to behaviour in carefully designed tasks. The value of functional neuroimaging is to link model-derived variables (which relate to an algorithmic level of description) to macro-scale neural activity patterns (which relate to neural implementation) (**Figure 1B**). In principle, this can also help adjudicate between competing algorithmic hypotheses (Huys et al., 2021), with an ultimate aspiration being to uncover 'computational phenotypes' for targeted treatments, outcome prediction, and diagnosis.

An example of such model-based neuroimaging in psychiatry has been an investigation of prediction error expression in psychosis. Here, a correspondence between dopaminergic activity and model-free RPEs opened a possibility of understanding how symptoms arise from abnormal mesostriatal dopamine signalling (Abi-Dargham et al., 2000; Howes et al., 2012; Jauhar et al., 2017; Laruelle, 1998; Laruelle et al., 1996; Laurelle et al., 1999; McCutcheon et al., 2018). This rested on a parallel move to cast symptoms such as paranoia and hallucinations in the language of prediction error-mediated learning and inference (i.e., aberrant salience attribution) (Adams et al., 2013; Fletcher and Frith, 2009; Heinz, 2002; Howes and Nour, 2016; Kapur, 2003; Maia and Frank, 2017). To this end, fMRI studies in patients have measured prediction errors using a variety of tasks (e.g., classical conditioning, instrumental conditioning, and reversal learning), finding abnormalities (typically reductions) in mesostriatal and/or

mesocortical BOLD responses (Deserno et al., 2013; Ermakova et al., 2018; Gradin et al., 2011; Haarsma et al., 2021; Katthagen et al., 2020; Koch et al., 2010; Maia and Frank, 2017; Murray et al., 2008; Radua et al., 2015; Romaniuk et al., 2010; Schlagenhauf et al., 2014; Waltz et al., 2009). By contrast, in depression an fMRI study found no difference in striatal RPE signalling compared to control participants (Rutledge et al., 2017) (in contradistinction to some earlier studies (Gradin et al., 2011; Kumar et al., 2008)). Tasks have also been designed to engage algorithms that leverage an understanding (i.e., predictive internal model) of task structure (Corlett et al., 2007; Iglesias et al., 2013; Kaplan et al., 2016; Nour et al., 2018; Powers et al., 2017; Schwartenbeck et al., 2016). A challenge to knowledge synthesis in this field arises from the widespread use of different modelling conventions and task-based statistical contrasts to operationalise constructs such as RPE (Radua et al., 2015).

Computational psychiatry's translational gap

While the computational psychiatry literature has identified associations between model-informed neural activity and psychiatric variables, effective clinical translation has been lacking. In part, this reflects a difficulty in identifying neural or behavioural effects of a magnitude, robustness, and reliability that can afford individual-level clinical utility. Although generic factors contribute to this situation (discussed in 'Perspectives on an impasse', below), computational task-based approaches present unique challenges.

Firstly, the validity of model-derived findings is conditional on a correspondence between a hypothesised generative model and 'ground truth' neurocognitive processes engaged by the task, and in many cases, an assumption of homogeneity in these processes both within and across participants (Bennett et al., 2019; Wilson and Collins, 2019). Yet, behaviour even in simple tasks can reflect contributions from multiple cognitive processes, which can vary over time and differ between participants with the same diagnosis (Ashwood et al., 2022; Castro-Rodrigues et al., 2022; Collins and Frank, 2012; Collins et al., 2014, 2016; Feher da Silva and Hare, 2020; Roy et al., 2020; Schlagenhauf et al., 2014). Thus, disentangling the relative contributions of distinct latent processes within, and between, participants requires carefully crafted tasks and detailed model comparison. At the same time, more sophisticated tasks, by virtue of their complexity and duration, present a challenge for translation to clinical populations characterised by cognitive or motivational impairments (Bennett et al., 2019), and are typically unsuitable for inclusion in large multi-site imaging studies (Gratton et al., 2022).

A second challenge is to derive meaningful individual-level effects to serve as clinically useful biomarkers. Most tasks in cognitive neuroscience are designed to elicit robust group-

level behavioural and neural effects; an objective that mandates reducing between-participant effect variance. However, it is precisely this between-participant variance that renders a task useful for individual-level prediction (Hedge et al., 2018). Moreover, even when variance in task activation covaries with psychiatric variables, interpretation remains a challenge. This is particularly the case when task behaviour covaries with clinical variables, and where there is uncertainty regarding the neural coding principles underlying measured neuroimaging signals (Lebreton et al., 2019).

These challenges invite a sober assessment of effect sizes expected from task-based neuroimaging approaches, and their ultimate utility for informing clinical practice (although it should be noted that concerns about small predictive effect sizes in mental health research extend to behavioural and non-task imaging studies (Kelley et al., 2022; Marek et al., 2022; Rosenberg and Finn, 2022)). We offer suggestions as to how theory-driven computational psychiatry might navigate these challenges in the second half of this review ('Cognition reconsidered').

Moving beyond the mean: multivariate analyses and representational structure

Much task-based neuroimaging in psychiatry relies on univariate analyses that relate activation dynamics within individual voxels (or sensors) to task events. More recently, multivariate methods have assumed increasing prominence, including representational similarity analyses (RSA) and neural decoding (Diedrichsen and Kriegeskorte, 2017; Guest and Love, 2017; Haynes and Rees, 2006; Kriegeskorte, 2008). These methods exploit multivoxel/multisensor activity patterns (typically evoked by task stimuli, or accompanying task performance) to probe the representational content of neural responses. For example, using RSA the multivoxel/multisensor activity patterns evoked by individual task stimuli (or states) are used to construct a representational dissimilarity matrix (RDM), reflecting the representational structure of neural responses (e.g., in a given brain region) (Diedrichsen and Kriegeskorte, 2017; Kriegeskorte, 2008). This neural RDM is then compared to representational structures predicted by competing computational hypotheses (e.g., hidden layers of a convolutional neural network, task transition structure, or semantic/perceptual similarity (Baram et al., 2021; Barron et al., 2020; Cichy et al., 2014; Diedrichsen and Kriegeskorte, 2017; Groen et al., 2018; Khaligh-Razavi and Kriegeskorte, 2014; Kriegeskorte, 2008; Luyckx et al., 2019)). When applied to M/EEG data, decoding and RSA methods have been shown to reveal the temporal evolution of representational patterns with millisecond resolution (Cichy et al., 2014; Liu et al., 2019; Luyckx et al., 2019).

Such analyses, whilst relatively new, can reveal representations of abstract aspects of cognition of relevance for understanding psychiatric symptoms (discussed further in 'Cognition reconsidered'). For example, people with a diagnosis of schizophrenia exhibit abnormalities in the representation of inferred relational features of task states (i.e., ordinal position in a sequence) (Nour et al., 2021) (**Figure 1C**), where this may index an internal model of the task environment (i.e., a 'cognitive map').

'Resting states' and the brain's functional architecture

Characterising activity in the 'resting' brain

A second dominant approach in psychiatric neuroimaging focuses on the study of neural activity at 'rest'. This focus arose from observations that task performance tends to elicit 'deactivations' in widespread brain regions (including medial prefrontal cortex, lateral and medial parietal regions extending to posterior cingulate cortex and retrosplenial cortex, and medial temporal lobe). These same regions show heightened cerebral blood flow and metabolic rate at rest, leading to a labelling as a 'default mode' network (DMN) (Buckner and Vincent, 2007; Gusnard and Raichle, 2001; Gusnard et al., 2001; Raichle, 1998; Raichle et al., 2001; Shulman et al., 1997). A related observation was that the covariance pattern of spontaneous neural activity across brain regions (termed 'functional connectivity', and thought to reflect shared information processing) was high between DMN regions, and low between the DMN and more 'task positive' brain areas such as dorsolateral prefrontal cortex (Buckner and Vincent, 2007; Fox et al., 2005; Greicius et al., 2003; De Luca et al., 2006) (**Figure 2A**).

Resting state functional connectivity (RSFC) measures have been widely used to characterise whole-brain 'resting state networks', with linkages to cognitive and sensorimotor processes, often based on neuroanatomy and correspondence to task-related activation patterns (**Figure 2A**). This characterisation draws on a mathematical and engineering literature, including network science, graph theory, dynamical systems analysis, and latent state space modelling, and has yielded insights into the spatiotemporal structure of the brain's functional organisation, including relationships to genetic and trait-level cognitive variables (Baker et al., 2014; Braun et al., 2018; Deco et al., 2011, 2013; Finn et al., 2015; Quinn et al., 2018; Rubinov and Sporns, 2010; Shine et al., 2016; Vidaurre et al., 2017).

Resting state approaches in psychiatric neuroimaging

Resting state studies make minimal demands on participant motivation or attention, and typically use relatively short scanning durations (often <10 minutes). Owing in part to these

advantages over task-based paradigms, a vast resting state literature has emerged encompassing the entire spectrum of psychiatric disorders (over 500 articles published in 2021 alone, according to PubMed). These studies draw on diverse analytic approaches, including measuring RSFC between a priori brain regions (network nodes), extracting RSFC networks empirically using Independent Component Analyses (ICA), graph-theoretic analyses of whole-brain RSFC networks, and characterising network (re)organisation within a single scanning session (Daws et al., 2022; Fornito et al., 2012; Garrity et al., 2007; Greicius et al., 2007; Lynall et al., 2010; Whitfield-Gabrieli and Ford, 2012; Whitfield-Gabrieli et al., 2009; Ye et al., 2015). For example, depression has been associated with subgenual cingulate and thalamic hyperconnectivity with DMN (Greicius et al., 2007), and increased network modularity (Ye et al., 2015), where the latter might be reduced following psilocybin therapy (Daws et al., 2022). Schizophrenia has also been associated with DMN hyperconnectivity (Whitfield-Gabrieli et al., 2009; Zhou et al., 2007).

As is the case for much psychiatric research, issues of replicability bedevil the field. For example, a meta-analysis of a depression resting state literature (n = 556 patients) reported DMN hyperconnectivity (Kaiser et al., 2015), while a subsequent single large study (n = 848 patients) found DMN hypoconnectivity (Yan et al., 2019). Similarly, in schizophrenia, a large meta-analysis of seed-to-voxel RSFC studies (n > 2000 patients) reported DMN hypoconnectivity (in contrast to earlier reports of hyperconnectivity) (Dong et al., 2018). This study found a complex pattern of inter-network alterations, including reduced functional connectivity between salience network nodes (e.g., insula and anterior cingulate cortex) and both DMN and frontoparietal network , in line with a disconnection hypothesis (Friston et al., 2016).

Heterogeneity in analytic pipelines precludes any easy synthesis of RSFC findings. One high-level formulation is that functional network alterations in clinical samples transcend categorical diagnostic boundaries and exist at more abstract network-levels of description (Zhang et al., 2021a). This accords with a suggestion that abnormal inter-network interactions represent a transdiagnostic mechanism of symptom generation (Menon, 2011). For example, a meta-analysis of seed-based functional connectivity studies (including over 8000 patients spanning 8 psychiatric conditions across 242 case-control studies) found a common pattern of RSFC abnormality between DMN, salience network, and frontoparietal network across disorders (Sha et al., 2019).

Such considerations have motivated a shift away from categorical diagnoses towards probing associations between RSFC and psychological traits in large cross-sectional

observational studies (termed 'brain wide association studies', BWAS (Marek et al., 2022)) (**Figure 2B**). For example, a study of university students (n = 605, of whom 133 had at least one DSM-IV diagnosis) found a link between inter-network RSFC (e.g., DMN to visual cortex hyperconnectivity) and a transdiagnostic general symptom factor ('p factor') (Elliott et al., 2018) (**Figure 2B**). Another study of 999 young people used sparse canonical correlation analysis to identify a common pattern of reduced network segregation (between DMN, frontoparietal, and salience networks) related to several transdiagnostic symptom dimensions (Xia et al., 2018). More recent findings suggest that the true magnitude of such cross-sectional BWAS effects in population samples is likely to be far smaller than required for individual-level prediction, and that sample sizes in the thousands are required for robust estimation (Marek et al., 2022).

Explanatory aspirations

It is common for resting state studies to venture hypotheses as to how brain network organisation relates to cognitive and clinical constructs (i.e., an explanatory aspiration). Explanatory proposals have drawn an analogy between the attractor-like dynamics of stimulus-independent thought and resting state activation patterns, and have speculated that alterations in these dynamics might underlie depression (Carhart-Harris and Friston, 2019; Daws et al., 2022). A related theme is a linkage between the DMN and cognitive processes such as self-referential cognition, mental simulation, imagination (e.g., scene construction), memory consolidation, and the representation of dynamic models of the world (Andrews-Hanna et al., 2010; Buckner and Carroll, 2007; Gusnard et al., 2001; Yeshurun et al., 2021). These functions seem particularly relevant to understanding hallucinations, ruminations, obsessions, and worry - not least as these mental phenomena tend to manifest during stimulus-independent thought (Daws et al., 2022; Hamilton et al., 2011; Whitfield-Gabrieli and Ford, 2012; Zhou et al., 2020). Finally, from a network- and information-theoretic perspective, higher-level properties such as whole-brain RSFC modularity and inter-region synergy are hypothesised to be important for maintaining a balance between information segregation and integration across brain regions (Daws et al., 2022; Luppi et al., 2022; Rubinov and Sporns, 2010; Shine et al., 2016).

Notwithstanding these explanatory proposals, conventional resting state studies make no explicit attempt to relate time-varying neural activity to concomitant cognitive processes and focus instead on relating activity to out-of-scanner trait or state measures. Moreover, resting state studies tend to be descriptive in their treatment of neural data. This ignores the reality that bridging a gap between descriptive accounts of neural data and psychopathology

requires a model that relates network properties (e.g., whole brain RSFC) to specific computational processes. Absent such a model, we argue that further large-scale data collection will be insufficient to yield breakthroughs in probing a fundamental understanding of cognition or psychiatric illness (further discussed in 'Perspectives on an impasse', below).

A new synthesis: bridging the task-rest dichotomy

Task-based and resting state studies in psychiatry, while embracing a common aim of delivering clinically meaningful insights and translational tools, are typically the purview of separate research communities who exploit distinct analytic approaches and theoretical frameworks (Liu et al., 2022). Yet, brain activity measured during tasks and at rest exhibit considerable overlap in energy consumption (Raichle and Gusnard, 2002), functional network architecture (Chen et al., 2022; Cole et al., 2014; Elliott et al., 2019; Finn et al., 2015; Gratton et al., 2018), and proposed information-processing functions (Mattar and Daw, 2018). These observations have motivated efforts to bridge the task-rest dichotomy. For example, understanding task-related neural activity benefits from approaches originally developed in a resting state literature, including graph-theoretic functional connectivity network characterisation (Braun et al., 2015; Cole et al., 2014; Shine et al., 2016). Network-based approaches have also been used to characterise whole-brain dynamics during working memory performance in schizophrenia (e.g., network flexibility and controllability), including detailing a relationship to dopaminergic and glutamatergic neurotransmission (Braun et al., 2016, 2021). Moreover, hyper/hypoactivation loci identified during task fMRI in schizophrenia have been interpreted as reflecting the brain's intrinsic network architecture (Crossley et al., 2015).

Conversely, decoding-based techniques originally used in task paradigms are increasingly applied to resting state data. Examples include classification of fMRI rest data according to presence of auditory hallucinations in patients with schizophrenia (Fovet et al., 2022), and detection of mood fluctuations in a patient with depression as part of a closed-loop DBS system (Scangos et al., 2021). Another case of methodological convergence is an application of dynamical modelling to both rest and task EEG data in patients with psychosis, detailing a putative circuit mechanism that might contribute to cortical excitation-inhibition imbalance (Adams et al., 2022; Nour and Dolan, 2022).

A recent development is the application of decoding to track task-relevant neural reactivations, including sequential reactivations (i.e., 'replay'), during rest (Kurth-Nelson et al., 2016; Liu et al., 2019; Momennejad et al., 2018; Schapiro et al., 2018; Schuck and Niv, 2019). Non-clinical MEG studies reveal a potential role of replay in memory retrieval, credit

assignment, relational inference, and aversive learning, which might be relevant for conditions associated with pathological avoidance, rumination, and model-based planning (Heller and Bagot, 2020; Liu et al., 2019, 2021a; Wimmer et al., 2020; Wise et al., 2021). Applying this approach to MEG data from patients with schizophrenia has identified reduced neural replay during rest (Nour et al., 2021) (**Figure 3B**), convergent with findings from a genetic mouse model (Suh et al., 2013). A related study in healthy volunteers revealed a tight temporal coupling between replay events and DMN activity, providing a novel perspective on the role of DMN in task-related cognition (Higgins et al., 2021) (**Figure 2C**). Extending the latter approach to study psychiatric populations might shed light on the functional significance of reported resting state abnormalities across a range of conditions (Liu et al., 2022).

PERSPECTIVES ON AN IMPASSE

Casting a cold eye on the psychiatric neuroimaging literature invites a conclusion that, despite 30 years of intense research and considerable technological advances, this enterprise has not delivered a neurobiological account (i.e., a mechanistic explanation) for any psychiatric disorder, nor has it provided a credible imaging-based biomarker of clinical utility.

Obstacles

Generic obstacles to clinical translation include concerns over test-retest reliability of measures derived from short duration scans (Braun et al., 2012; Cao et al., 2014; Elliott et al., 2020; Li et al., 2020; Noble et al., 2017, 2019; Nord et al., 2017; Termenon et al., 2016; Wang et al., 2011) and high sensitivity to analytic choices (Botvinik-Nezer et al., 2020; Domhof et al., 2021; Poldrack et al., 2017; Simmons et al., 2011). These factors contribute to low replicability rates (Marek et al., 2022; Nee, 2019; Nosek et al., 2022; Turner et al., 2018) and impinge on the magnitude and meaningfulness of measured effects, thus limiting the utility of neuroimaging in theory-driven research, individual differences research, and biomarker development as envisioned under a Research Domain Criteria (RDoC) framework (Insel et al., 2010; Nielson et al., 2021). Proposed mitigation measures include study pre-registration, alignment of analytic pipelines, renewed consideration of test-retest reliability in task design, and collection of sufficient data (both within participants and total sample size) to ensure adequate measurement stability and statistical power (Button et al., 2013; Dang et al., 2020; Elliott et al., 2019, 2020; Enkavi et al., 2019; Gordon et al., 2017; Gratton et al., 2018; Hedge

et al., 2018; Poldrack et al., 2017). One potential avenue might be an approach akin to the International Brain Lab, which explicitly facilitates collaborations between theoretical and experimental neuroscientists and promotes standardisation of paradigms and analytic approaches (Ashwood et al., 2022; Roy et al., 2020; The International Brain Laboratory, 2017; The International Brain Laboratory et al., 2021).

The questionable biological validity of psychiatric classification frameworks presents another obstacle. Discrete categorical diagnoses encompass heterogeneous and evolving clinical presentations, likely to reflect multiple causal pathways. Moreover, diagnostic labels are neither singular nor static within individuals, and even 'gold standard' diagnostic instruments show limited validity and reliability (Caspi et al., 2020; Cuthbert and Insel, 2013; Fried and Nesse, 2015; Fried et al., 2022; Gillan and Seow, 2020; Huys et al., 2021; Insel et al., 2010; Lilienfeld and Treadway, 2016; Plana-Ripoll et al., 2019). These factors limit the magnitude and meaningfulness of effects detected in case-control designs. As outlined, some researchers have begun to pivot towards data-driven identification of latent symptom dimensions in large population datasets (Elliott et al., 2018; Xia et al., 2018) and 'transdiagnostic' studies that seek to identify common neural abnormalities across diagnostic categories (Sha et al., 2019). While this general approach can shed light on the specificity of identified brain-clinical associations (Gillan et al., 2016), cross-sectional transdiagnostic studies are subject to many of the same concerns as those using categorical diagnosis. A move to incorporate longitudinal clinical assessments within individuals (e.g., leveraging data from experience sampling apps or social media use), represents an effort to mitigate these limitations (Kelley and Gillan, 2022; Wichers and Groot, 2016), but has yet to be fully embraced by the neuroimaging community.

There is wide agreement that mitigating these generic obstacles can help progress a mechanistic understanding of psychiatric disorders and clinical translation. However, efforts to improve reliability and validly of measurements, or increasing study power, do not, in and of themselves, inform researchers as to the kinds of questions functional neuroimaging studies need to address if they are to deliver clinically meaningful advances. Here we detail two perspectives on this question, at opposing poles of an explanation-prediction spectrum.

Cognition reconsidered

Theory-driven psychiatric neuroimaging aspires to reveal how alterations in brain activity cause symptom expression, on an assumption this understanding will enable the

development of both mechanistically-grounded therapies (Bennett et al., 2019; Maia et al., 2017) and imaging biomarkers with improved signal-to-noise ratio (Gratton et al., 2022; Rosenberg and Finn, 2022). This aspirational goal invokes two challenges: firstly, a need to characterise psychiatric symptoms in the language of neural computation; secondly, a need to characterise neural activity at a level that most faithfully reflects such computation.

The pressing need to understand behaviour and symptoms

The challenge of characterizing symptoms at the level of generative algorithmic processes is addressed by theory-based computational psychiatry (Bennett et al., 2019; Huys et al., 2016, 2021; Maia et al., 2017). Here, one source of inspiration is progress in cognitive neuroscience and experimental psychology, which demonstrate the exquisite power of behavioural modelling to dissect the algorithmic building blocks of behaviour (Krakauer et al., 2017; Niv, 2021). Computational psychiatry applies a similar approach to symptoms, which are often hypothesised to reflect dysfunction in isolated computational processes (examples include a linkage between fear conditioning and anxiety, or between associative learning and delusions) (Adams et al., 2021; Corlett and Schoenbaum, 2021; Corlett et al., 2007; Nielson et al., 2021; Schmack et al., 2021). Yet, real-world symptoms are invariably complex and multi-faceted, complicating a search for simple mappings to well-demarcated algorithmic constructs. Moreover, standard behavioural paradigms tend to use stimuli, goals, and contexts devoid of any connection to a participant's personal history, self-conception, idiosyncratic insecurities, or momentary desires – factors that nevertheless contribute to the generation of symptoms and imbue their subjective quality. Conversely, even carefully controlled experimental settings might become suffused with valanced meaning in people experiencing alterations in mental state (e.g., during a prodromal phase of psychosis (Howes and Nour, 2016)). These considerations serve to highlight the extraordinary complexity of psychiatric phenomena as objects of study, especially when considering social, contextual, and psychological influences on symptom expression, and the likelihood that a weighting of these factors can change over the course of a single scanning session.

An explanatory gap: from neural activity to representations

A second challenge is to characterise neural activity at a 'level of analysis' appropriate for explaining symptoms and other forms of abstract cognition. Barack and Krakauer (2021) have invited a closer consideration of the representational nature of such abstract cognition. Here, a representation is defined as a (neural) state that is 'about' some aspect of the world,

and which may be instantiated independently of its referents (e.g., in memory retrieval or planning). Computation and cognition are synonymous with the transformation and combination of representations in a manner that guides behaviour (Barack and Krakauer, 2021).

This formulation has implications for a neurobiological understanding of psychiatric symptoms, such as paranoia and worry, examples par excellence of representational phenomena. Barack and Krakauer (2021) argue that neural activity can be construed at several levels of description, which differ in their ability to explain representational phenomena. 'Circuit level' descriptions (i.e., those that characterise neural activity at the level of single neurons or brain regions, and the connections between them), ubiquitous in preclinical neuroscience, are considered to lack explanatory power to serve as primary ('first-level') explanations of abstract cognitive (and, by extension, psychiatric) phenomena. Instead, they suggest an adequate neural account must detail how population neural activity evolves on (and is constrained by) a lower dimensional manifold, as embedded within the high-dimensional neural space of multi-unit or multivoxel recordings. Computations underlying cognition are thus isomorphic with states, excursions, and transformations in these lower-dimensional neural manifolds (termed 'representational spaces') (Barack and Krakauer, 2021; Bernardi et al., 2020; Flesch et al., 2022; Gallego et al., 2017; Nieh et al., 2021). The task of cognitive neuroscience, then, is to uncover a mapping between cognitive and neural 'representational spaces'. The former might be uncovered using algorithmic models of cognition (as above), while the latter require statistical tools capable of describing lower-dimensional neural spaces that constrain population activity.

In the context of functional neuroimaging, such a 'representation rich' approach might involve multivariate decoding or RSA (Behrens et al., 2018; Diedrichsen and Kriegeskorte, 2017; Liu et al., 2022). For example, in visually-evoked MEG data, decoding and RSA can uncover temporal windows that contain information pertaining to abstract features of task structure (e.g., ordinal position in a learned sequence, or geometric primitives used for compositional cognition) (Liu et al., 2019; Luyckx et al., 2019; Nour et al., 2021; Al Roumi et al., 2021) (**Figure 1C**), where this type of information emerges after learning (Nour et al., 2021) and is reinstated spontaneously during subsequent rest periods (Liu et al., 2019).

A 'representational turn' is relatively new in psychiatry, though we consider it holds much promise in advancing an understanding of meaning-laden symptoms that are at the heart of many conditions. However, interpretation of findings from decoding-based studies is not trivial. For example, fMRI studies tend to deploy decoding or RSA analyses on anatomically-restricted subsets of voxels, and can thus can shed light on how neural representations are

transformed along a cortical processing hierarchy (Baram et al., 2021; Barron et al., 2020; Cichy et al., 2014; Momennejad et al., 2018; Schapiro et al., 2018; Schuck and Niv, 2019; Schuck et al., 2015). By contrast, M/EEG studies often use whole-brain data for similar purposes (Liu et al., 2019; Luyckx et al., 2019; Nour et al., 2021), such that, absent behavioural data and a guiding theoretical framework, the functional importance of decoded patterns can remain an open question.

Integration across species and levels of description

Finally, a full understanding of psychiatric symptoms will ultimately require integrating findings from imaging studies (which are largely correlational, and anatomically coarse-grained) with a rich pre-clinical research programme that speaks to cellular and circuit-level processes. One point of contact is the use computationally-informed behavioural tasks that engage analogous cognitive processes in humans and other animals (Badre et al., 2015; Corlett and Schoenbaum, 2021), exemplified in recent cross-species studies investigating the neural basis of abnormal belief updating and hallucination-like perception (Reed et al., 2020; Schmack et al., 2021). A second point of contact is the use of a representation-rich analytic approach, which allows a mapping of task-related neural responses, measured using species-appropriate investigational tools and at different spatial scales, to a common representational space (Barron et al., 2020, 2021; Liu et al., 2021b, 2022) (**Figure 3A**). A third bridge comes from biophysical circuit models, which leverage prior anatomy and neurophysiology knowledge to predict how cellular and circuit-level abnormalities manifest in observable behaviour and macro-scale neural activity patterns (Badre et al., 2015; Cavanagh et al., 2020; Huys et al., 2016).

As preclinical studies permit fine-grained measurement and manipulation of neural activity (e.g., optogenetic stimulation or silencing), cross-species integration can help elucidate the functional (causal) role of task-related activity patterns detected using human neuroimaging. Circuit-level knowledge derived from animal studies can also inform the development of tasks and analytic methods in human studies. For example, fMRI and MEG studies have indexed grid-like coding (Constantinescu et al., 2016; Doeller et al., 2010; Park et al., 2021) and neural replay in hippocampal-entorhinal cortex (Liu et al., 2019; Schuck and Niv, 2019), where these patterns were originally characterised in rodents (Diba and Buzsáki, 2007; Foster and Wilson, 2006; Fyhn et al., 2004; Hafting et al., 2005; Wilson and McNaughton, 1994). With some

exceptions, these approaches have yet to be applied to clinical samples (Nour et al., 2021) (**Figure 3B**).

Prediction and pragmatism

A progress impasse has prompted some to question the necessity of mechanistic understanding for clinical impact in psychiatry, and instead propose identifying direct mappings between neural features and clinically useful variables using predictive machine learning tools (sometimes termed 'data-driven' computational psychiatry (Bennett et al., 2019; Huys et al., 2016; Maia et al., 2017; Paulus, 2015) (**Figure 2B**). An argument in favour of this predictive approach is that, given the complexity of both psychiatric phenomena and the brain, mechanistic (brain-based) explanations of symptoms are unlikely to be correct and are susceptible to 'searchlight biases' (Paulus, 2015; Summerfield, 2022). Theory-orientated researchers, echoing a principle that "all models are wrong but some are useful" (Box, 1979), might counter that simplified models are essential for interpreting data in terms of underlying mechanistic processes (Gershman, 2021; Maia et al., 2017). Moreover, mechanistic hypotheses are increasingly informed by an understanding of the neural and algorithmic basis of cognition derived from preclinical and theoretical research.

Neuroimaging measures for data-driven predictive studies typically derive from structural and/or short-duration resting state scans, which minimise a requirement for participant engagement, rendering them amenable for inclusion in large sample multi-site consortia (Gratton et al., 2022) (e.g., UK Biobank (Miller et al., 2016)). Outcome phenotypes range from common variation in cognitive or psychological traits in population samples (Chen et al., 2022; Elliott et al., 2018; Genon et al., 2022; Marek et al., 2022; Xia et al., 2018), to treatment response and prognosis in clinical samples (e.g., in depression (Dinga et al., 2019; Drysdale et al., 2017; Pan et al., 2017; Williams, 2016, 2017; Wu et al., 2020; Zhang et al., 2021b)). Similar approaches can be applied to task-based neuroimaging measures (e.g., short-duration tasks from large cohort scanning studies (Barch et al., 2013; Casey et al., 2018; Chen et al., 2022; Van Essen et al., 2013; Miller et al., 2016; Schumann et al., 2010)), or multimodal datasets involving genetic, clinical, and neurocognitive variables (Koutsouleris et al., 2020). These approaches confer several advantages, including high confidence in identified statistical associations, improved generalizability of findings from more representative samples, and a laudable focus on cross-validation and out-of-sample prediction (Dinga et al., 2019; Mihalik et al., 2020).

Nevertheless, data-driven approaches are associated with significant shortcomings. Firstly, no approach is ever purely 'data-driven'. A decision as to which neuroimaging measures to include in a predictive model is inherently 'theory-laden', and ideally should leverage an understanding (i.e., model) of how selected features relate to the clinical phenotype (Gershman, 2021; Maia et al., 2017). This is particularly relevant when considering that 'functional connectivity' and task-related 'activations' represent coarse-grained statistical summaries of neural data, where the relationship to neurophysiology or computation remains incompletely understood (Kullmann, 2020; Lebreton et al., 2019). This situation differs from the successful application of predictive machine learning in other domains, such as protein folding (Jumper et al., 2021), where there is an understanding of the causal relationship between input (primary amino acid sequence) and output (3D protein structure) data, thereby conferring increased confidence that the input data contains sufficient information to predict an output. By contrast, the ubiquity of resting state measures in large sample predictive studies arguably reflects the ease with which such measures can be collected (compared to task-based measures), rather than a principled demonstration that RSFC confers superior predictive potential (Gratton et al., 2022; Rosenberg and Finn, 2022). One intriguing suggestion is the use of theory-driven computational models to first reduce high-dimensional neural data into a more behaviourally-meaningful low dimensional feature space, which can then serve as an input to data-driven machine learning pipelines (Huys et al., 2016).

A second reason to temper enthusiasm relates to the magnitude of the predictive effect sizes that data-driven methods have delivered to-date. In cross-sectional observational studies, RSFC and cortical thickness explain a small proportion of common variance in cognitive or psychological traits, insufficient for clinical utility (Marek et al., 2022). As discussed, the expectation is for larger predictive effects when using imaging measures derived from within-subject interventional studies, particularly when these have been designed to engage neurocomputational processes causally implicated in symptom generation or treatment response (as is the case for biomarkers in other areas of medicine) (Gratton et al., 2022; Marek et al., 2022; Rosenberg and Finn, 2022). However, we note there is scant evidence that common task paradigms, which are explicitly designed to index such processes, yield superior predictive effect size estimates with respect to cognitive, psychological, or clinical traits (Marek et al., 2022).

CONCLUSION

We have questioned the extent to which functional neuroimaging has advanced, let alone uncovered, a neurobiological basis for any common psychiatric disorder (a goal of theory-based computational psychiatry), or generated predictive models that guide clinical decision making (a goal of precision psychiatry). While fMRI and MEG are powerful tools, their clinical utility is constrained by the questions they are tasked to answer (Barack and Krakauer, 2021; Buzsáki, 2020; Gershman, 2021; Jonas and Kording, 2017; Liu et al., 2022). These questions are especially challenging in psychiatry (a field that aspires to understand the relationship between neural activity and mental phenomena) compared to, say, neurology (where neural activity, anatomy, and sensorimotor function are often primary objects of investigation) (Barack and Krakauer, 2021). While an aspiration to derive a neurobiological account of psychiatric symptoms is a goal of mechanistic (explanatory) research, we argue it is also highly relevant for developing interpretable clinical decision tools. Our overarching view is that a deeper engagement between psychiatric neuroimaging researchers and the broader neuroscience and AI communities, exemplified by the growth of computational psychiatry, provides a basis for cautious optimism that, over a medium-term horizon, we will yet benefit from clinically relevant mechanistic insights and translational impact.

AUTHOR CONTRIBUTIONS

M.M.N. researched and synthesized data for article, wrote the manuscript, and contributed substantially to discussion of the content, review and editing of the manuscript. Y.L. contributed to discussion of the content of the manuscript. R.J.D. provided direction and guidance on the scope and content of the manuscript, and contributed substantially to writing, reviewing, and editing of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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FIGURE LEGENDS

Figure 1 Task-based approaches

(A) Early task-based studies examined cognitive/emotional constructs in simple subtraction contrasts (e.g., comparing neutral and valanced conditions). Examples include processing of emotional/aversive stimuli (Hariri et al., 2002), n-back working memory tasks (Owen et al., 2005) and monetary incentive delay tasks (Knutson et al., 2000).

(B) Combining task-based neuroimaging with computational modelling of behaviour provides a window into the neural basis of latent cognitive and computational processes. *Top left:* Classical conditioning task. An agent learns a predictive relationship between the presentation of a conditioned stimulus (CS) and presentation of a rewarding or unrewarding unconditioned stimulus (UCS). *Top right:* A temporal difference (TD) learning algorithm model. The value of the state at time t, V(t), is updated on each trial in proportion to a reward prediction error (RPE), δ, and a learning rate, α. *Bottom:* Conditioning tasks in conjunction with neural recordings identify a correspondence between phasic activity of putative dopamine neurons and TD RPE in awake monkeys (*left*, using in vivo electrophysiology (Schultz et al., 1997)) and humans (*right*, using model-based fMRI, which is not capable of resolving a dopamine-specific response (O'Doherty et al., 2003)). Figures adapted from (O'Doherty et al., 2003; Schultz et al., 1997), with permission.

(C) Multivariate methods such as RSA permit investigation of the representational structure of neural responses (over sensors or voxels) for task stimuli. *Left & middle:* Illustration taken from an MEG sequence learning task, in which participants learned the ordinal embedding of 8 task pictures in two sequences. After learning, an RSA analysis on visually-evoked neural data revealed an increase in multi-sensor pattern similarity for pictures that occupy the same ordinal position in different sequences in control participants (a 'position code' representation, peaking at ~500ms after stimulus picture onset). This increase in representational similarity is absent in people with a diagnosis of schizophrenia (PScz). *Right:* The change in pairwise representational similarity at 480 ms post-stimulus onset in controls and PScz separately (note the correspondence between the control participant similarity matrix and the hypothesized 'position' design matrix shown in the *left* panel). Adapted from (Nour et al., 2021).

Figure 2 Resting state approaches

(A) *Left:* Resting state studies tend to focus on spontaneous neural activity fluctuations in brain regions of interest (ROIs) or voxels, as measured by fMRI BOLD or M/EEG signal amplitude.

The correlation between spontaneous activity fluctuations in two brain regions, termed 'resting state functional connectivity' (RSFC), is thought to reflect shared information processing. *Right:* Spatially distributed resting state networks (RSNs) and network-based parcellations can be defined based on functional connectivity strength between pairs of brain regions (nodes or voxels). Figure adapted from (Power et al., 2011) showing RSFC-based brain network parcellation, with default mode network (DMN) and frontoparietal task control network highlighted.

(B) *Left:* Mapping RSFC to symptom dimensions using machine learning (a data-driven predictive approach). *Right:* Figure adapted from (Elliott et al., 2018), and shows pattern of altered RSFC between visual association cortex seeds and frontoparietal network and DMN as a function of a transdiagnostic latent psychopathology factor ('p factor) in a large population sample (measured using fMRI).

(C) *Left:* Inferring the fast dynamics of RSN activations from MEG resting state data, using a time embedding delayed hidden Markov modelling (TDE-HMM) approach. *Top:* Inferred RSN (i.e., hidden state) activation probabilities for a single subject over 60s. *Bottom:* Two RSN TDE-HMM observation models inferred from concatenated MEG rest data over 55 healthy volunteers. *Right:* Mean (± SEM) RSN activation dynamics at the onset of sequential neural replay events, where the latter is detected using a multivariate neural decoding approach applied to MEG rest data. A temporal association between replay onset and RSNs 1&2 (parietal alpha network and DMN, shown in *left* panels) is evident. Figure adapted from (Higgins et al., 2021).

Figure 3 Cross-species integration in cognitive neuroscience.

(A) Barron et al, (2020) studied inferential reasoning in mice and humans using an aligned inference task, wherein an unobserved association (X→Z) is inferred from observations of X→Y and Y→Z. *Middle:* Species-specific investigational tools (fMRI in humans, and in vivo recordings and optogenetics in mice) identified involvement of hippocampus in inferential reasoning. *Right:* An RSA approach as applied to hippocampal multi-voxel/multi-neuron data in humans (*top*) and mice (*bottom*), respectively, revealed a common neural representation of inferred task structure after learning. Figures adapted from (Barron et al., 2020).

(B) *Left & middle:* Offline (resting state) hippocampal place cell replay was originally identified in rodents performing spatial navigation tasks (e.g., running linear tracks) using in vivo electrophysiology recordings. Similar sequential learning, inference, and planning tasks have been developed to study replay in humans undergoing functional neuroimaging.

Multivariate decoding can be used to infer similar spontaneous neural replay signatures in human functional neuroimaging data (Kurth-Nelson et al., 2016; Liu et al., 2019; Schuck and Niv, 2019). Schematic shows one such approach (Temporally Delayed Linear Modelling, TDLM) applied to human MEG data (Liu et al., 2021b). *Right:* People with a diagnosis of schizophrenia (PScz) exhibit reduced offline neural replay compared to matched control participants, after performing a sequential inference task in MEG (mean ± SEM over participants) (Nour et al., 2021). Figures adapted from (Nour et al., 2021).

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