Spatiotemporal Precision of Neuroimaging in Psychiatry

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ABSTRACT
Aberrant patterns of cognition, perception, and behavior seen in psychiatric disorders are thought to be driven by a complex interplay of neural processes that evolve at a rapid temporal scale. Understanding these dynamic processes in vivo in humans has been hampered by a trade-off between spatial and temporal resolutions inherent to current neuroimaging technology. A recent trend in psychiatric research has been the use of high temporal resolution imaging, particularly magnetoencephalography, often in conjunction with sophisticated machine learning decoding techniques. Developments here promise novel insights into the spatiotemporal dynamics of cognitive phenomena, including domains relevant to psychiatric illnesses such as reward and avoidance learning, memory, and planning. This review considers recent advances afforded by exploiting this increased spatiotemporal precision, with specific reference to applications that seek to drive a mechanistic understanding of psychopathology and the realization of preclinical translation.

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An important goal within cognitive neuroscience is to determine the precise neurophysiological features that contribute to the expression of psychiatric phenomena, with the ultimate goal to inform psychiatric diagnosis and treatment. Given the multitude of neuroimaging tools accessible to researchers today, it may seem surprising that neuroimaging research has had scant impact on clinical psychiatry (1,2). Several non-competing explanations have been put forward (3), pointing to either the historical limitations of neuroimaging analyses and their interpretation (4–9) or the restrictive, subjective, and arbitrary nature of clinical diagnosis (6,8,10). Here, we focus on the former. We argue that the utility of neuroimaging in psychiatry has reached an inflection point beyond which recent methodological advancements can now dramatically improve the spatiotemporal precision of functional brain mapping, opening new approaches to elucidating the neurocognitive dynamics underlying complex human behavior and psychopathology.

Our ability to precisely capture spatiotemporal patterns of neural activity has, until recently, been limited by 2 primary obstacles. One relates to a trade-off between spatial and temporal resolutions that is inherent to a reliance on noninvasive neuroimaging approaches. This limits the ability of any single methodology to provide a complete picture of both the where and the when of the neural processes that underlie complex human cognition and behavior, potentially obscuring core aspects of neural dynamics that play causal roles in the genesis of psychiatric illnesses.

A second obstacle is the extent to which it is possible to ascribe precise mechanistic significance to in vivo–recorded brain activity; in other words, the what and the how of a neural process. For example, an increased blood oxygen level–dependent signal in the striatum after receipt of a reward is interpreted as indicating a functional role for this structure in reward processing, but this observation lacks specificity as to what that functional role actually is (11). Mechanistic specificity can be gained from designing highly controlled experiments that attempt to isolate a precise cognitive function, usually informed by a computational model, though this often entails reduced ecological validity and generalizability (12,13).

The dynamic nature and real-world relevance of features that characterize psychiatric disorders mean that both spatiotemporal and functional precision are crucial to improving our understanding and, ultimately, guiding development of targeted treatments (14). In this review, we outline current trends in human neuroimaging that advance a quest for increased spatiotemporal precision. First, we provide an overview of the current spatiotemporal resolution achievable in neuroimaging. Second, we illustrate how to enhance spatiotemporal precision by extracting meaningful state representations from neuroimaging data, as well as how to track the dynamic reinstatement of these processes in the brain, taking recent breakthroughs in the detection of hippocampal replay using magnetoencephalography (MEG) as a case example. Finally, we explore how uncovering the spatiotemporal dynamics of mechanistically relevant neural activity can be combined with generative modeling of pathological behavior and cognition, with specific relevance to the burgeoning field of computational psychiatry (15).

SPATIOTEMPORAL PRECISION OF NEUROIMAGING
Noninvasive neuroimaging methods range from modern ultrahigh-field magnetic resonance imaging that delivers a
spatial resolution as fine as 0.5 mm (16), to older technologies such as electroencephalography (EEG) and MEG that provide measurements of mass neural activity at a millisecond resolution (17,18). Each of these modalities has strengths and weaknesses with regard to spatial and temporal resolution, in addition to factors such as tolerance in freedom of movement (19) and the precise physiological processes used to index neural activity.

In psychiatry, it can be conjectured that processes underlying psychopathology encompass rapidly evolving and spatially specific neural dynamics. For example, disordered belief formation in schizophrenia has been ascribed to aberrant activity in the prefrontal cortex and hippocampus related to reduced synaptic gain, causing an imprecise coding of prior beliefs, which in turn influences neural responses to surprising stimuli as early as 50 ms post stimulus onset (11). Similarly, depression has been thought of as a disconnection syndrome, where connectivity between anatomically discrete brain regions is reduced (20,21) but where the rapid, dynamic evolution of this connectivity (i.e., subsecond transient changes in distinct spatial neuronal populations) differ between clinical subtypes (22,23), providing a potential biomarker for the efficacy of electroconvulsive therapy (24). Thus, despite apparent progress using conventional approaches, it is nevertheless the case that fundamental research questions related to neural dynamics likely require a level of spatiotemporal precision that has historically been extremely difficult to realize (25).

**Multimodal Imaging**

Considerable effort has been invested in attaining higher spatiotemporal precision by deriving converging results from separate neuroimaging methodologies with complementary spatial and temporal resolutions, recorded either simultaneously (e.g., simultaneous EEG–functional MRI [fMRI]) or in separate sessions (e.g., MEG followed by fMRI) (26). In many cases, this multimodal approach to neuroimaging has been informative about brain dynamics underlying psychopathology (27). For instance, the amplitude of a fast-latency signature of reward processing detected with EEG correlates with the BOLD signal in the striatum, and together, this fast striatal reward responsivity is reported as blunted in a subtype of depression characterized by impaired mood reactivity (28). Thus, multimodal imaging has the potential to enhance the detectability of subtle neurobiological effects that would otherwise be difficult to detect through reliance on a single modality (26,29). Multimodal imaging studies, however, impose a significantly higher demand on resources, and a lack of a unifying model can lead to difficulties in interpreting convergent or discrepant multimodal findings (27,30).

**Increasing Granularity Using Statistical Learning**

A recently developed approach to enhancing spatiotemporal precision of a single neuroimaging modality involves the exploitation of machine (or statistical) learning, which harnesses a range of statistical techniques to distinguish between neural or behavioral states (see Table 1 for a list of terms and definitions). This approach has demonstrated that even the most nuanced fluctuations in spatiotemporal neural data may contain relevant information (31). These nuances, such as small differences in the angle of neighboring dipoles in the MEG data, create statistically separable patterns that are identifiable using multivariate pattern classification algorithms.

An early example of a machine learning approach to neuroimaging data involved decoding visual orientation from the human visual cortex using multivoxel pattern analysis of fMRI data (32). Although orientation-selective cortical columns are

| Term                              | Definition                                                                                                                                 |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Machine Learning                  | A methodological approach in which an algorithm (e.g., a support vector machine) is iteratively improved to capture relationships between variables in a training dataset (123). The optimized algorithm is then applied to a test dataset to predict the same relationships. Machine learning may be supervised or unsupervised and is generally model agnostic. |
| Statistical Learning              | A branch of machine learning in which a suitable statistical model (e.g., logistic regression) is deliberately selected and fit to a training dataset to infer relationships between variables, in accordance with the assumptions of the selected model (59). The optimized model may then be used to predict relationships in a test dataset. |
| MVPA                              | A supervised classification problem that captures the relationship between spatial patterns of BOLD signal across voxels and a particular experimental condition in a training dataset (120). These spatial patterns can then be detected by applying classifiers to a test dataset. |
| Neural Representation             | A spatiotemporal pattern of neural activity that is reliably evoked by a specific mental or physical state, indicating that the pattern encodes the state (121). |
| Cognitive Map                     | A neural representation of how different states relate to each other (74).                                                                 |
| Structural Inference              | The ability to infer how an environment is structured, given previous experience of state-to-state transitions, as well as any higher-order information (74). In other words, the ability to construct, utilize, and update a cognitive map. |
| Replay                            | A neurophysiological phenomenon whereby neural representations of states are reactivated in a specific order, indicating their relationships within a cognitive map (122). |
| Computational Psychiatry          | A field of research in which generative mathematical models are constructed to explain the relationships between behavior, cognition, environment, and the underlying neurobiology of psychiatric disorders (11). |
| Reinforcement Learning            | A computational model describing how decision making is influenced by past experiences of reward (123).                                  |
| CBT                               | A talking therapy that aims to reduce symptoms of mental disorders by challenging dysfunctional beliefs (cognition) and their associated behaviors (124). |

BOLD, blood oxygen level–dependent; CBT, cognitive behavioral therapy; MVPA, multivoxel pattern analysis.
much smaller than the spatial resolution of fMRI (3 mm²), orientation selectivity can be reliably estimated from signals generated by entire ensembles of voxels. Remarkably, orientation selectivity (33) and retinotopic maps in primary visual cortex (34) have now been reliably estimated from MEG data using support vector machine classifiers, despite source-reconstructed MEG having a resolution in the order of several millimeters at the cortical surface. This example demonstrates that modern analytic approaches can exploit subtle variations in coarse spatial or temporal information to detect and classify neural processes that unfold at a finer scale than the resolution of the imaging modality itself. Such a feat can be achieved by biology-agnostic machine learning methods that distill spatiotemporal information from rich sources of neuroimaging data (as just described), and also by biophysically realistic models that use prior knowledge of neurophysiological activity (provided by other modalities; e.g., invasive electrophysiological recordings in animals), to capture traces of such processes present in noninvasive human neuroimaging data [e.g., dynamic causal modeling of fMRI and MEG/EEG (35)]. Thus, both biologically informed models and biology-agnostic machine learning methods can be used to offset spatiotemporal constraints of current neuroimaging methodologies.

**HIPPOCAMPAL REPLAY AS A CASE EXAMPLE**

A striking example of the use of statistical learning to extract precise spatiotemporal information from MEG data comes from pioneering studies demonstrating hippocampal replay in humans (36). A central tenet of this review is that noninvasive measurement of hippocampal replay in humans is likely to represent a major advance not only for cognitive neuroscience but also for biological psychiatry. The approach indicates that neuroimaging data can provide a sufficiently rich source of spatiotemporal information to signal rapid, dynamic shifts in mental states, thereby allowing for a more precise estimate of when and where cognitive processes unfold in the brain. Below, we detail this approach and discuss how it has been, and can be, exploited to further the field of biological psychiatry.

**The Methodological Challenge of Replay**

Replay was first observed in rodents in the 1990s where, during post-task rest, hippocampal place cells indexing the trajectory of an animal through an environment rapidly reactivated in the same order in which these locations were experienced, albeit with a pronounced temporal compression (37–39). This spontaneous and rapid unfolding activity pattern was subsequently shown to play a causal role in memory consolidation (40–43) and has been linked to higher-order cognitive functions such as reward learning (44–50) and planning (51–55).

In humans, measuring hippocampal replay noninvasively presents a considerable methodological challenge because one of its putative sources (the hippocampus) is located deep within the brain, and the speed with which replay events unfold is extremely fast (in animals, the sequential reactivation of place cells indexing discrete locations is typically separated by tens of milliseconds). This challenge is shared by neuroimaging research in psychiatry, where there is often a need for both spatial and temporal precision. For example, in mood disorders, fast latency activity in deep brain structures, such as the amygdala, is believed to play a pivotal role in the genesis and maintenance of symptoms but is notoriously difficult to measure in vivo (25). Moreover, replay by its very nature involves reactivation of anatomically specific neural populations (e.g., specific place cells) that represent specific mental states (e.g., different locations in space). Thus, measuring replay in humans from noninvasive neuroimaging data necessitates innovative approaches, such as the exploitation of statistical learning to extract fast sequential reactivation of state representations (56,57).

**Measuring Hippocampal Replay**

An approach to quantifying replay from noninvasive neuroimaging data is temporally delayed linear modeling (56), which estimates evidence for sequential state reactivation. Temporally delayed linear modeling capitalizes on the fact that reactivation of a particular state within the hippocampus causes a cascade of related activities across a distributed network that includes the entorhinal cortex (58), medial temporal cortex (59), visual cortex (60), and prefrontal cortex (61–64). Thus, while hippocampal activity can be challenging to identify from MEG recordings [but far from impossible; see (65,66)], information related to a specific memory or state can be decoded from unique spatial patterns of neural activity to uncover rapid, sequential reactivation of prior experiences (57,67–73). This ability to detect subtle but relevant spatial information increases both temporal and representational precision (e.g., specific memories) even at relatively low spatial resolution. Importantly, in psychiatry research, representational precision might often be considered more valuable than spatial precision, such as when investigating whether a therapeutic intervention instantiates a change in cognitive processes.

How can specific states be isolated and captured? Investigators commonly use visual stimuli presented in a particular order to represent distinct states. A key idea here is that the brain organizes information—spatial or otherwise—into cognitive maps constructed from information such as conceptual associations or temporal-order relationships (74). By using visually and conceptually unique images, machine learning algorithms can accurately and reliably classify spatial patterns of neural activity associated with viewing each image (Figure 1A). The sheer size of the visual system in the human brain means that visual stimuli can be classified from distributed spatiotemporal activity generated primarily from occipital and temporal cortices, with classification accuracy typically in the range of 37% to 50%, which is 3 to 8 times higher than what would be expected by chance (68,70,72,75). Classifiers are typically trained on neural activity patterns recorded during an initial functional localizer when participants view images before learning about task-related temporal-order relationships (56). Hence, this constitutes a supervised machine learning approach, where identity labels are known (e.g., whether participants were viewing image A or image B). The associated MEG sensor patterns then provide a reliable estimate of activity when these states are subsequently reactivated, for example, during a cognitive task such as planning (online) or during a rest period (offline) (Figure 1). The hippocampus and
medial temporal lobe as well as the visual cortex have been identified as likely sources of such replay events in humans (68, 69, 72).

Overall, investigating replay in the human brain exemplifies how a rapidly evolving neurophysiological signal can be detected and characterized at an extremely fine temporal resolution. More importantly, these studies provide a representational specificity (e.g., states in a cognitive map) that is not easily obtained using traditional neuroimaging analyses. This implies that a representation-rich characterization of neuroimaging data can greatly enhance the granularity of observable neural dynamics (36), allowing exploration of more abstract neural processes underlying complex cognition.

MECHANISTIC SPECIFICITY

Computational Modeling of Behavior

The ability to uncover hidden spatiotemporal dynamics of cognition from neuroimaging data has the potential to unlock crucial information about psychiatric disorders that might otherwise be undetectable from behavior alone. As an example, consider the cognitive processes that contribute to planning. These include an ability to learn and retrieve a cognitive model of the environment that captures how the states are connected, the consequences of taking different actions at different states, and the effective appraisal of prospective reward and loss (76). Computations such as these evolve dynamically over time, where one type of processing (e.g., the accessibility of an aversive memory) may influence another (e.g., the perceived probability of being punished) (77). These dynamics are pervasive in existing computational psychiatry models of behavior, which reveal information about how specific cognitive mechanisms operate differently in psychiatric disorders (78).

Spatiotemporally precise neuroimaging can bestow cognitive models with biological plausibility, revealing how modeled dynamics of cognition (where cognition is either a construct, as in algorithmic models such as reinforcement learning, or a biophysically realistic process, as in synthetic models such as attractor network models) are supported by the temporal profile of network activity (79). Therefore, it seems reasonable to conjecture that clinical translation of computational psychiatry may be catalyzed by approaches to neuroimaging analysis that enhance spatiotemporal precision by 1) validating the dynamics of theory-driven cognitive processes through convergent biological evidence; 2) assigning a neurophysiological basis to modeled cognitive mechanisms, potentially revealing targets for treatment; and 3) enhancing the informational content of models by revealing hidden states. Below, we describe recent studies that pair spatiotemporally precise neuroimaging, such as sequential state reactivation during replay, with computational psychiatry models, with a particular focus on structural inference and reward learning.

Inferring Environment Structure

Decoded state representations shed light on how we learn, store, and retrieve structured representations of our environment. The spontaneous reactivation of sequences—both experienced and imagined—is implicated in constructing and using internal representations of the environment. For instance, an ordered reactivation of previously experienced states during a post-task rest period has been shown to

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**Figure 1.** Capturing mental states using statistical learning. (A) Mental states, such as viewing an image, can be differentiated by the unique patterns of evoked spatiotemporal brain activity captured with magnetoencephalography (MEG). These spatiotemporal state classifiers can then be applied to MEG data during a task of interest (e.g., decision making), revealing the time course of state reactivation associated with specific aspects of cognition and behavior. (B) Visual orientation can be classified from MEG and electroencephalography (EEG) sensor data due to unique configurations of angled dipoles along the cortical surface. [Adapted from Stokes et al. (31)]. (C) Different mental states may also evoke different neural network configurations, producing unique patterns of activity across MEG sensors.
correspond not to an experienced structure but instead to an inferred structure that participants abstracted based on a learned task rule (70,72). This sensitivity of reactivated state representations to inferred structural features implies that MEG-decoded replay can provide a neurobiological signature of an ability to structurally reorganize our model of the world. A breakdown in structural inference has been conjectured to underlie psychiatric symptoms that indicate inflexible or repetitive thinking, including compulsive behavior in obsessive-compulsive disorder (OCD), detrimental drug consumption in addiction disorders, and incoherent thought in schizophrenia (80–84). This accords with findings of relatively stronger evidence for model-free decision making (i.e., habitual behavior that disregards environment structure), compared with model-based control (i.e., deliberate behavior that grants flexibility and accuracy at the cost of increased cognitive load) (84), in these clinical populations.

In schizophrenia, we can ask whether a putative deficit in structural inference is reflected in spontaneous neural replay. After completing a task in which the temporal order of a stimulus sequence needs to be inferred, even though the true order is never experienced, patients with schizophrenia show weaker evidence for reorganization of ordered state reaction during rest compared with healthy control subjects, an effect that localizes to the hippocampus and corresponds with behavior (72). This finding is consistent with the theory of reduced synaptic gain in schizophrenia, which is thought to significantly affect synaptic plasticity and attractor dynamics within the hippocampus (85–87). This points to a link between an observable cognitive process (impaired structural inference, possibly manifesting as incoherent thought) and a previously unobservable neurophysiological process (replay of an inferred cognitive map in the hippocampus) that might guide prognosis, as well as pharmacological and therapeutic treatment (85).

Making Inferences Under Uncertainty
A feature of several psychiatric disorders is an impaired ability to update beliefs about the structure of an environment when something changes unexpectedly. For instance, behavioral modeling of decision making has shown that paranoia and delusions can be explained by having a general expectation that stimulus-outcome contingencies will change more frequently, resulting in poorer learning in volatile environments (88–92). This translates to an overweighting of unlikely explanations (i.e., paranoid delusions), the quality of which depends on a complex interplay of other parameters such as mood, prior habits, and whether beliefs pertain to social interaction (90).

Dysfunctional belief updating is a target of cognitive behavioral therapy (CBT), which reports success in correcting beliefs about risk and uncertainty in the context of OCD (93) as well as in reducing negative beliefs in depression through cognitive restructuring methods (94). There are, however, instances where CBT inexplicably fails, such as with the long-term persistence of paranoid delusions (95) and with treatment resistance in specific subtypes of OCD (96), even when administered alongside psychotherapy. The ability to derive a precise neural signature of how beliefs evolve over time, much in the same way that state representations are decoded to indicate neural replay (56), can, in principle, help reveal whether cognitive restructuring in CBT has a significant impact on generative processes throughout the course of treatment, potentially serving also as a posttreatment predictor of relapse (see Table 2).

Research on healthy participants has demonstrated that dynamic belief updating can indeed be detected via spatiotemporal decoding of MEG data. Weiss et al. (97) investigated the computational and neural mechanisms underlying structural inference in uncertain environments with and without an ability to control how information was sampled. They found that being able to choose which information to sample made environments appear more stable, echoing beliefs people with OCD hold about compulsive and repetitive behaviors (98). Moreover, MEG pattern classification revealed crucial temporal and spatial dynamics of how evidence was evaluated against current beliefs during information gathering. Specifically, activity in temporal and visual cortex encoded how consistent each piece of evidence was with current beliefs, revealing changes of mind that occurred throughout a trial prior to making a response. These changes of mind were delayed when participants had control over information sampling, consistent with participants reportedly viewing these environments as being more stable. This work elegantly demonstrates how neural pattern classification can reveal temporally precise trajectories of beliefs with a neuroanatomical grounding, which could provide novel information about such cognitive processes in conditions such as OCD (97,99).

Tracking the Dynamics of Reward Learning
Disordered belief updating leads to dysfunctional decision making, which is a cause of disruption to everyday life in people with certain psychiatric disorders (83). In mood disorders, a bias toward using negative information to update beliefs (which we can consider analogous to learning) (100) can be computationally deduced (e.g., by reinforcement learning models) from patterns of dysfunctional decision making, such as increased risk aversion in anxiety and reduced reward-seeking behavior in depression (83). Neuroimaging can complement such computational models of decision making in psychopathology by measuring a reward prediction error signal (i.e., the difference between the reward that was received and the reward that was expected), a key computational component in reinforcement learning and active inference models (101). Reward prediction error signals localize to specific neurochemical circuitry (e.g., dopaminergic pathways) and are observable in both MEG/EEG (102,103) and fMRI (104).

Reward prediction error signals, detected with fMRI, accurately predict response to CBT in depression, where an increased responsivity of the amygdala and striatum to unexpected rewards has been interpreted as indicating susceptibility to subsequent belief updating during cognitive restructuring during CBT (105). In contrast, reward prediction errors derived from computational modeling of behavior alone have not yet been shown to predict treatment response, highlighting the power of mechanism-focused neuroimaging analysis for detecting subtle but clinically relevant effects. Extending this,
we might consider that belief updating occurs not only at outcome receipt (when reward prediction errors occur) but also in anticipation of an event (e.g., worrying about the future in anxiety) (77) and when recollecting and reinterpretating past events (e.g., rumination in depression or postevent processing in social anxiety) (77,106). Uncovering hidden temporal dynamics of belief updating could broaden our understanding of how events are evaluated and deliberated upon before and after decision making, potentially enabling a closer mapping to specific symptoms such as rumination and worry (see Table 2).

In animals, understanding the temporal dynamics of reward learning has benefited from machine learning. An elegant example is that of Rich and Wallis (107), who used linear discriminant analysis to capture patterns of neural firing in the orbitofrontal cortex corresponding to 4 potential choice options, each represented by unique images. While the animals deliberated on their choice, neural activity patterns in the orbitofrontal cortex alternated approximately every 230 ms between the chosen and unchosen option at each trial, with the chosen option becoming increasingly decodable across deliberation time. This also corresponded to fewer switches toward an unchosen option, as well as faster decision making and less deliberation. Building on this, recent studies have classified patterns of activity in the orbitofrontal cortex that represent not only the dynamics of outcome representations but also features such as task structure (e.g., preconditioned associations between states, predictions of upcoming states) and the expected reward value of each state (108–110).

Tracking representations of reward over time provide added value to the computational models of decision making. For example, Eldar et al. (111) investigated whether a person’s mood relates to differences in receptivity to reward, a process thought to play a significant role in the onset of depression and bipolar disorder (112–114). Here, reinforcement learning models suggested 2 underlying mechanisms of reward learning: a fast learning process that rapidly forgot and a slower learning process that persisted across multiple days. This model then formed the basis for a parameterized dataset containing trial-by-trial estimates of the prediction errors produced by fast and slow learning rates and where statistical learning analysis showed these 2 types of prediction errors were decodable from heart rate and EEG data (recorded from a single wearable electrode) collected over the course of the experiment. Crucially, these physiological representations of prediction error accurately predicted self-reported mood at short and long timescales, revealing a relationship not evident from behavior alone (111).

An increasing number of studies now use decoded state representations to investigate how reward is algorithmically processed, with considerable potential for understanding mood disorders such as depression and anxiety (115). One formulation of value-guided decision making is the successor representation (116), which describes how we build a

Table 2. Outstanding Questions in Psychiatry That May Be Addressed by Using Increasing Spatiotemporal Resolution of Neuroimaging Data

| Research Question                                                                 | Existing Data                                                                                          | Potential Use Cases                                                                                     |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| What are the fine-grained neurobiological causes of psychiatric symptoms, and can knowledge of this assist with prognosis and/or treatment? | Schizophrenia: Disorganized replay suggests a neurophysiological basis for impaired structural inference, implying abnormal NMDA receptor function in the hippocampus (72,86). Schizophrenia: Multimodal imaging shows a coupling of computationally derived belief updates with BOLD signal in striatum that relates to dopamine receptor functionality measured with PET (125). Depression: Functional connectivity measured with fMRI in depression is markedly reduced at rest (20,21). Subsecond transient changes in the microstates of functional connectivity detected with EEG are significantly different between the clinical subtypes of depression (22,23). | Schizophrenia: Replay of reorganized state sequences may be used as an indicator of the efficacy of dopaminergic antagonists on increasing synaptic gain in the hippocampus, supporting structural inference capabilities. Depression: MEG may be used as a more spatially precise measure of rapid changes in the microstates of functional connectivity, a measure that could help predict patient-specific efficacy of electroconvulsive therapy (24). |
| How can we better estimate the efficacy of CBT in restructuring dysfunctional beliefs? | Depression: Reward prediction error signals related to learning in the amygdala and striatum (measured with fMRI) predict response of patients with depression to CBT (105). General: The perceived congruence between current evidence and prior beliefs can be decoded from MEG activity and used to indicate the time course of belief updating and subsequent decision making (97). | Depression: By using decoding to track how rewarding outcomes are neurally represented during choice deliberation, we could assess the efficacy of CBT in increasing the representation of reward in a manner that relates to improved choice behavior. OCD: Neural signatures of belief updating could indicate how acting on an environment to sample information (as is the case in compulsive behavior) influences beliefs about uncertain environments, and whether this is influenced by CBT (67). |
| How do thought patterns (conscious or unconscious) differ between clinical subtypes, and can this guide personalized therapy? | Anxiety: Replay supports a flexible avoidance of potential threat by simulating inferred trajectories to threat (126). General: Replay reflects an ability to infer trajectories that lead to future reward in changing environments (88). | Anxiety: Patients with anxiety may differ in whether they anxiously anticipate the future or ruminate on the past, which could reflect different magnitudes of the forward replay of paths leading to threat vs. backward replay after outcome receipt. These signatures, if present, could therefore serve as biological markers of anxiety subtypes. |

BOLD, blood oxygen level–dependent; CBT, cognitive behavioral therapy; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PET, positron emission tomography.
predictive map of state values. Recent decoding of functional MRI data has shown that during decision making, the successor representation predicts which states are reactivated in the brain more accurately than other behavioral models (117). In a similar vein, MEG investigations have shown that neural reactivation of outcomes during choice deliberation is modulated by both the subjective value and probability of an outcome (118) and predicts subsequent choice behavior (119).

CONCLUSIONS

We highlight a recent trend in the application of statistical learning to neuroimaging data, particularly MEG, where the goal has been to uncover rapid reactivation of state representations that might otherwise go undetected, either due to spatiotemporal limitations of neuroimaging modalities or due to the complexity of the evolving state representation. These decoded representations can serve as rich and dynamic support for, or as latent variables within, computational models of complex cognitive processes, allowing investigation of a range of candidate processes that may go awry in psychiatric disorders. When combined with neurophysiological recordings, such as MEG, pattern classification provides a level of spatiotemporal precision that is virtually impossible to gain from behavior-only models or from conventional neuroimaging analyses. In turn, combining neural decoding of states with computational models of behavior or cognition provides a level of representational precision not easily attained using conventional neuroimaging analysis alone. Moreover, by classifying holistic mental states, researchers can access highly temporally resolved signatures of disorder-related representations, opening new avenues for examining cognition and behavior in ecological contexts that involve a high degree of representational complexity, including indexing the impact of treatments.

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