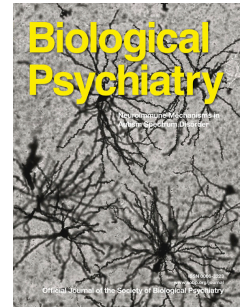


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Spatiotemporal precision of neuroimaging in psychiatry

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1 Abstract

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

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

23 Our ability to precisely capture spatiotemporal patterns of neural activity has, until recently, been limited by
24 two primary obstacles. One relates to a trade-off between spatial and temporal resolution that is inherent
25 to a reliance on non-invasive neuroimaging approaches. This limits the ability of any single methodology to
26 provide a complete picture of both the “where” and “when” of the neural processes that underlie complex
27 human cognition and behaviour, potentially obscuring core aspects of neural dynamics that play causal
28 roles in the genesis of psychiatric illnesses.

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

36 The dynamic nature and real-world relevance of features that characterise psychiatric disorders mean that
37 both spatiotemporal and functional precision are crucial to improving our understanding and, ultimately,
38 guiding development of targeted treatments (14). In this review, we outline current trends in human
39 neuroimaging that advance a quest for increased spatiotemporal precision. First, we provide an overview
40 of the current spatiotemporal resolution achievable in neuroimaging. Second, we illustrate how to enhance
41 spatiotemporal precision by extracting meaningful state representations from neuroimaging data, as well
42 as how to track the dynamic reinstatement of these processes in the brain, taking recent breakthroughs in

43 the detection of hippocampal replay using magnetoencephalography (MEG) as a case example. Finally,
44 we explore how uncovering the spatiotemporal dynamics of mechanistically-relevant neural activity can be
45 combined with generative modelling of pathological behaviour and cognition, with specific relevance to the
46 burgeoning field of computational psychiatry (15).

47 Spatiotemporal precision of neuroimaging

48 Non-invasive neuroimaging methods range from modern ultra-high-field MRI that delivers a spatial
49 resolution as fine as 0.5 millimetres (16), to older technologies such as electroencephalography (EEG) and
50 MEG that provide measurements of mass neural activity at a millisecond resolution (17,18). Each of these
51 modalities have strengths and weaknesses with regards to spatial and temporal resolution, in addition to
52 factors such as tolerance in freedom of movement (19) and the precise physiological processes used to
53 index neural activity.

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

65 Multimodal imaging

66 Considerable effort has been invested in attaining higher spatiotemporal precision by deriving converging
67 results from separate neuroimaging methodologies with complementary spatial and temporal resolutions,
68 either recorded simultaneously (e.g., simultaneous EEG-fMRI) or in separate sessions (e.g., MEG, followed
69 by fMRI) (26). In many cases, this multimodal approach to neuroimaging has been informative about brain
70 dynamics underlying psychopathology (27). For instance, the amplitude of a fast-latency signature of

71 reward processing detected with EEG correlates with BOLD signal in striatum and, together, this fast striatal
72 reward responsivity is reported as blunted in a subtype of depression characterised by impaired mood
73 reactivity (28). Thus, multimodal imaging has the potential to enhance detectability of subtle, neurobiological
74 effects that would otherwise be difficult to detect through reliance on a single modality (26,29). Multimodal
75 imaging studies, however, impose a significantly higher demand on resources, and a lack of a unifying
76 model can lead to difficulties with interpreting convergent or discrepant multimodal findings (27,30).

77 Increasing granularity using statistical learning

78 A recently developed approach to enhancing spatiotemporal precision of a single neuroimaging modality
79 involves the exploitation of machine (or “statistical”) learning, which harnesses a range of statistical
80 techniques to distinguish between neural or behavioural states. This approach has demonstrated that even
81 the most nuanced fluctuations in spatiotemporal neural data may contain relevant information (31). These
82 nuances, such as small differences in the angle of neighbouring dipoles in MEG data, create statistically-
83 separable patterns that are identifiable using multivariate pattern classification algorithms.

84 An early example of a machine learning approach to neuroimaging data involved decoding visual orientation
85 from human visual cortex using multi-voxel pattern analysis (MVPA) of functional MRI data (32). Although
86 orientation-selective cortical columns are much smaller than the spatial resolution of functional MRI (3
87 mm³), orientation selectivity can be reliably estimated from signals generated by entire ensembles of voxels.
88 Remarkably, orientation selectivity (33) and retinotopic maps in primary visual cortex (34) have now been
89 reliably estimated from MEG data using support vector machine (SVM) classifiers, despite source-
90 reconstructed MEG having a resolution in the order of several millimetres at the cortical surface. This
91 example demonstrates that modern analytic approaches can exploit subtle variation in coarse spatial or
92 temporal information to detect, and classify, neural processes that unfold at a finer scale than the resolution
93 of the imaging modality itself. Such a feat can be achieved by biology-agnostic machine learning methods
94 that distil spatiotemporal information from rich sources of neuroimaging data (as just described), and also
95 by biophysically-realistic models that utilise prior knowledge of neurophysiological activity (provided by
96 other modalities; e.g., invasive electrophysiological recordings in animals), to capture traces of such
97 processes present in non-invasive human neuroimaging data (e.g., dynamic causal modelling of fMRI and
98 M/EEG; (35)). Thus, both biologically-informed models and biology-agnostic machine learning methods can
99 be used to offset spatiotemporal constraints of current neuroimaging methodologies.

100 Hippocampal replay as a case example

101 A striking example of the use of statistical learning to extract precise spatiotemporal information from MEG
102 data comes from pioneering studies demonstrating hippocampal replay in humans (43). A central tenet of
103 this review is that non-invasive measurement of hippocampal replay in humans is likely to represent a major
104 advance not only for cognitive neuroscience but also biological psychiatry. The approach indicates that
105 neuroimaging data can provide a sufficiently rich source of spatiotemporal information to signal rapid,
106 dynamic, shifts in mental states, thereby allowing for a more precise estimate of when and where cognitive
107 processes unfold in the brain. Below, we detail this approach and discuss how it has been, and can be,
108 exploited to further the field of biological psychiatry.

109 The methodological challenge of replay

110 Replay was first observed in rodents in the 1990s where, during post-task rest, hippocampal place cells
111 indexing the trajectory of an animal through an environment rapidly reactivated in the same order in which
112 these locations were experienced, albeit with a pronounced temporal compression (44–46). This
113 spontaneous and rapid unfolding activity pattern was subsequently shown to play a causal role in memory
114 consolidation (47–50), and has been linked to higher-order cognitive functions such reward learning (51–
115 57) and planning (58–62).

116 In humans, measuring hippocampal replay non-invasively presents a considerable methodological
117 challenge, as one of its putative source (the hippocampus) is located deep within the brain, and the speed
118 with which replay events unfold is extremely fast (in animals, the sequential reactivation of place cells
119 indexing discrete locations is typically separated by tens of milliseconds). This challenge is shared by
120 neuroimaging research in psychiatry, where there is often a need for both spatial and temporal precision.
121 For example, in mood disorders, fast latency activity in deep brain structures, such as the amygdala,
122 allegedly play a pivotal role in the genesis and maintenance of symptoms but is notoriously difficult to
123 measure in vivo (25). Moreover, replay by its very nature involves reactivation of anatomically-specific
124 neural populations (e.g., specific place cells) that represent specific mental states (e.g., different locations
125 in space). Thus, measuring replay in humans from non-invasive neuroimaging data necessitates innovative
126 approaches, such as the exploitation of statistical learning to extract fast sequential reactivation of state
127 representations (37,63).

128 Measuring hippocampal replay

129 An approach to quantifying replay from non-invasive neuroimaging data is Temporally Delayed Linear
130 Modelling (TDLM) (37), which estimates evidence for sequential state reactivation. TDLM capitalises on the
131 fact that reactivation of a particular state within the hippocampus causes a cascade of related activity across
132 a distributed network that includes the entorhinal cortex (64), medial temporal cortex (65), visual cortex
133 (66), and prefrontal cortex (67–70). Thus, while hippocampal activity can be challenging to identify from
134 MEG recordings (but far from impossible: see 71,72), information related to a specific memory or state can
135 be decoded from unique spatial patterns of neural activity to uncover rapid, sequential reactivation of prior
136 experiences (63,73–79). This ability to detect subtle but relevant spatial information increases both temporal
137 and representational precision (e.g., specific memories) even at relatively low spatial resolution.
138 Importantly, in psychiatry research, representational precision might often be considered more valuable
139 than spatial precision, such as when investigating whether a therapeutic intervention instantiates a change
140 in cognitive processes.

141 How can specific states be isolated and captured? Investigators commonly use visual stimuli presented in
142 a particular order to represent distinct “states”. A key idea here is that the brain organises information —
143 spatial or otherwise — into “cognitive maps” constructed from information like conceptual associations or
144 temporal-order relationships (39). By using visually- and conceptually-unique images, machine learning
145 algorithms can accurately and reliably classify spatial patterns of neural activity associated with viewing
146 each image (**Fig. 1A**). The sheer size of the visual system in the human brain means that visual stimuli can
147 be classified from distributed spatiotemporal activity generated primarily from occipital and temporal
148 cortices, with classification accuracy typically in the range of 37% to 50%, which is 3 to 8 times higher than
149 what would be expected by chance (74,76,78,80). Classifiers are typically trained on neural activity patterns
150 recorded during an initial functional localiser, when participants view images before learning about task-
151 related temporal-order relationships (37). Hence, this constitutes a “supervised” machine learning
152 approach, where identity labels are known (e.g., whether participants were viewing image A or image B).
153 The associated MEG sensor patterns then provide a reliable estimate of activity when these states are
154 subsequently reactivated, for example during a cognitive task such as planning (online) or during a rest
155 period (offline) (**Fig. 2**). Both hippocampus and medial temporal lobe, as well as visual cortex, have been
156 identified as likely sources of such replay events in humans (74,75,78).

157 Overall, investigating replay in the human brain exemplifies how a rapidly-evolving neurophysiological
158 signal can be detected and characterised at an extremely fine temporal resolution. More importantly, these
159 studies provide a representational specificity (e.g., states in a cognitive map) that is not easily obtained
160 using traditional neuroimaging analyses. This implies that a “representation-rich” characterisation of
161 neuroimaging data can greatly enhance the granularity of observable neural dynamics (43), allowing
162 exploration of more abstract neural processes underlying complex cognition.

163 Mechanistic specificity

164 Computational modelling of behaviour

165 The ability to uncover hidden spatiotemporal dynamics of cognition from neuroimaging data has the
166 potential to unlock crucial information about psychiatric disorders that might otherwise be undetectable from
167 behaviour alone. As an example, consider the cognitive processes that contribute to planning. These
168 include an ability to learn and retrieve a cognitive model of the environment that captures how states are
169 connected, the consequences of taking different actions at different states, and the effective appraisal of
170 prospective reward and loss (81). Computations such as these evolve dynamically over time, where one
171 type of processing (e.g., the accessibility of an aversive memory) may influence another (e.g., the perceived
172 probability of being punished) (82). These dynamics are pervasive in existing computational psychiatry
173 models of behaviour, which reveal information about how specific cognitive mechanisms operate differently
174 in psychiatric disorders (83).

175 Spatiotemporally-precise neuroimaging can bestow cognitive models with biological plausibility, revealing
176 how modelled dynamics of cognition (where cognition is either a construct, as in algorithmic models like
177 reinforcement learning, or a biophysically-realistic process, as in synthetic models like attractor network
178 models) are supported by the temporal profile of network activity (84). Therefore, it seems reasonable to
179 conjecture that clinical translation of computational psychiatry may be catalysed by approaches to
180 neuroimaging analysis that enhance spatiotemporal precision by: a) validating the dynamics of theory-
181 driven cognitive processes through convergent biological evidence, b) assigning a neurophysiological basis
182 to modelled cognitive mechanisms, potentially revealing targets for treatment, and c) enhancing the
183 informational content of models by revealing hidden states. Below, we describe recent studies that pair
184 spatiotemporally-precise neuroimaging, such as sequential state reactivation during replay, with
185 computational psychiatry models, with a particular focus on structural inference and reward learning.

186 Inferring environment structure

187 Decoded state representations shed light on how we learn, store, and retrieve structured representations
188 of our environment. The spontaneous reactivation of sequences — both experienced and imagined — is
189 implicated in constructing and utilising internal representations of the environment. For instance, an ordered
190 reactivation of previously-experienced states during a post-task rest period has been shown to correspond
191 not to an experienced structure, but instead to an *inferred* structure that participants abstracted based on a
192 learned task rule (76,78). This sensitivity of reactivated state representations to inferred structural features
193 implies that MEG-decoded replay can provide a neurobiological signature of an ability to structurally
194 reorganise our model of the world.

195 A breakdown in structural inference has been conjectured to underlie psychiatric symptoms that indicate
196 inflexible or repetitive thinking, including compulsive behaviour in obsessive-compulsive disorder,
197 detrimental drug consumption in addiction disorders, and incoherent thought in schizophrenia (85–89). This
198 accords with findings of relatively stronger evidence for model-free decision-making (i.e., habitual behaviour
199 that disregards environment structure), compared to model-based control (i.e., deliberate behaviour that
200 grants flexibility and accuracy at the cost of increased cognitive load) (89), in these clinical populations.

201 In schizophrenia, we can ask whether a putative deficit in structural inference is reflected in spontaneous
202 neural replay. After completing a task in which the temporal order of a stimulus sequence needs to be
203 inferred, even though the “true” order is never experienced, patients with schizophrenia show weaker
204 evidence for reorganisation of ordered state reactivation during rest compared with healthy controls, an
205 effect that localises to hippocampus and corresponds with behaviour (78). This finding is consistent with a
206 theory of reduced synaptic gain in schizophrenia, which is thought to significantly impact synaptic plasticity
207 and attractor dynamics within hippocampus (90–92). This points to a link between an observable cognitive
208 process (impaired structural inference, possibly manifesting as incoherent thought) and a previously
209 unobservable neurophysiological process (replay of an inferred cognitive map in hippocampus) that might
210 guide prognosis, as well as pharmacological and therapeutic treatment (90).

211 Making inferences under uncertainty

212 A feature of several psychiatric disorders is an impaired ability to update beliefs about the structure of an
213 environment when something changes unexpectedly. For instance, behavioural modelling of decision-
214 making has shown that paranoia and delusions can be explained by having a general expectation that

215 stimulus-outcome contingencies will change more frequently, resulting in poorer learning in volatile
216 environments (93–97). This translates to an overweighting of unlikely explanations (i.e., paranoid
217 delusions), the quality of which depends on a complex interplay of other parameters such as mood, prior
218 habits, and whether beliefs pertain to social interaction (95).

219 Dysfunctional belief updating is a target of cognitive behavioural therapy (CBT), which reports success in
220 correcting beliefs about risk and uncertainty in the context of obsessive-compulsive (OCD) disorder (98),
221 as well as in reducing negative beliefs in depression through “cognitive restructuring” methods (99). There
222 are, however, instances where CBT inexplicably fails, such as with the long-term persistence of paranoid
223 delusions (100) and with treatment resistance in specific subtypes of OCD (101), even when administered
224 alongside pharmacotherapy. The ability to derive a precise neural signature of how beliefs evolve over time,
225 much in the same way that state representations are decoded to indicate neural replay (37), can in principle
226 help reveal whether cognitive restructuring in CBT is having a significant impact on generative processes
227 throughout the course of treatment, potentially serving also as a post-treatment predictor of relapse.

228 Research on healthy participants has demonstrated that dynamic belief updating can indeed be detected
229 via spatiotemporal decoding of MEG data. Weiss et al. (2021) investigated the computational and neural
230 mechanisms underlying structural inference in uncertain environments with and without an ability to control
231 how information was sampled (102). They found that being able to choose which information to sample
232 made environments appear more stable, echoing beliefs people with OCD hold about compulsive and
233 repetitive behaviours (103). Moreover, MEG pattern classification revealed crucial temporal and spatial
234 dynamics of how evidence was evaluated against current beliefs during information gathering. Specifically,
235 activity in temporal and visual cortex encoded how consistent each piece of evidence was with current
236 beliefs, revealing changes of mind that occurred throughout a trial prior to making a response. These
237 changes of mind were delayed when participants had control over information sampling, consistent with
238 participants reportedly viewing these environments as being more stable. This work elegantly demonstrates
239 how neural pattern classification can reveal temporally-precise trajectories of beliefs with a neuroanatomical
240 grounding, which could provide novel information about such cognitive processes in conditions such as
241 OCD (102,104).

242 Tracking the dynamics of reward learning

243 Disordered belief updating leads to dysfunctional decision-making, which is a cause of disruption to
244 everyday life in people with certain psychiatric disorders (88). In mood disorders, a bias towards using

245 negative information to update beliefs (which we can consider analogous to “learning”) (105) can be
246 computationally deduced (e.g., by reinforcement learning models) from patterns of dysfunctional decision-
247 making, such as increased risk aversion in anxiety and reduced reward-seeking behaviour in depression
248 (88). Neuroimaging can complement such computational models of decision-making in psychopathology
249 by measuring a “reward prediction error” signal (i.e., the difference between the reward that was received
250 and the reward that was expected), a key computational component in reinforcement learning and active
251 inference models (106). Reward prediction error signals localise to specific neurochemical circuitry (e.g.,
252 dopaminergic pathways) and are observable in both M/EEG (107,108) and fMRI (109).

253 Reward prediction error signals, detected with fMRI, accurately predict response to CBT in depression,
254 where an increased responsivity of amygdala and striatum to unexpected rewards has been interpreted as
255 indicating a susceptibility to subsequent belief updating during cognitive restructuring during CBT (110). In
256 contrast, reward prediction errors derived from computational modelling of behaviour alone have not yet
257 been shown to predict treatment response, highlighting the power of mechanism-focused neuroimaging
258 analysis for detecting subtle but clinically relevant effects. Extending this, we might consider that belief
259 updating occurs not only at outcome receipt (when reward prediction errors occur) but also in anticipation
260 of an event (e.g., worrying about the future in anxiety) (82) and when recollecting and re-interpreting past
261 events (e.g., rumination in depression or “post-event processing” in social anxiety) (82,111). Uncovering
262 hidden *temporal* dynamics of belief updating could broaden our understanding of how events are evaluated
263 and deliberated upon before and after decision-making, potentially enabling a closer mapping to specific
264 symptoms such as rumination and worry.

265 In animals, understanding the temporal dynamics of reward learning has benefited from machine learning.
266 An elegant example is that of Rich and Wallis (2016), who used linear discriminant analysis (LDA) to capture
267 patterns of neural firing in OFC corresponding to four potential choice options, each represented by unique
268 images. While the animals deliberated on their choice, neural activity patterns in OFC alternated
269 approximately every 230 ms between the chosen and unchosen option at each trial, with the chosen option
270 becoming increasingly decodable across deliberation time. This also corresponded to fewer switches
271 towards an unchosen option, as well as faster decision-making and less deliberation (112). Building on this,
272 recent studies have classified patterns of activity in OFC that represent not only the dynamics of outcome
273 representations, but also features such as task structure (e.g., preconditioned associations between states,
274 predictions of upcoming states) and the expected reward value of each state (113–115).

275 Tracking representations of reward over time provide added value to computational models of decision-
276 making. For example, Eldar et al. (2018) investigated whether a person's mood relates to differences in
277 receptivity to reward, a process thought to play a significant role in the onset of depression and bipolar
278 disorder (116–118). Here, reinforcement learning models suggested two underlying mechanisms of reward
279 learning: a fast learning process that rapidly forgot, and a slower learning process that persisted across
280 multiple days. This model then formed the basis for a parameterised data set containing trial-by-trial
281 estimates of the prediction errors produced by fast and slow learning rates and where a statistical learning
282 analysis showed these two types of prediction errors were decodable from heart rate and EEG data
283 (recorded from a single wearable electrode) collected over the course of the experiment. Crucially, these
284 physiological representations of prediction error accurately predicted self-reported mood at short and long
285 timescales, revealing a relationship not evident from behaviour alone (119).

286 An increasing number of studies now use decoded state representations to investigate how reward is
287 algorithmically processed, with considerable potential for understanding mood disorders such as
288 depression and anxiety (120). One formulation of value-guided decision-making is the “successor
289 representation”(121), which describes how we build a predictive map of state values. Recent decoding of
290 functional MRI data has shown that, during decision-making, the successor representation predicts which
291 states are reactivated in the brain more accurately than other behavioural models (122). In a similar vein,
292 MEG investigations have shown that neural reactivation of outcomes during choice deliberation is
293 modulated by both the subjective value and probability of an outcome (123), and predicts subsequent
294 choice behaviour (124).

295

296 Conclusion

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

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316 Disclosures

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578 Figure legends

579 **Figure 1. Capturing mental states using statistical learning. (A)** Mental states, such as viewing an image, can be
580 differentiated by the unique patterns of evoked spatiotemporal brain activity, captured with MEG. These spatiotemporal
581 state classifiers can then be applied to MEG data during a task of interest (e.g., decision-making), revealing the time-
582 course of state reactivation associated with specific aspects of cognition and behaviour. **(B)** Visual orientation can be
583 classified from MEG and EEG sensor data due to unique configurations of angled dipoles along the cortical surface.
584 Adapted from Stokes et al. (2015). **(C)** Different mental states may also evoke different neural network configurations,
585 producing unique patterns of activity across MEG sensors.

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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 data set (43). The optimised algorithm is then applied to a test data set 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 data set in order to infer relationships between variables, in accordance with the assumptions of the selected model (44). The optimised model may then be used to predict relationships in a test data set.
Multi-voxel pattern analysis (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 data set (43). These spatial patterns can then be detected by applying classifiers to a test data set.
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 (45).
Cognitive map	A neural representation of how different states relate to each other (46).
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 (46). In other words, the ability to construct, utilise, 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 (47).
Computational psychiatry	A field of research in which generative mathematical models are constructed to explain the relationships between behaviour, cognition, environment, and underlying neurobiology of psychiatric disorders (17).
Reinforcement learning	A computational model describing how decision-making is influenced by past experiences of reward (48).
Cognitive behavioural therapy (CBT)	A talking therapy that aims to reduce symptoms of mental disorders by challenging dysfunctional beliefs (cognition) and their associated behaviours (49).

588 **Table 1. Key terms and definitions**

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?	<p>Schizophrenia: Disorganised replay suggests a neurophysiological basis for impaired structural inference, implying abnormal NMDA receptor function in hippocampus (85,98).</p> <p>Schizophrenia: Multimodal imaging shows a coupling of computationally-derived belief updates with BOLD signal in striatum that relates to dopamine receptor functionality measured with positron-emission tomography (PET) (132).</p> <p>Depression: Functional connectivity measured with fMRI in depression is markedly reduced at rest (27,28). Sub-second transient changes in microstates of functional connectivity detected with EEG is significantly different between clinical subtypes of depression (29,30).</p>	<p>Schizophrenia: Replay of reorganised state sequences may be used as an indicator of the efficacy of dopaminergic antagonists on increasing synaptic gain in hippocampus, supporting structural inference capabilities.</p> <p>Depression: MEG may be used as a more spatially-precise measure of rapid changes in microstates of functional connectivity, a measure that could help to predict patient-specific efficacy of electroconvulsive therapy (31).</p>
How can we better estimate the efficacy of CBT in restructuring dysfunctional beliefs?	<p>Depression: Reward prediction error signals related to learning in amygdala and striatum (measured with fMRI) predict response of depressed patients to CBT (117).</p> <p>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 (109).</p>	<p>Depression: By using decoding to track how rewarding outcomes are neurally represented during choice deliberation, we could assess the efficacy of CBT in increasing representation of reward in a manner that relates to improved choice behaviour.</p> <p>OCD: Neural signatures of belief updating could indicate how acting on an environment to sample information (as is the case in compulsive behaviour) influences beliefs about uncertain environments, and whether this is influenced by CBT (109).</p>
How do thought patterns (conscious or unconscious) differ between clinical subtypes, and can this guide personalised therapy?	<p>Anxiety: Replay supports flexible avoidance of potential threat by simulating inferred trajectories to threat (133).</p> <p>General: Replay reflects an ability to infer trajectories that lead to future reward in changing environments (81).</p>	<p>Anxiety: Patients with anxiety may differ in whether they anxiously anticipate the future or ruminate on the past, which could reflect different magnitudes of forwards replay of paths leading to threat versus backwards replay after outcome receipt. These signatures, if present, could therefore serve as biological markers of anxiety subtypes.</p>

590 **Table 2. Outstanding questions in psychiatry that may be addressed by using increasing spatiotemporal resolution of neuroimaging data**

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