BJPsych The British Journal of Psychiatry (2026)
228, 3, 185–186. doi: 10.1192/bjp.2025.10517

Check for updates

BJPsych Editorial

Why doesn't neuroimaging work in psychiatry?

Robert A. McCutcheon, Sameer Jauhar and Toby Pillinger

Summary

Half a century of neuroimaging has transformed our understanding of psychiatric disorders but not our clinical practice. This piece examines why that promise remains unfulfilled and argues that the future lies not in ever newer tools but in rigorous, mechanistically grounded and clinically embedded imaging approaches that bridge brains, behaviours and treatments.

Keywords

Neuroimaging; biomarkers; MRI; diagnosis and classification; precision medicine.

Copyright and usage

© The Author(s), 2025. Published by Cambridge University Press on behalf of Royal College of Psychiatrists.

All aspects of human experience can, in principle, be related to brain states. Psychiatric disorders are no exception, so it was reasonable to expect that modern neuroimaging – computed tomography, then positron emission tomography, magnetic resonance imaging (MRI), functional MRI (fMRI) and diffusion imaging – would reveal the underlying pathophysiology of major psychiatric disorders such as schizophrenia, bipolar disorder, major depressive disorder and so-called 'functional' illnesses. Fifty years and thousands of studies later, neuroimaging has had surprisingly little direct impact on everyday clinical practice. Where did it all go wrong?

The history of neuroimaging in schizophrenia may help to illustrate why this promise remains largely unfulfilled. There was early success, following the advent of computed tomography. In 1976, Eve Johnstone and colleagues demonstrated that the cerebral ventricles of 18 individuals with schizophrenia were enlarged compared with those of eight healthy controls.[1] The landscape had shifted, and schizophrenia was now placed firmly within the skull. Positron emission tomography subsequently refined our understanding of dopamine dysfunction, showing that although antipsychotic drugs block postsynaptic dopamine receptors, it is presynaptic hyperdopaminergia that drives positive psychotic symptoms. MRI during cognitive tasks revealed widespread cortical and subcortical dysfunction, whereas resting-state fMRI and diffusion-weighted imaging identified alterations in the large-scale organisation of functional and structural networks.[2]

These advances deepened our mechanistic understanding of both disease and treatment. Yet, five decades later, we still lack reliable, individual-level tools for diagnosis or treatment selection. At a group level, cases differ from controls; but at the individual level, distributions overlap so extensively that imaging contributes little diagnostically or clinically. Why, after so much progress, are our findings still too blurred for clinical use? Does the problem lie with our tools, diagnostic constructs or study designs?

Technological constraints remain. We cannot record single-neuron activity across the human brain *in vivo*, nor can we ethically biopsy the living cortex at scale. Post-mortem work has progressed but remains heavily confounded by environmental exposures. Molecular imaging is powerful but sparse, costly and limited to selected targets. It is likely that when considering functional measures such as fMRI, far larger data-sets are required.[3] Although publicly available imaging repositories are expanding, their scale still lags behind the sample sizes that transformed genetic discovery by orders of magnitude. Bigger imaging samples alone may not solve this mapping problem; even with thousands of individuals, reliable inter-individual brain–behaviour relationships remain elusive.[3]

Psychiatric syndromes themselves are heterogeneous and dimensional. Symptoms and neurobiological features blur across diagnostic boundaries,[4,5] and neurobiological 'pathologies' may be better conceptualised as deviations along continuous dimensions of normative brain variation rather than categorical disease states. Pathological markers analogous to amyloid plaques or anti-NMDA antibodies may simply not exist for most people with psychiatric disorders. Psychiatric morbidity may be better understood in many cases as maladaptive dynamics in otherwise intact tissue, a software problem in learning, control and inference. Imaging can interrogate this but is likely to require a multimodal approach, potentially paired with computational models that formalise algorithms of behaviour.

When considering study designs, large samples are key to establishing robust findings. In-depth sample characterisation (phenotyping) is also needed if we are to disentangle disease-related effects from environmental confounders. Social adversity, trauma, sleep, substance use and medication histories confound brain measures and outcomes.[6] Unless accurately measured and modelled, they may blur or mimic disease signals. The most useful case for imaging in a clinical setting is likely to be treatment personalisation, as opposed to diagnosis. Current studies seeking to develop biomarkers of treatment response employ baseline scans to predicts symptom change after treatment. This approach, however, will primarily identify general prognostic markers (who gets better anyway) rather than differential treatment effects (who benefits from drug A versus B). Without appropriate design and analytic frameworks, decision-guiding predictors will remain out of reach.[7]

What then is the solution? There is no single remedy, but several steps could help build a foundation to enable neuroimaging to provide genuine value to psychiatry.

(a) Target clinical utility, beginning with a pragmatic research question: will this measure alter a clinical decision? To develop genuinely useful precision medicine approaches, imaging biomarkers should be embedded within randomised trials. When this approach is paired with the appropriate analytic framework, we will be able to detect differential treatment effects rather than simple prognostic associations.

(b) Phenotype deeply and integrate across modalities and time: social determinants should not be treated merely as confounders but as components of the causal chain; they must be measured with rigour and modelled explicitly. Similarly, imaging should be paired with computational models of learning, belief-updating and control. This 'middle layer' links algorithmic descriptions of behaviour to neural implementation, sharpening hypotheses and improving interpretability beyond symptom-based classifications. Lessons from neurology, dementia and other

https://doi.org/10.1192/bjp.2025.10517 Published online by Cambridge University Press

biomedical fields suggest that progress will depend on multimodal integration – linking neuroimaging to molecular, digital and behavioural markers rather than pursuing single-modality breakthroughs. Equally, most imaging findings to date are cross-sectional. Longitudinal imaging, capturing within-subject trajectories rather than static group contrasts, may prove more informative – especially when integrated with longer-term clinical outcomes, which are readily available through electronic health records.

(c) Target engagement and pharmacodynamics: imaging already adds value in drug development – verifying target engagement, quantifying dose–occupancy relations and mapping downstream network effects. These approaches can increase the likelihood of selecting successful candidate compounds, refine dosing and guide go/no-go decisions. Moving beyond receptor occupancy, multimodal imaging could illuminate how pharmacological interventions sculpt neurobiology in clinically relevant directions.[8]

(d) Build mechanistic bridges across species: cross-species mapping holds promise for both drug discovery and pathophysiological insight. Comparative neuroanatomy and functional alignment approaches are beginning to delineate homologous cortical and subcortical circuits across species, enabling formal translation between animal models and human neuroimaging findings.[9] By anchoring human neuroimaging features to conserved biological substrates, these methods can help to link cellular mechanisms to systems-level dynamics. Such biologically grounded frameworks may complement 'biology-first' clustering approaches, in which patient subgroups are defined by shared neurobiological mechanisms rather than symptom similarity. When integrated with computational models and perturbation paradigms (for example, pharmacological challenges or neuromodulation), this alignment between species can illuminate the causal pathways linking molecular, circuit and behavioural levels and ultimately support mechanistically informed drug discovery.

(e) Increase methodological rigour: increase sample sizes; preregister analyses; use transparent, harmonised pipelines; validate models externally; share data and code; and publish null results. These tasks are not always easy but will be required before any tool reaches the clinic.

(f) Don't believe the hype: emerging tools such as organoids, single-cell sequencing and neuropixels provide unprecedented access to cellular and molecular detail, yet they involve even greater challenges in linking observations to behaviour and clinical phenomena. For psychiatric research, similar limitations exist: small and often selective samples, coupled with complex high-dimensional data, reproduce many of the statistical pitfalls that accompanied the early era of neuroimaging, including issues of multiple comparisons and limited reproducibility. Neuroimaging, despite its imperfections, remains among the most mature *in vivo* systems-level approaches available. Its future will depend less on technological novelty than on the disciplined integration of diverse methods in pursuit of clinically meaningful questions.

If one accepts that behaviour and conscious experience arise from neurobiology, then neuroimaging must have a role in psychiatry. Even when causes are predominantly social, the brain is likely to bear the knots and scars of experience. Understanding and eventually loosening these knots may be aided by measurements of the living brain. Neuroimaging has already reshaped the conceptual landscape of psychiatry and informed pharmacology. It remains, however, with few exceptions, distant from the clinic. That distance reflects limitations of our tools, the complexity and heterogeneity of our constructs, and the weaknesses of our designs and metrics. Yet neuroimaging can – and should – still mature into what it was always meant to be: a disciplined set of methods linking brains, behaviours and treatments, patient by patient.

Robert A. McCutcheon, Department of Psychiatry, University of Oxford, Oxford, UK; Oxford Health NHS Foundation Trust, Oxford, UK; and Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; **Sameer Jauhar**, Division of Psychiatry, Imperial College London, London, UK; **Toby Pillinger**, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; and South London and Maudsley NHS Foundation Trust, London, UK

Correspondence: Robert A. McCutcheon. Email: robert.mccutcheon@psych.ox.ac.uk

First received 10 Nov 2025, final revision 14 Nov 2025, accepted 19 Nov 2025

Acknowledgements

The work of R.A.M. is funded by a Wellcome Trust Clinical Research Career Development Fellowship (224625/Z/21/Z) and is supported by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. T.P. is supported by the NIHR, Maudsley Charity, the Brain and Behaviour Research Foundation, the UK Academy of Medical Sciences and the UK Research and Innovation Hub for Metabolic Psychiatry (grant reference MR/Z503563/1, platform grant code MR/Z000548/1).

Author contributions

R.A.M. wrote the initial draft. All authors reviewed and amended the draft and approved the final version.

Declaration of interest

R.A.M. has received speaker and/or consultancy fees from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Karuna, Lundbeck, Newron, Otsuka and Viatris and co-directs a company that designs digital resources to support treatment of mental ill-health. T.P. has received speaker or consultancy fees from Bristol Myers Squibb, Boehringer Ingelheim, Recordati, Lundbeck, Otsuka, Janssen, CNX Therapeutics, Sunovion, ROVI Biotech, Schwabe Pharma and Lecturing Minds Stockholm AB; he receives book royalties from Wiley Blackwell and co-directs a company that designs digital resources to support treatment of mental illness. S.J. has received honoraria for educational talks given for Lundbeck, Janssen, Boehringer Ingelheim, Recordati and Sunovian. He has sat on an advisory board for Boehringer Ingelheim and consulted for LB Pharmaceuticals. He has sat on panels for the Wellcome Trust and National Institute of Health and Care Excellence.

References

1 Johnstone EC, Frith CD, Crow TJ, Husband J, Kreel L. Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *Lancet* 1976; **308**: 924–6.

2 Voineskos AN, Hawco C, Neufeld NH, Turner JA, Ameis SH, Anticevic A, et al. Functional magnetic resonance imaging in schizophrenia: current evidence, methodological advances, limitations and future directions. *World Psychiatry* 2024; **23**: 26–51.

3 Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. Reproducible brain-wide association studies require thousands of individuals. *Nature* 2022; **603**: 654–60.

4 McCutcheon RA, Pillinger T, Guo X, Rogdaki M, Welby G, Vano L, et al. Shared and separate patterns in brain morphometry across transdiagnostic dimensions. *Nat Mental Health* 2023; **1**: 55–65.

5 Jauhar S, McCutcheon RA, Nour MM, Veronese M, Rogdaki M, Bonoldi I, et al. Dopamine and mood in psychotic disorders: an 18F-DOPA PET study. *JAMA Psychiatry* 2025; **82**: 1009.

6 McCutcheon R, Bloomfield MAP, Dahoun T, Quinlan M, Terbeck S, Mehta M, et al. Amygdala reactivity in ethnic minorities and its relationship to the social environment: an fMRI study. *Psychol Med* 2018; **48**: 1985–92.

7 Künzel SR, Sekhon JS, Bickel PJ, Yu B. Metalearners for estimating heterogeneous treatment effects using machine learning. *Proc Natl Acad Sci USA* 2019; **116**: 4156–65.

8 McCutcheon RA, Cowen P, Nour MM, Pillinger T. Psychotropic taxonomies: constructing a therapeutic framework for psychiatry. *Biol Psychiatry* 2025; **98**: 446–54.

9 Beauchamp A, Yee Y, Darwin BC, Raznahan A, Mars RB, Lerch JP. Whole-brain comparison of rodent and human brains using spatial transcriptomics. *eLife* 2022; **11**: e79418.

https://doi.org/10.1192/bjp.2025.10517 Published online by Cambridge University Press