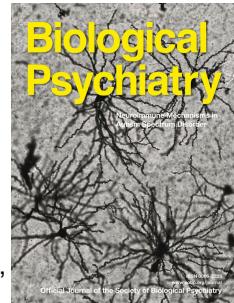


Journal Pre-proof



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PII: S0006-3223(25)00102-7

DOI: <https://doi.org/10.1016/j.biopsych.2025.02.004>

Reference: BPS 15717

To appear in: *Biological Psychiatry*

Received Date: 14 September 2024

Revised Date: 15 January 2025

Accepted Date: 10 February 2025

Please cite this article as: Tsikonomilos K., Kumar A., Ampatzis K., Garrett D.D. & Måansson K.N.T., THE PROMISE OF INVESTIGATING NEURAL VARIABILITY IN PSYCHIATRIC DISORDERS, *Biological Psychiatry* (2025), doi: <https://doi.org/10.1016/j.biopsych.2025.02.004>.

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Invited review, Biological Psychiatry

THE PROMISE OF INVESTIGATING NEURAL VARIABILITY IN PSYCHIATRIC DISORDERS

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Short running title: Neural variability in psychiatry

Keywords:

1. Neural variability
2. Psychiatry
3. Biomarkers
4. Computational models
5. Task-based design

ABSTRACT

The synergy of psychiatry and neuroscience has recently sought to identify biomarkers that can diagnose mental health disorders, predict their progression, and forecast treatment efficacy. However, biomarkers have achieved limited success to date, potentially due to a narrow focus on specific aspects of brain signals. This highlights a critical need for methodologies that can fully exploit the potential of neuroscience to transform psychiatric practice. In recent years, there is emerging evidence of the ubiquity and importance of moment-to-moment neural variability for brain function. Single-neuron recordings and computational models have demonstrated the significance of variability even at the microscopic level. Concurrently, studies involving healthy humans using neuroimaging recording techniques have strongly indicated that neural variability, once dismissed as undesirable noise, is an important substrate for cognition. Given the cognitive disruption in several psychiatric disorders, neural variability is a promising biomarker in this context and careful consideration of design choices is necessary to advance the field. This review provides an overview of the significance and substrates of neural variability across different recording modalities and spatial scales. We also review the existing evidence supporting its relevance in the study of psychiatric disorders. Finally, we advocate for future research to investigate neural variability within disorder-relevant, task-based paradigms and longitudinal designs. Supported by computational models of brain activity, this framework holds the potential for advancing precision psychiatry in a powerful and experimentally feasible manner.

MAIN TEXT

INTRODUCTION

Modern medicine is rapidly progressing towards individualized patient care, striving towards precision medicine that tailors treatment to individuals' characteristics. Psychiatric practice is lagging in this domain. Scientists and clinicians are investing in the development of biomarkers that can aid the diagnosis and prognosis of mental health disorders, and prediction of treatment efficacy (1). Despite persistent efforts, generalizable biomarkers have remained elusive (2). Among other approaches, neuroimaging-based markers have gained significant attention, but their predictive utility (3) and cost-effectiveness (4) have been questioned. It has also been proposed that samples of thousands of individuals are required to establish robust brain-behavior relationships (3,5). However, the limited reliability of the measures commonly employed (e.g., mean activation, functional connectivity) is a fundamental impediment. These measures have demonstrated low test-retest reliability, with intraclass correlation lower than 0.4 on average, meaning they fail to generalize even within the same pool of subjects (6,7). This low reliability would be difficult to overcome solely by increasing sample sizes, given that required sample size scales non-linearly with decreasing reliability (see curves in **Figure 1A**). There is a need for measures of neural activity with better reliability, validity and predictive accuracy that will allow robust detection of experimental effects with moderate sample sizes.

While inadequate sample sizes and low reliability may contribute to the limited success of neural biomarkers in psychiatric research, it is also expected that predictive models are more useful if relevant brain features are used as input (8). Indeed, multiple candidate measures are available, stemming from the high complexity of neural activity and the decades of research aimed at analyzing its rich spatiotemporal structure. One such candidate is neural variability (NV), a broad family of measures encompassing local estimates of brain dynamics (**Figure 2**). NV has been frequently regarded as undesired noise (9), but continues to gain considerable support from studies on cognition in healthy individuals (10,11). In parallel,

studies in both healthy and clinical populations illustrated in **Figure 1**, have suggested that NV exhibits high split-half and test-retest reliability at various time intervals and spatial scales (12–17). Although NV has received less attention in the psychiatry and neuroimaging literatures, (compared to e.g., functional connectivity; see **Figure 3**), it has already shown early promise as a biomarker in psychiatric contexts, demonstrating its potential for both diagnosis (18) and treatment outcome prediction (12). It is therefore an important marker to study alongside the seemingly non-reliable standard measures of neural activity.

Attesting to its potential for targeting disease-specific pathophysiological mechanisms, NV has been extensively studied at the microscopic level, particularly across repeated presentations of the same stimulus (19,20). The mechanistic basis of NV has been explored through computational models of neural networks with specific structural and biophysical features (21–24), underscoring the potential of NV to facilitate an understanding of the underlying pathophysiology and uncover targets for therapeutic interventions. Furthermore, NV can be formalized within dynamical systems theory (25,26), a modeling approach that uses differential equations to describe the behavior of complex systems over time. This can serve as a basis to integrate psychiatry and computational neuroscience (26,27) and allowing an exploration of the computational advantages that variability can confer. Such insights from *in-vivo* and *in-silico* models can complement the existing initial evidence on the biological underpinnings of NV in humans (28,29), thus reinforcing the potential of this approach to enable targeted treatments.

Presently, however, the field of psychiatry exhibits a narrow view of the brain, with most studies assessing either mean activation under a task-based design, or connectivity and topology of functional connectomes under resting-state conditions (30). From a mechanistic point of view, the descriptive formulations of the connectomics-based approach often fall short of elucidating how distributed activity arises from local activity—a link that necessitates investigation into local dynamics (25,31).

In this review, we present an integrated view of NV as a powerful, yet underappreciated family of measures for psychiatry capable of reflecting a multitude of disruptions both in

underlying biological mechanisms and in cognitive capacities (summarized in **Figure 4**). In turn, this allows integrative cross-scale studies of mental disorders using a variety of neural data types and measures (**Figure 2**). We will explore key experimental studies at the microscopic level alongside relevant computational models inspired by these observations, followed by a review of the role of NV in cognition within the healthy brain. We will then turn our attention to psychiatric disorders, where studies have focused predominantly on resting-state-based designs, aligning with the prevailing paradigm in psychiatric neuroimaging. Considering the cognitive disruptions observed in psychiatric disorders, exploring neural variability under disorder-relevant, task-based designs holds promise for achieving increased specificity compared to resting-state. We also discuss the implications of this approach for experimental design and initial evidence for allowing future studies of moderate sample sizes to robustly detect experimental effects with less data within and across subjects. An adoption of variability could accelerate progress towards an improved understanding (and potentially treatment) of mental disorders through an integrative approach that links theoretical and experimental accounts of brain function.

NEURAL VARIABILITY AT THE MICROSCALE: COMPUTATIONAL ACCOUNTS

The brain is a multiscale system, and dynamics can be observed at all spatial scales (32). Thus, it is expected that brain activity will exhibit temporal variability both within and across trials that can be investigated with multiple types of brain signals and measures illustrated in **Figure 2**.

From a neural coding perspective, moment-to-moment variability facilitates sensory processing by allowing neurons that receive a large number of inputs to produce graded output (33). Across-trial variability in the activity of single neurons has been extensively studied at the level of the whole organism (34,35). Initially, fluctuations in neuronal activity were treated as noise but Arieli et al. (20) noted that the across-trial fluctuations are of comparable magnitude as the mean response and that evoked responses can be largely determined by such fluctuations. Moreover, across-trial variability in stimulus-evoked activity is reduced in different cortical regions for a variety of tasks (19).

An important model family, the so-called normative accounts (36), attempt to address the computational benefits that guide neural activity, with respect to explicit goals of the system in question. A popular proposal sees variability as *mediating probabilistic inference*, a view that enjoys both experimental (37), and computational (38,39) support, in line with prior accounts proposing that variability might reflect the brain's representation of uncertainty and the process of integrating prior knowledge with new evidence (e.g., see Bayesian accounts of brain function (40,41)). Another well-known account of how variability can be beneficial lies in the concept of stochastic resonance, whereby the presence of noise can improve the detection of weak stimuli(42). Finally, two lines of investigation worth noting have been exploring the fundamental link between NV quenching and response sub-additivity, a known computationally beneficial property of neural circuits (36,39), as well as the benefits of

variability under a machine-learning framework, for example in improving the robustness of artificial neural networks (43,44).

Besides elucidating NV's computational roles, modeling has also been instrumental in understanding its mechanistic substrate, and this has been found to depend on biophysical and structural features of the relevant neuronal networks (see **Box 1** for example mechanisms). Overall, this body of work provides support for a causative link from biological mechanisms to NV and suggests that utilizing computationally informed task-based studies to quantify variability can provide greater sensitivity in detecting valid brain-behavior associations.

THE RELEVANCE OF NEURAL VARIABILITY FOR BEHAVIOR IN THE HEALTHY HUMAN BRAIN

Evidence has been accumulating on the importance of NV in the healthy brain across multiple cognitive domains (10), demonstrating modulations within-subjects, and indexing between-subjects differences in performance during tasks implicating functions ranging from perception to memory (45) (**Figure 4, right**). With respect to perception, NV comprises a candidate neural measure to mirror the considerable complexity of the outside world. Indeed, this has been demonstrated in the visual cortex for stimuli of varying complexity (46) and in hippocampal regions during memory formation (47). Regarding cognitive domains, NV in multiple regions increases with cognitive demand compared to rest and correlates with task difficulty and individuals' performance (13,48). Increased neocortical NV has also been shown to index performance in a working memory task (49) and during task-switching (50). This appears to be dependent on the attentional focus required, whether internal or external (51), with the appropriate level of variability likely matching environmental demands (50). Convergent findings have been reported in independent samples using functional near-infrared spectroscopy (52,53), demonstrating the generalizability of NV beyond functional magnetic resonance imaging (fMRI). Using electroencephalography (EEG), Kloosterman et al. (54) showed that NV indexes the ability to adapt to environmental demands. NV has also been shown to compress as uncertainty is reduced during a learning task (55), in line with earlier experimental (51,56) and theoretical (39–41,44,57) arguments on its relevance under a framework of Bayesian brain function. Key studies in this set of task-based investigations have compared NV to mean activation (45,46,48,53,54,58), and demonstrated excellent test-retest reliability of NV within the same scanning session (**Figure 1C**; correlations above 0.9 (13) and replicable brain-behavior associations (54) across split-half datasets). This also points to the possibility of using smaller volumes of data per subject, thus facilitating NV's practical application in longitudinal designs (59).

These results have proven powerful in demonstrating the advantages of NV when using tasks relevant to the condition of interest. As an illustrative example from the literature on NV and aging, tasks that require attention to external stimuli have been found more effective than tasks focused on internal thoughts in distinguishing younger from older participants based on their NV (51).

An emerging body of work aims to integrate NV with functional connectivity. Dynamic functional connectivity (the temporal variations in functional connectome configurations), has been linked to cognitive flexibility (60,61), with the spatial pattern implicating the default mode network, similar to previous NV studies (49). Such a dynamic approach can also be applied using variability measures, resulting in modulation of variability states (or “meta-variability” (10)), which is a promising avenue to link the two families of measures into a unified framework whereby functional connectivity is influenced by (and arises from) local variability of individual regions (62). This integrated view has been previously theorized (63), observed (64), and was comprehensively demonstrated by Krohn et al. (31). In this fMRI study, structured complexity (a measure of variability) linked dynamics from local to distributed scales, thus providing a parsimonious and behaviorally relevant account of brain function. Further, variability was found to mediate hallmark findings involving distributed functional connectomes, such as large-scale structure-function relationships (31). In this and a previous study (65), it was shown that similarity in regional variability highly correlates with interregional coupling, thus providing an explanatory framework linking cross-scale dynamics and challenging a restricted focus on functional network properties.

Neurobiological and neurochemical basis of neural variability

Similarly to the microscale findings, it is important to consider the neurobiological significance of NV using macroscale signals at the whole-brain level. While this line of investigation is still nascent, Baracchini et al. (66) have recently shown that whole-brain NV topographies map unto multiscale neurobiological features including cytoarchitectural, microstructural and transcriptional gradients, receptor density and E/I ratio maps, as well neurometabolic and neurovascular components. Complementary to these correlational findings, initial evidence

also exists on the neurochemical underpinnings of NV, often based on pharmacological manipulations (**Figure 5**). A prominent neuromodulator thought to influence NV is dopamine, with systemic pharmacological boosting using amphetamine and levodopa shown to increase variability and performance in working memory tasks (29,64). Using positron emission tomography, Guitart-Masip et al. (49) linked variability and dopaminergic neurotransmission in a region-specific manner, in line with other studies demonstrating a differential pattern of variability between cortical and subcortical regions (31), as well as previous work showing the region-dependent association of variability and performance (45,58,67) (but also see (56,62,68) regarding the thalamic modulation of relevant cortical dynamics). NV has also been associated with inhibitory neurotransmission, as pharmacological GABA agonism using lorazepam was shown to boost NV in older, poorer performing adults (28), and mediate NV modulation during a visual task (69). Relatedly, the power spectral exponent (thought to index the E/I ratio (70)), has in turn been directly correlated with an entropy-based measure of variability (71). This spectral slope reflects the aperiodic component of the neural signal, also traditionally thought of as noise. However, relevance for cognition is being increasingly acknowledged (72–74), and both markers have been found to correlate with E/I ratio on the same dataset (75). E/I modulations are also likely to mediate the experimentally observed noradrenergic influence on NV and perceptual variability (76). Finally, psychedelic compounds such as psilocybin and lysergic acid diethylamide (LSD) influencing serotonergic neurotransmission (77), have also been shown to increase the complexity (78) and variability (79) of brain activity. The increasing evidence regarding the impact of different neurotransmitters on variability, combined with the computational studies mentioned earlier, indicates that it may be possible to understand and control neural variability, making it a viable target in therapeutic settings.

NEURAL VARIABILITY IN PSYCHIATRIC DISORDERS

Despite the growing evidence for its relevance to cognition, the potential of NV as a neural measure of interest in psychiatric studies remains untapped (**Figure 3, inset**). Following early studies on schizophrenia studying the ‘noise’ component of neural activity (80,81), the growing attention to NV in the healthy brain has translated into an emerging interest in investigating its implication in psychiatric disorders. Several disorders have been studied, including schizophrenia (18,82–85), depression (18,86), bipolar disorder (18,83,84,86–90), attention deficit/hyperactivity disorder (87,91–95), borderline personality disorder (87), and anxiety (12,96). A study by Wei et al. (18), has followed an integrative approach, investigating NV patterns associated with diagnosis, their correlation with symptom severity, and their spatial alignment with neurotransmitter, gene expression and cognitive function profiles, in patients spanning three psychiatric disorders. This revealed two transdiagnostic patterns of aberrant variability, associated with distinct genetic and receptor substrates, and cognitive functions. This comprehensive approach is important in illustrating the mechanistic basis of aberrant variability, its functional consequences, and its ability to serve as a sensitive marker of a putative common pathophysiological mechanism. Furthermore, as shown e.g., by Martino et al. for the contrast between depressed and manic patients (89), aberrant variability across distributed brain systems in either direction can hold diagnostic power both within and across disorders, suggesting that a mismatch between NV and environmental demands could be the substrate of cognitive disruptions (50).

While these initial studies have provided a solid foundation by introducing NV as a promising biomarker, they are limited in several key domains, illustrated in **Figure 6**. First, most of these studies quantify variability under resting-state conditions. Second, they typically do not compare variability with other established measures such as mean activation or functional connectivity. Third, most have a cross-sectional design and focus on diagnosis (i.e., separating patient and control groups, or different patient groups, and potentially on correlating NV with symptom severity). We believe that such a narrow focus could potentially lack the

sensitivity afforded by disorder-relevant tasks. Furthermore, it makes a weak case of the benefits variability can provide compared to other neural markers, which is better demonstrated through direct benchmarking of their performance (e.g. predictive power) (58). Furthermore, the clinical utility of any brain measure is gauged by indexing or predicting treatment success, and thus a restricted focus on diagnostic, cross-sectional designs might impede translational efforts. Longitudinal designs employing multiple scanning sessions will also be crucial to obtain robust insights from moderate sample sizes (97) and will be necessary to gauge the reliability of the brain measures employed.

A recent study addressing some of these shortcomings (12), has quantified NV in social anxiety disorder patients under a disorder-relevant socio-affective task, and explored variability as a predictive biomarker for the outcome of cognitive behavioral therapy, thus paving the way for integrating variability into the precision psychiatry framework. NV under task conditions was shown to be more predictive of treatment outcome compared to mean-based activation during task and NV during rest. It also afforded superior test-retest reliability both at the voxel-wise level (**Figure 1B**), and when used as the basis for predictive models of treatment outcome when comparing scanning sessions several weeks apart (intraclass correlation of 0.8 for NV compared to 0.4 for mean activity). This pattern was robust even when using small data volumes of 80 seconds or less. Demonstrating high reliability is crucial to establish and implement new clinical applications. NV should thus be a strong candidate, having already demonstrated moderate to excellent intra and inter-session test-retest reliability (14–17). Moreover, shortening scanning time from the current recommendations of over 10 minutes for resting-state data (98,99) could be beneficial in studies of psychiatric populations allowing more extensive sampling including multiple tasks, and higher throughput in terms of sample size, thereby enabling a more comprehensive characterization of the disorder under study.

NEURAL VARIABILITY: A POWERFUL FRAMEWORK FOR PSYCHIATRY

The continued transformation of neuroscientific psychiatric research could benefit from reliable and generalizable biomarkers. We argue that NV is an excellent candidate, being a theoretically grounded family of measures boasting findings across spatial scales that point to its relevance to cognition, and its disruption in psychiatric disorders. We posit that psychiatric research quantifying NV can materialize this promise through various avenues of investigation outlined below.

Preclinical models can immediately benefit from the existing literature on variability in model organisms and human cohorts and apply similar analyses and experimental designs. The set of existing results provides a solid basis to form hypotheses against which to evaluate any disruptions in neural dynamics, delve into the mechanistic substrate of disorders, and develop interventions. Such investigations should be conducted in the light of the recent discoveries in neurotransmitter switching (a form of plasticity whereby neurons change their neurotransmitter identity) and its implications for behavior (100), and adopt a multidimensional perspective on the ratio of different neurotransmitters (101), deviating from a static view on the underlying molecular mechanisms.

Similarly, computational studies may also benefit from adopting an NV-based approach. Despite the scarcity of studies integrating experimental observations with computational models of aberrant variability (46,82,102), there is a growing focus on explaining the connectome characteristics of patient groups (103). We believe that further work in this interface will spillover both towards preclinical work, where it is possible to validate theoretical predictions at the microscopic scale, and towards clinical investigations by providing a parsimonious mechanistic explanation of experimental observations (27,104) and identifying targets for treatment. Indeed, recent work has shown the advantages of integrating

cross species data and computational approaches to provide parsimonious explanations of NV-based observations (105).

It is important to note that the consequences of disrupted NV will depend on the computational role of each neural circuit and the behavioral context. For example, excess variability may be detrimental in sensory areas aiming to represent an incoming stimulus and propagate this representation to downstream regions (106), while appropriate levels (50,63,107) of variability in higher-order cortical areas might facilitate complex behaviors such as decision making (55). In psychiatric disorders, a mixture of effects might be present across different networks (12,89) (and their NV-based local reliability might also be heterogeneous (66)) and the cross-trial variability in engagement of different regions also warrants investigation (108). Finally, disturbances in variability would be compatible with Bayesian accounts of psychiatric disorders (109), and have also been theorized to reflect disruptions in subjective time perception (88).

For psychiatric studies, we advocate a shift from the one-size-fits-all approach of resting-state functional connectivity that is dominating the field. Although there are efforts to uncover the potential underlying causes of altered connectivity through generative modeling (110), local NV has been shown to mediate key results of the connectivity-based approach (31). The variability-based approach will benefit from being investigated not only under resting-state designs, but also using disorder-relevant, task and stimulus-based designs that will allow a focus on regions of interest (12,111,112) and permit a partitioning of trial-by-trial from moment-to-moment temporal variability (63,111,113–116). Novel approaches to quantify the quality of inferences derived from neuroimaging datasets (117) should also prove useful in benchmarking task-based with resting-state designs. Moving beyond the current status quo necessitates a deep dive into the intricacies of each disorder and application of best practices for predictive modeling (118). Focusing on theoretically grounded measures such as variability (119), will be imperative to address the complexity of psychiatric illnesses, and we expect such an approach under longitudinal designs that maximize signal-to-noise-ratio for the effects of interest (97) to aid resolving the recent crisis of non-reproducible brain-behavior associations

(120). Similarly, the longitudinal design approach will benefit by expanding reliability estimates beyond group-level and into individual-specific reliability (see consistency vs agreement-based definitions in McGraw and Wong (121)). We also expect future studies to continue exploring the transdiagnostic potential of NV by implementing a dimension-based design (87) that transcends diagnostic categories. By aligning with the RDoC framework (122), which encourages an understanding of psychiatric disorders through the study of neurobehavioral functioning, NV can bridge cognition and physiology, potentially leading to a more nuanced view of psychiatric disorders aligned with our integrated framework illustrated in **Figure 4**.

Adopting a NV-based framework has important implications for the design of future studies. It has been argued that clinically useful predictive models require large sample sizes (3) and that neuroimaging-based features do not improve their predictive capacity (2). NV under a task-based design can afford high test-retest reliability (12–14), thereby increasing sensitivity to experimental effects using moderate sample sizes (7). This high reliability can be achieved using smaller volumes of data (i.e., brain signal recording durations) (12,13), allowing high throughput studies and dense sampling of participants. Nevertheless, future large-scale studies would benefit from incorporating NV into their planning, particularly under task conditions, as its validity could support generalizability to target populations. Existing datasets can also be reanalyzed at no additional cost, providing an important first step for the integration of NV in future protocols. We also urge researchers to perform benchmarking of the predictive power of the various features of brain activity (e.g., mean, variability); in practice, we expect the various measures to be complementary (12,58) such that a combination of features will yield the best performing models.

Despite mounting evidence for the utility of NV within single imaging domains (10), studies linking NV metrics across imaging modalities (within-subjects) are rarely available. Future multi-modal work in the clinical domain should especially aim to integrate hemodynamic and electrophysiological views of NV (123), as observed effects might be similar with regards to their relationship with the phenotype of interest and yet have complementary physiological origins (124). Similarly, since NV can be investigated using multiple measures (10) and

recording techniques, we recommend careful consideration of the assumptions underlying each method (e.g., the reflection of temporal scale-specific dynamics in standard measures of multiscale entropy; see Kosciessa et al. (125)), accurate and transparent reporting, and adherence to best practices relevant to the recording modality and measure being used to avoid interpretational pitfalls (125–128). It will also be important to test the robustness of any finding using multiple NV metrics, which will also advance the understanding of the relationships within and outside of the family of NV measures. Alternatively, researchers could base their choice of metric on previous studies investigating psychiatric disorders, a relevant cognitive domain, or ideally on reliability (12,15,129). Researchers may also consider adopting a massive feature extraction and combination approach (130). Such a broadening of the search space of NV measures could further facilitate cross-modal investigations of NV (131) as well as identification of disorder-specific signatures based on brain dynamics (132).

CONCLUSIONS

Experimental findings across spatial scales and theoretical work support the ubiquitous presence of NV in brain function, the potential computational benefits it may confer, its relevance to behavior, and its disruption in psychiatric disorders. We hope that the widespread exploration of NV in psychiatric research can bring about a shift that will help materialize the promise of precision medicine. The advantages of NV as a reliable and valid biomarker with considerable predictive power can inform tailored treatments and improve the quality of life of patients suffering from psychiatric illness.

ACKNOWLEDGEMENTS

This work was supported by a Karolinska Institutet Research Incubator (KIRI) fellow grant [KM and KA]. StratNeuro [KM], Karolinska Institutet [KM], Swedish Brain Foundation (#FO2022-0183), [KM], Swedish Research Council (#2018-06729; #2023-01362) [KM].

DISCLOSURES

The authors report no biomedical financial interests or potential conflicts of interest.

Supplement Description:

Supplement Text and Tables S1-S2

REFERENCES

1. Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M (2017): The new field of “precision psychiatry.” *BMC Med* 15: 80.
2. Chekroud AM, Hawrilenko M, Loho H, Bondar J, Gueorguieva R, Hasan A, et al. (2024): Illusory generalizability of clinical prediction models. *Science* 383: 164–167.
3. Poldrack RA, Huckins G, Varoquaux G (2020): Establishment of Best Practices for Evidence for Prediction: A Review. *JAMA Psychiatry* 77: 534–540.
4. Chekroud AM, Koutsouleris N (2018): The perilous path from publication to practice. *Mol Psychiatry* 23: 24–25.
5. Marek S, Tervo-Clemmens B, Calabro FJ, Montez DF, Kay BP, Hatoum AS, et al. (2022): Reproducible brain-wide association studies require thousands of individuals. *Nature*.
<https://doi.org/10.1038/s41586-022-04492-9>
6. Noble S, Scheinost D, Constable RT (2019): A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis. *Neuroimage* 203: 116157.
7. Elliott ML, Knott AR, Ireland D, Morris ML, Poulton R, Ramrakha S, et al. (2020): What Is the Test-Retest Reliability of Common Task-Functional MRI Measures? New Empirical Evidence and a Meta-Analysis. *Psychol Sci* 31: 792–806.
8. Spisak T, Bingel U, Wager TD (2023, March): Multivariate BWAS can be replicable with moderate sample sizes. *Nature*, vol. 615. pp E4–E7.
9. Uddin LQ (2020): Bring the Noise: Reconceptualizing Spontaneous Neural Activity. *Trends Cogn Sci* 24: 734–746.
10. Waschke L, Kloosterman NA, Obleser J, Garrett DD (2021): Behavior needs neural variability. *Neuron* 109: 751–766.
11. Garrett DD, Samanez-Larkin GR, MacDonald SWS, Lindenberger U, McIntosh AR, Grady CL (2013): Moment-to-moment brain signal variability: a next frontier in human brain mapping? *Neurosci Biobehav Rev* 37: 610–624.
12. Måansson KNT, Waschke L, Manzouri A, Furmark T, Fischer H, Garrett DD (2022): Moment-to-Moment Brain Signal Variability Reliably Predicts Psychiatric Treatment

- Outcome. *Biol Psychiatry* 91: 658–666.
13. Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2013): The modulation of BOLD variability between cognitive states varies by age and processing speed. *Cereb Cortex* 23: 684–693.
14. Zuo X-N, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, et al. (2010): The oscillating brain: complex and reliable. *Neuroimage* 49: 1432–1445.
15. Wehrheim MH, Faskowitz J, Schubert A-L, Fiebach CJ (2024): Reliability of variability and complexity measures for task and task-free BOLD fMRI. *Hum Brain Mapp* 45: e26778.
16. Keilholz S, Maltbie E, Zhang X, Yousefi B, Pan W-J, Xu N, et al. (2020): Relationship Between Basic Properties of BOLD Fluctuations and Calculated Metrics of Complexity in the Human Connectome Project. *Front Neurosci* 14: 550923.
17. Niu Y, Sun J, Wang B, Hussain W, Fan C, Cao R, et al. (2020): Comparing Test-Retest Reliability of Entropy Methods: Complexity Analysis of Resting-State fMRI. *IEEE Access* 8: 124437–124450.
18. Wei W, Deng L, Qiao C, Yin Y, Zhang Y, Li X, et al. (2023): Neural variability in three major psychiatric disorders. *Mol Psychiatry*. <https://doi.org/10.1038/s41380-023-02164-2>
19. Churchland MM, Yu BM, Cunningham JP, Sugrue LP, Cohen MR, Corrado GS, et al. (2010): Stimulus onset quenches neural variability: a widespread cortical phenomenon. *Nat Neurosci* 13: 369–378.
20. Arieli A, Sterkin A, Grinvald A, Aertsen A (1996): Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science* 273: 1868–1871.
21. Mazzucato L (2022): Neural mechanisms underlying the temporal organization of naturalistic animal behavior. *eLife* 11. <https://doi.org/10.7554/eLife.76577>
22. Litwin-Kumar A, Doiron B (2012): Slow dynamics and high variability in balanced cortical networks with clustered connections. *Nat Neurosci* 15: 1498–1505.
23. Guo L, Kumar A (2023): Role of interneuron subtypes in controlling trial-by-trial output

- variability in the neocortex. *Commun Biol* 6: 874.
24. Bujan AF, Aertsen A, Kumar A (2015): Role of Input Correlations in Shaping the Variability and Noise Correlations of Evoked Activity in the Neocortex. *J Neurosci* 35: 8611–8625.
25. Deco G, Jirsa VK, McIntosh AR (2011): Emerging concepts for the dynamical organization of resting-state activity in the brain. *Nat Rev Neurosci* 12: 43–56.
26. Rolls ET, Deco G (2010): *The Noisy Brain: Stochastic Dynamics as a Principle of Brain Function*. Oxford University Press.
27. Stephan KE, Iglesias S, Heinze J, Diaconescu AO (2015): Translational Perspectives for Computational Neuroimaging. *Neuron* 87: 716–732.
28. Lalwani P, Garrett DD, Polk TA (2021): Dynamic Recovery: GABA Agonism Restores Neural Variability in Older, Poorer Performing Adults. *J Neurosci* 41: 9350–9360.
29. Garrett DD, Nagel IE, Preuschhof C, Burzynska AZ, Marchner J, Wiegert S, et al. (2015): Amphetamine modulates brain signal variability and working memory in younger and older adults. *Proc Natl Acad Sci U S A* 112: 7593–7598.
30. Zhang J, Kucyi A, Raya J, Nielsen AN, Nomi JS, Damoiseaux JS, et al. (2021): What have we really learned from functional connectivity in clinical populations? *Neuroimage* 242: 118466.
31. Krohn S, von Schwanenflug N, Waschke L, Romanello A, Gell M, Garrett DD, Finke C (2023): A spatiotemporal complexity architecture of human brain activity. *Sci Adv* 9: eabq3851.
32. Faisal AA, Selen LPJ, Wolpert DM (2008): Noise in the nervous system. *Nat Rev Neurosci* 9: 292–303.
33. Shadlen MN, Newsome WT (1998): The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. *J Neurosci* 18: 3870–3896.
34. Vogels R, Spileers W, Orban GA (1989): The response variability of striate cortical neurons in the behaving monkey. *Exp Brain Res* 77: 432–436.

35. Tomko GJ, Crapper DR (1974): Neuronal variability: non-stationary responses to identical visual stimuli. *Brain Res* 79: 405–418.
36. Goris RLT, Coen-Cagli R, Miller KD, Priebe NJ, Lengyel M (2024): Response sub-additivity and variability quenching in visual cortex. *Nat Rev Neurosci* 25: 237–252.
37. Festa D, Aschner A, Davila A, Kohn A, Coen-Cagli R (2021): Neuronal variability reflects probabilistic inference tuned to natural image statistics. *Nat Commun* 12: 1–11.
38. Orbán G, Berkes P, Fiser J, Lengyel M (2016): Neural Variability and Sampling-Based Probabilistic Representations in the Visual Cortex. *Neuron* 92: 530–543.
39. Echeveste R, Aitchison L, Hennequin G, Lengyel M (2020): Cortical-like dynamics in recurrent circuits optimized for sampling-based probabilistic inference. *Nat Neurosci* 23: 1138–1149.
40. Beck JM, Ma WJ, Kiani R, Hanks T, Churchland AK, Roitman J, et al. (2008): Probabilistic population codes for Bayesian decision making. *Neuron* 60: 1142–1152.
41. Ma WJ, Beck JM, Latham PE, Pouget A (2006): Bayesian inference with probabilistic population codes. *Nat Neurosci* 9: 1432–1438.
42. McDonnell MD, Abbott D (2009): What is stochastic resonance? Definitions, misconceptions, debates, and its relevance to biology. *PLoS Comput Biol* 5: e1000348.
43. Dapello J, Feather J, Le H, Marques T, Cox DD, McDermott JH, et al. (2021): Neural population geometry reveals the role of stochasticity in robust perception. *Adv Neural Inf Process Syst* 15595–15607.
44. Basalyga G, Salinas E (2006): When response variability increases neural network robustness to synaptic noise. *Neural Comput* 18: 1349–1379.
45. Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2011): The Importance of Being Variable. *J Neurosci* 31: 4496–4503.
46. Garrett DD, Epp SM, Kleemeyer M, Lindenberger U, Polk TA (2020): Higher performers upregulate brain signal variability in response to more feature-rich visual input. *Neuroimage* 217: 116836.
47. Waschke L, Kamp F, van den Elzen E, Krishna S, Lindenberger U, Rutishauser U,

- Garrett D (2025): Single-neuron spiking variability in hippocampus dynamically tracks sensory content during memory formation in humans. *Nat Commun* 16: 236.
48. Garrett DD, McIntosh AR, Grady CL (2014): Brain signal variability is parametrically modifiable. *Cereb Cortex* 24: 2931–2940.
49. Guitart-Masip M, Salami A, Garrett D, Rieckmann A, Lindenberger U, Bäckman L (2016): BOLD Variability is Related to Dopaminergic Neurotransmission and Cognitive Aging. *Cereb Cortex* 26: 2074–2083.
50. Armbruster-Genç DJN, Ueltzhöffer K, Fiebach CJ (2016): Brain Signal Variability Differentially Affects Cognitive Flexibility and Cognitive Stability. *J Neurosci* 36: 3978–3987.
51. Grady CL, Garrett DD (2018): Brain signal variability is modulated as a function of internal and external demand in younger and older adults. *Neuroimage* 169: 510–523.
52. Li H, Han Y, Niu H (2024): Greater up-modulation of intra-individual brain signal variability makes a high-load cognitive task more arduous for older adults. *Neuroimage* 290: 120577.
53. Halliday DWR, Mulligan BP, Garrett DD, Schmidt S, Hundza SR, Garcia-Barrera MA, et al. (2018): Mean and variability in functional brain activations differentially predict executive function in older adults: an investigation employing functional near-infrared spectroscopy. *Neurophotonics* 5: 011013.
54. Kloosterman NA, Kosciessa JQ, Lindenberger U, Fahrenfort JJ, Garrett DD (2020): Boosts in brain signal variability track liberal shifts in decision bias. *eLife* 9.
<https://doi.org/10.7554/eLife.54201>
55. Skowron A, Kosciessa JQ, Lorenz R, Hertwig R, van den Bos W, Garrett DD (2024, January 12): Neural variability compresses with increasing belief precision during Bayesian inference. *BioRxiv*. p 2024.01.11.575180.
56. Kosciessa JQ, Lindenberger U, Garrett DD (2021): Thalamocortical excitability modulation guides human perception under uncertainty. *Nat Commun* 12: 2430.
57. Friston K, Breakspear M, Deco G (2012): Perception and self-organized instability. *Front*

- Comput Neurosci* 6: 44.
58. Garrett DD, Kovacevic N, McIntosh AR, Grady CL (2010): Blood oxygen level-dependent signal variability is more than just noise. *J Neurosci* 30: 4914–4921.
59. Garrett DD, Skowron A, Wiegert S, Adolf J, Dahle CL, Lindenberger U, Raz N (2021): Lost Dynamics and the Dynamics of Loss: Longitudinal Compression of Brain Signal Variability is Coupled with Declines in Functional Integration and Cognitive Performance. *Cereb Cortex* 31: 5239–5252.
60. Douw L, Wakeman DG, Tanaka N, Liu H, Stufflebeam SM (2016): State-dependent variability of dynamic functional connectivity between frontoparietal and default networks relates to cognitive flexibility. *Neuroscience* 339: 12–21.
61. Kupis L, Goodman ZT, Kornfeld S, Hoang S, Romero C, Dirks B, et al. (2021): Brain Dynamics Underlying Cognitive Flexibility Across the Lifespan. *Cereb Cortex* 31: 5263–5274.
62. Garrett DD, Epp SM, Perry A, Lindenberger U (2018): Local temporal variability reflects functional integration in the human brain. *Neuroimage* 183: 776–787.
63. Dinstein I, Heeger DJ, Behrmann M (2015): Neural variability: friend or foe? *Trends Cogn Sci* 19: 322–328.
64. Alavash M, Lim S-J, Thiel C, Sehm B, Deserno L, Obleser J (2018): Dopaminergic modulation of hemodynamic signal variability and the functional connectome during cognitive performance. *Neuroimage* 172: 341–356.
65. Baracchini G, Mišić B, Setton R, Mwilambwe-Tshilobo L, Girn M, Nomi JS, et al. (2021): Inter-regional BOLD signal variability is an organizational feature of functional brain networks. *Neuroimage* 237: 118149.
66. Baracchini G, Zhou Y, da Silva Castanheira J (2023): The biological role of local and global fMRI BOLD signal variability in human brain organization. *bioRxiv*. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10634715/>
67. Samanez-Larkin GR, Kuhnen CM, Yoo DJ, Knutson B (2010): Variability in nucleus accumbens activity mediates age-related suboptimal financial risk taking. *J Neurosci* 30:

- 1426–1434.
68. Rikhye RV, Gilra A, Halassa MM (2018): Thalamic regulation of switching between cortical representations enables cognitive flexibility. *Nat Neurosci* 21: 1753–1763.
69. Lalwani P, Polk TA, Garrett DD (2022, September 17): Modulation of neural variability: Age-related reduction, GABAergic basis, and behavioral implications. *BioRxiv*. p 2022.09.14.507785.
70. Gao R, Peterson EJ, Voytek B (2017): Inferring synaptic excitation/inhibition balance from field potentials. *Neuroimage* 158: 70–78.
71. Waschke L, Wöstmann M, Obleser J (2017): States and traits of neural irregularity in the age-varying human brain. *Sci Rep* 7: 17381.
72. Ahmad J, Ellis C, Leech R, Voytek B, Garces P, Jones E, et al. (2022): From mechanisms to markers: novel noninvasive EEG proxy markers of the neural excitation and inhibition system in humans. *Transl Psychiatry* 12: 467.
73. Donoghue T, Haller M, Peterson EJ, Varma P, Sebastian P, Gao R, et al. (2020): Parameterizing neural power spectra into periodic and aperiodic components. *Nat Neurosci* 23: 1655–1665.
74. Waschke L, Donoghue T, Fiedler L, Smith S, Garrett DD, Voytek B, Obleser J (2021): Modality-specific tracking of attention and sensory statistics in the human electrophysiological spectral exponent. *eLife* 10. <https://doi.org/10.7554/eLife.70068>
75. Waschke L, Tune S, Obleser J (2019): Local cortical desynchronization and pupil-linked arousal differentially shape brain states for optimal sensory performance. *eLife* 8. <https://doi.org/10.7554/eLife.51501>
76. Pfeffer T, Avramiea A-E, Nolte G, Engel AK, Linkenkaer-Hansen K, Donner TH (2018): Catecholamines alter the intrinsic variability of cortical population activity and perception. *PLoS Biol* 16: e2003453.
77. Glennon RA, Titeler M, McKenney JD (1984): Evidence for 5-HT2 involvement in the mechanism of action of hallucinogenic agents. *Life Sci* 35: 2505–2511.
78. Murray CH, Frohlich J, Haggarty CJ, Tare I, Lee R, de Wit H (2024): Neural complexity is

- increased after low doses of LSD, but not moderate to high doses of oral THC or methamphetamine. *Neuropsychopharmacology*. <https://doi.org/10.1038/s41386-024-01809-2>
79. Tagliazucchi E, Carhart-Harris R, Leech R, Nutt D, Chialvo DR (2014): Enhanced repertoire of brain dynamical states during the psychedelic experience. *Hum Brain Mapp* 35: 5442–5456.
80. Winterer G, Ziller M, Dorn H, Frick K, Mulert C, Wuebben Y, et al. (2000): Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin Neurophysiol* 111: 837–849.
81. Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR (2004): Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry* 161: 490–500.
82. Yang GJ, Murray JD, Repovs G, Cole MW, Savic A, Glasser MF, et al. (2014): Altered global brain signal in schizophrenia. *Proc Natl Acad Sci U S A* 111: 7438–7443.
83. Lui S, Yao L, Xiao Y, Keedy SK, Reilly JL, Keefe RS, et al. (2015): Resting-state brain function in schizophrenia and psychotic bipolar probands and their first-degree relatives. *Psychol Med* 45: 97–108.
84. Meda SA, Wang Z, Ivleva EI, Poudyal G, Keshavan MS, Tamminga CA, et al. (2015): Frequency-Specific Neural Signatures of Spontaneous Low-Frequency Resting State Fluctuations in Psychosis: Evidence From Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium. *Schizophr Bull* 41: 1336–1348.
85. Hoptman MJ, Zuo X-N, Butler PD, Javitt DC, D'Angelo D, Mauro CJ, Milham MP (2010): Amplitude of low-frequency oscillations in schizophrenia: a resting state fMRI study. *Schizophr Res* 117: 13–20.
86. Liu C-H, Ma X, Wu X, Li F, Zhang Y, Zhou F-C, et al. (2012): Resting-state abnormal baseline brain activity in unipolar and bipolar depression. *Neurosci Lett* 516: 202–206.
87. Kebets V, Favre P, Houenou J, Polosan M, Perroud N, Aubry J-M, et al. (2021): Fronto-limbic neural variability as a transdiagnostic correlate of emotion dysregulation. *Transl*

- Psychiatry* 11: 545.
88. Northoff G, Magioncalda P, Martino M, Lee H-C, Tseng Y-C, Lane T (2018): Too Fast or Too Slow? Time and Neuronal Variability in Bipolar Disorder-A Combined Theoretical and Empirical Investigation. *Schizophr Bull* 44: 54–64.
89. Martino M, Magioncalda P, Huang Z, Conio B, Piaggio N, Duncan NW, *et al.* (2016): Contrasting variability patterns in the default mode and sensorimotor networks balance in bipolar depression and mania. *Proc Natl Acad Sci U S A* 113: 4824–4829.
90. Lu D, Jiao Q, Zhong Y, Gao W, Xiao Q, Liu X, *et al.* (2014): Altered baseline brain activity in children with bipolar disorder during mania state: a resting-state study. *Neuropsychiatr Dis Treat* 10: 317–323.
91. Nomi JS, Schettini E, Voorhies W, Bolt TS, Heller AS, Uddin LQ (2018): Resting-State Brain Signal Variability in Prefrontal Cortex Is Associated With ADHD Symptom Severity in Children. *Front Hum Neurosci* 12: 90.
92. Depue BE, Burgess GC, Willcutt EG, Bidwell LC, Ruzic L, Banich MT (2010): Symptom-correlated brain regions in young adults with combined-type ADHD: their organization, variability, and relation to behavioral performance. *Psychiatry Res* 182: 96–102.
93. Yu-Feng Z, Yong H, Chao-Zhe Z, Qing-Jiu C, Man-Qiu S, Meng L, *et al.* (2007): Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain and Development* 29: 83–91.
94. Perermann M, Bluschke A, Roessner V, Beste C (2019): The Modulation of Neural Noise Underlies the Effectiveness of Methylphenidate Treatment in Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* 4: 743–750.
95. Helps S, James C, Debener S, Karl A, Sonuga-Barke EJS (2008): Very low frequency EEG oscillations and the resting brain in young adults: a preliminary study of localisation, stability and association with symptoms of inattention. *J Neural Transm* 115: 279–285.
96. Li L, Wang Y, Ye L, Chen W, Huang X, Cui Q, *et al.* (2019): Altered Brain Signal Variability in Patients With Generalized Anxiety Disorder. *Front Psychiatry* 10: 84.

97. Gratton C, Nelson SM, Gordon EM (2022, May 4): Brain-behavior correlations: Two paths toward reliability. *Neuron*, vol. 110. Elsevier BV, pp 1446–1449.
98. Ma L, Braun SE, Steinberg JL, Bjork JM, Martin CE, Keen LD li, Moeller FG (2024): Effect of scanning duration and sample size on reliability in resting state fMRI dynamic causal modeling analysis. *Neuroimage* 292: 120604.
99. Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR, et al. (2013): The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *Neuroimage* 83: 550–558.
100. Dulcis D, Jamshidi P, Leutgeb S, Spitzer NC (2013): Neurotransmitter Switching in the Adult Brain Regulates Behavior. *Science* 340: 449–453.
101. Sohal VS, Rubenstein JLR (2019): Excitation-inhibition balance as a framework for investigating mechanisms in neuropsychiatric disorders. *Mol Psychiatry* 24: 1248–1257.
102. Mana L, Vila-Vidal M, Köckeritz C, Aquino K, Fornito A, Kringsbach ML, Deco G (2023): Using in silico perturbational approach to identify critical areas in schizophrenia. *Cereb Cortex* 33: 7642–7658.
103. Deco G, Kringsbach ML (2014): Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. *Neuron* 84: 892–905.
104. Saggar M, Uddin LQ (2019): Pushing the Boundaries of Psychiatric Neuroimaging to Ground Diagnosis in Biology. *eNeuro* 6. <https://doi.org/10.1523/ENEURO.0384-19.2019>
105. Ito T, Brincat SL, Siegel M, Mill RD, He BJ, Miller EK, et al. (2020): Task-evoked activity quenches neural correlations and variability across cortical areas. *PLoS Comput Biol* 16: e1007983.
106. Rowland JM, van der Plas TL, Loidolt M, Lees RM, Keeling J, Dehning J, et al. (2023): Propagation of activity through the cortical hierarchy and perception are determined by neural variability. *Nat Neurosci* 26: 1584–1594.
107. Pool R (1989): Is it healthy to be chaotic? *Science* 243: 604–607.
108. Gao Z, Duberg K, Warren SL, Zheng L, Hinshaw SP, Menon V, Cai W (2024): Reduced temporal and spatial stability of neural activity patterns predict cognitive control deficits

- in children with ADHD. *bioRxiv*. <https://doi.org/10.1101/2024.05.29.596493>
109. Friston KJ, Stephan KE, Montague R, Dolan RJ (2014): Computational psychiatry: the brain as a phantastic organ. *Lancet Psychiatry* 1: 148–158.
110. Betzel RF, Bassett DS (2017): Generative models for network neuroscience: prospects and promise. *J R Soc Interface* 14. <https://doi.org/10.1098/rsif.2017.0623>
111. Huang Z, Zhang J, Wu J, Liu X, Xu J, Zhang J, et al. (2018): Disrupted neural variability during propofol-induced sedation and unconsciousness. *Hum Brain Mapp* 39: 4533–4544.
112. Roalf DR, Figuee M, Oathes DJ (2024): Elevating the field for applying neuroimaging to individual patients in psychiatry. *Transl Psychiatry* 14: 87.
113. Wolff A, Yao L, Gomez-Pilar J, Shoaran M, Jiang N, Northoff G (2019): Neural variability quenching during decision-making: Neural individuality and its prestimulus complexity. *Neuroimage* 192: 1–14.
114. Wolff A, Chen L, Tumati S, Golesorkhi M, Gomez-Pilar J, Hu J, et al. (2021): Prestimulus dynamics blend with the stimulus in neural variability quenching. *Neuroimage* 238: 118160.
115. Bolt T, Anderson ML, Uddin LQ (2018): Beyond the evoked/intrinsic neural process dichotomy. *Netw Neurosci* 2: 1–22.
116. Einziger T, Devor T, Ben-Shachar MS, Arazi A, Dinstein I, Klein C, et al. (2023): Increased neural variability in adolescents with ADHD symptomatology: Evidence from a single-trial EEG study. *Cortex* 167: 25–40.
117. Tuominen J, Specht K, Vaisvilaite L, Zeidman P (2023): An information-theoretic analysis of resting-state versus task fMRI. *Netw Neurosci* 7: 769–786.
118. Dhamala E, Yeo BTT, Holmes AJ (2023): One Size Does Not Fit All: Methodological Considerations for Brain-Based Predictive Modeling in Psychiatry. *Biol Psychiatry* 93: 717–728.
119. Nelson B, McGorry PD, Wichers M, Wigman JTW, Hartmann JA (2017): Moving From Static to Dynamic Models of the Onset of Mental Disorder: A Review. *JAMA Psychiatry*

- 74: 528–534.
120. DeYoung CG, Sassenberg T, Abend R, Allen T, Beaty R, Bellgrove M, et al. (2022, June): Reproducible between-person brain-behavior associations do not always require thousands of individuals. <https://doi.org/10.31234/osf.io/sfnmk>
121. McGraw KO, Wong SP (1996): Forming inferences about some intraclass correlation coefficients. *Psychol Methods* 1: 30–46.
122. Morris SE, Sanislow CA, Pacheco J, Vaidyanathan U, Gordon JA, Cuthbert BN (2022): Revisiting the seven pillars of RDoC. *BMC Med* 20: 220.
123. Jacob MS, Roach BJ, Sargent KS, Mathalon DH, Ford JM (2021): Aperiodic measures of neural excitability are associated with anticorrelated hemodynamic networks at rest: A combined EEG-fMRI study. *Neuroimage* 245: 118705.
124. Kumral D, Şansal F, Cesnaite E, Mahjoory K, Al E, Gaebler M, et al. (2020): BOLD and EEG signal variability at rest differently relate to aging in the human brain. *Neuroimage* 207: 116373.
125. Kosciessa JQ, Kloosterman NA, Garrett DD (2020): Standard multiscale entropy reflects neural dynamics at mismatched temporal scales: What's signal irregularity got to do with it? *PLoS Comput Biol* 16: e1007885.
126. Zou Q-H, Zhu C-Z, Yang Y, Zuo X-N, Long X-Y, Cao Q-J, et al. (2008): An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods* 172: 137–141.
127. Wutte MG, Smith MT, Flanagin VL, Wolbers T (2011): Physiological Signal Variability in hMT+ Reflects Performance on a Direction Discrimination Task. *Front Psychol* 2: 185.
128. Garrett DD, Lindenberger U, Hoge RD, Gauthier CJ (2017): Age differences in brain signal variability are robust to multiple vascular controls. *Sci Rep* 7: 10149.
129. Sheng J, Zhang L, Feng J, Liu J, Li A, Chen W, et al. (2021): The coupling of BOLD signal variability and degree centrality underlies cognitive functions and psychiatric diseases. *Neuroimage* 237: 118187.
130. Shafiei G, Markello RD, Vos de Wael R, Bernhardt BC, Fulcher BD, Misic B (2020):

- Topographic gradients of intrinsic dynamics across neocortex. *Elife* 9: e62116.
131. Zhong XZ, Chen JJ (2022): Resting-state functional magnetic resonance imaging signal variations in aging: The role of neural activity. *Hum Brain Mapp* 43: 2880–2897.
132. Bryant AG, Aquino K, Parkes L, Fornito A, Fulcher BD (2024, June 10): Extracting interpretable signatures of whole-brain dynamics through systematic comparison. *BioRxivorg*. <https://doi.org/10.1101/2024.01.10.573372>
133. Lau ZJ, Pham T, Chen SHA, Makowski D (2022): Brain entropy, fractal dimensions and predictability: A review of complexity measures for EEG in healthy and neuropsychiatric populations. *Eur J Neurosci* 56: 5047–5069.
134. Saville CWN, Feige B, Kluckert C, Bender S, Biscaldi M, Berger A, et al. (2015): Increased reaction time variability in attention-deficit hyperactivity disorder as a response-related phenomenon: evidence from single-trial event-related potentials. *J Child Psychol Psychiatry* 56: 801–813.
135. Lazzaro I, Anderson J, Gordon E, Clarke S, Leong J, Meares R (1997): Single trial variability within the P300 (250–500 ms) processing window in adolescents with attention deficit hyperactivity disorder. *Psychiatry Res* 73: 91–101.
136. Sørensen L, Eichele T, van Wageningen H, Plessen KJ, Stevens MC (2016): Amplitude variability over trials in hemodynamic responses in adolescents with ADHD: The role of the anterior default mode network and the non-specific role of the striatum. *Neuroimage Clin* 12: 397–404.
137. Dinstein I, Heeger DJ, Lorenzi L, Minshew NJ, Malach R, Behrmann M (2012): Unreliable evoked responses in autism. *Neuron* 75: 981–991.
138. Buzsáki G, Watson BO (2012): Brain rhythms and neural syntax: implications for efficient coding of cognitive content and neuropsychiatric disease. *Dialogues Clin Neurosci* 14: 345–367.
139. Goldsworthy MR, Hordacre B, Rothwell JC, Ridding MC (2021): Effects of rTMS on the brain: is there value in variability? *Cortex* 139: 43–59.
140. London M, Roth A, Beeren L, Häusser M, Latham PE (2010): Sensitivity to

- perturbations *in vivo* implies high noise and suggests rate coding in cortex. *Nature* 466: 123–127.
141. Papoulis A (1991): *Probability, Random Variables, and Stochastic Processes*. McGraw-Hill.
142. Shew WL, Yang H, Yu S, Roy R, Plenz D (2011): Information capacity and transmission are maximized in balanced cortical networks with neuronal avalanches. *J Neurosci* 31: 55–63.
143. van Vreeswijk C, Sompolinsky H (1996): Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science* 274: 1724–1726.
144. Deco G, Hugues E (2012): Neural network mechanisms underlying stimulus driven variability reduction. *PLoS Comput Biol* 8: e1002395.
145. Mazzucato L, Fontanini A, La Camera G (2015): Dynamics of multistable states during ongoing and evoked cortical activity. *J Neurosci* 35: 8214–8231.
146. Rost T, Deger M, Nawrot MP (2018): Winnerless competition in clustered balanced networks: inhibitory assemblies do the trick. *Biol Cybern* 112: 81–98.
147. Moreno-Bote R, Beck J, Kanitscheider I, Pitkow X, Latham P, Pouget A (2014): Information-limiting correlations. *Nat Neurosci* 17: 1410–1417.
148. Stringer C, Pachitariu M, Steinmetz N, Carandini M, Harris KD (2019): High-dimensional geometry of population responses in visual cortex. *Nature* 571: 361–365.

FIGURE LEGENDS

Figure 1: Reliability of neuroimaging biomarkers is a major bottleneck that can be addressed by neural variability. **A)** Illustration the relationship between the reliability of neural measures and the sample size required to detect significant associations (correlations) with a phenotype of interest (whose reliability is fixed at 0.6) for three different true effect sizes (0.20, 0.25, 0.30). Note that the sample size necessary increases nonlinearly with decreasing reliability of the neural marker. Statistical power was set at 80% and the significance level at $\alpha = 0.05$. Calculations were performed similarly to Elliott et al. (7). Details of the methodology can be found in the supplementary material. **B)** The voxel-wise whole-brain test-retest reliability (measured using the Pearson correlation coefficient) of the standard deviation of the blood oxygen level-dependent signal obtained from functional magnetic resonance imaging from social anxiety disorder patients during scans 11 weeks apart was good for both task and resting conditions, and outperformed the reliability of the mean signal during task both in terms of effect size and spatial coverage. Reproduced from Figure S13 by Måansson et al. (12), © 2021 Society of Biological Psychiatry. Distributed under the terms of a CC-BY license. Published by Elsevier. **C)** Whole-brain levels of standard deviation of the blood oxygen-dependent signal are highly correlated between data halves in within-session split-half data from healthy adults during fixation and across multiple cognitive tasks. Reproduced from Figure 5 by Garrett et al. (13) with permission, © The Author, 2012. Published by Oxford University Press. **D)** Region-level within-session split-half reliability (measured using the Spearman-Brown-corrected correlation) of the standard deviation of the blood oxygen level-dependent signal obtained from functional magnetic resonance imaging of healthy participants is high for multiple brain regions during a gambling task. Adapted from Figure 2 by Wehrheim et al. (15), © 2024 The Author(s). Distributed under the terms of a CC-BY-NC. Published by Wiley Periodicals LLC.

Abbreviations: ICC: Intraclass correlation coefficient, SD: standard deviation, BOLD: blood oxygen level-dependent, Fix: fixation, PMT: perceptual matching, ATT: attentional cueing, DMS: delayed match to sample.

Figure 2: Example recording modalities and measures relevant to neural variability. Inner circle: Neural variability can be quantified using brain signals at multiple spatial scales. These include the single-cell level using patch-clamp electrophysiology, and neural populations using extracellular multi-electrode arrays or calcium imaging. Macroscopic signals including M/EEG and fMRI can also be used. **Outer circle:** Data collected from the recording modalities above are either timeseries (relevant to membrane voltage, local field potentials, calcium signals, scalp potentials and BOLD timeseries), or event-like (e.g., spikes from single neurons). Both types of signals can be discretized through a symbolic encoding approach into patterns/motifs. Alternatively, the time-domain samples and spike counts for each trial can be used directly for further analysis. In all cases, characteristics of the resulting distribution of values are quantified yielding variance (for timeseries samples; calculating the second central moment of the distribution, but potentially higher-order moments as well), Fano factor (for spike counts; calculating a ratio of variance and mean) and information-theoretic (for patterns/motifs; generally calculating the distribution entropy) measures of variability. Broadly speaking, variance-based measures give an estimate of the width of the distribution of neural signals considering each measurement as an independent sample. Information-theoretic/complexity measures, on the other hand, capture temporal correlations in the timeseries, which are ignored in variance-based measures. Intuitively, complexity measures can be thought of as quantifying the distributional width of signal patterns/motifs (defined using multiple rather than single points). Thus, variance-based, and complexity-based metrics capture neuronal variability at different timescales. For variance-based metrics we consider the value at each timepoint independently, while in complexity-based metrics we define temporal motifs of a certain window size. Another way to capture the signal variability at different timescales is to transform the signal into the frequency domain and the amplitude of the signal at specific frequencies (power), as well as the slope of the power spectrum provide estimates of variability at specific timescales. Using event-like data from extracellular recordings, a popular approach has been

to quantify shared variability by correlating spike counts across trials for pairs of neurons. See also Table 1 and Figure 2 in Waschke et al. (10) as well as Lau et al. (133) for a more detailed description. Of note, trial-by-trial variability using timeseries data has also been a measure of interest in psychiatric disorders (63,134–136), with converging observations of increased sensitivity compared to mean-based approaches (137). Although a comprehensive review of the role of oscillations and oscillatory power in psychiatric disorders is outside the scope of our review, we point the interested reader to the work by Buzsáki and Watson (138).

Abbreviations: M/EEG: Magneto-Electroencephalography, fMRI: functional magnetic resonance imaging, BOLD: Blood-oxygen-level-dependent.

Figure 3: Trends in publications utilizing functional connectivity/network theory and neural variability, including psychiatric populations, over time. Results were extracted from the PubMed Database using the PubMed by Year toolbox (<https://esperr.github.io/pubmed-by-year/index.html>). Y-axis values represent the number of hits per 100.000 publications in each respective year. A total of four distinct search queries were conducted, targeting studies involving functional connectivity/networks (indicative terms: "functional connectivity", "connectome"; solid blue curve), neural variability (indicative terms: "brain signal variability", "moment-to-moment fluctuations"; solid red curve) as well as investigations specifically focused on these measures within psychiatric populations (neural terms as above supplemented by clinical terms, e.g. "schizophrenia", "depression"; dashed curves). The search was conducted on June 3, 2024, with the complete queries detailed in **Table S1** of the supplementary material. Functional connectivity has been the dominant focus in the broader literature, exhibiting a supralinear increase, while neural variability has been understudied. **Inset:** Neural variability remains largely underappreciated in studies of psychiatric populations, compared to the total amount of neural variability studies.

Figure 4: Conceptual scheme of our cross-scale integrative framework for variability in psychiatric disorders. **Left:** Variability originates from activity patterns at the microscopic level (synapses, neurons and microcircuits). Key determinants of neural variability include neurotransmission (dopamine, GABA and serotonin shown here for illustrative purposes; glutamate and noradrenaline also influence neural dynamics), the dynamics of microcircuits with multiple subtypes of inhibitory interneurons and the balance of their inputs, and structural features such as clustered network architecture. **Middle:** At the macroscopic level of brain regions, variability can be conceptualized as moment-to-moment (but also trial-to-trial) fluctuations in the recorded signal (e.g. by functional magnetic resonance imaging, fMRI). Moreover, variability has been linked to the steepness of electrophysiological power spectra, commonly thought to reflect the ratio between excitation and inhibition. The degree of variability can vary with population, behavioral context and brain region. Importantly, higher signal entropy has been associated with flatter spectra and vice versa. **Right:** Evidence has been accumulating regarding the relevance of neural variability in various cognitive domains, using task-based paradigms with healthy individuals. Since multiple cognitive functions are potentially disrupted in psychiatric disorders, studies investigating variability in psychiatric populations under disorder-relevant task-based designs that probe the cognitive domains of interest comprise a promising avenue of investigation. An illustrative example of disrupted functions for various disorders is presented. Relevant cognitive domains are color-coded (see bottom). Colored rectangles for each disorder indicate candidate cognitive capacities at risk of disruption.

Abbreviations: PC: Pyramidal cells, PV: Parvalbumin, SST: Somatostatin, VIP: Vasoactive intestinal polypeptide, ASD: Autism spectrum disorder, MDD: Major depressive disorder, ADHD: Attention-deficit/hyperactivity disorder, BD: Bipolar disorder

Figure 5: Pharmacological modulation of neural variability. Key studies demonstrating modulation of neural variability using systemic pharmacological interventions are illustrated. **A)** Oral administration (pill) of dopamine agonists increases neural variability measured using functional magnetic resonance imaging (fMRI) in multiple brain regions. Garrett et al.: Administration of amphetamine increased neural

variability in older adults in regions including the dorsolateral prefrontal cortex, supplementary motor area and postcentral gyri (29). Alavash et al.: Administration of levodopa increased neural variability in healthy young listeners during an auditory working memory task in temporal, frontal and occipital regions (64). **B)** Pfeffer et al.: Oral administration (pill) of a noradrenaline reuptake inhibitor (atomoxetine) altered neural variability as measured by the scaling exponent estimated through detrended fluctuation analysis (DFA) using magnetoencephalography (MEG) in healthy participants in visual and parietal cortices (76). **C)** Lalwani et al.: Oral administration (pill) of a GABA agonist (lorazepam) increased neural variability as measured by fMRI in fusiform and occipital cortices, and in the cerebellum, in older adults (28). **D)** Administration of serotonin agonist psychedelic compounds increases neural variability. Murray et al.: Oral administration of lysergic acid diethylamide (LSD) in liquid form increases complexity measured by electroencephalography (EEG) in healthy controls in a global manner (78). Tagliazucchi et al.: Intravenous infusion of psilocybin increased neural variability as measured by fMRI in healthy subjects in the hippocampus and anterior cingulate cortex (79). **All panels:** Red circles on brain icons denote approximate locations of regions where experimental effects were identified using either fMRI (panels A, C, D) or source-reconstructed MEG. Red-colored EEG electrodes denote increased complexity. Brain regions are drawn approximately, and an indicative subset is selected. Please refer to the original publications for a full list of associated regions. Of note, NV has recently been proposed as a therapeutic target of repetitive transcranial magnetic stimulation (139), and we believe this comprises an important avenue for future investigations in psychiatric disorders.

Figure 6: Characteristics of psychiatric population studies quantifying neural variability. Studies were aggregated according to the following features: their acquisition protocol, neural measures quantified and study design. We identify a narrow focus on design choices, as current studies are focused on: **A)** resting-state as opposed to task-based paradigms, **B)** only quantifying neural variability instead of multiple measures, and **C)** implementing cross-sectional as opposed to repeated measures designs. The studies used and their characteristics can be found in **Table S2** of the supplementary material.

TABLES

Box 1: Example mechanisms underlying emergence and control of variability in neuronal activity.

A neuron in the brain receives spiking input from thousands of excitatory and inhibitory synapses. These synaptic inputs are the major contributors to the variability in neuron membrane potential and spiking activity (140). The mean and variance (i.e., moment-to-moment variability) of the membrane potential can be estimated using Campbell's theorem (141):

$$\mu_v = J_e \lambda_e \int EPSP dt - J_i \lambda_i \int IPSP dt$$

$$\sigma_v^2 = J_e \lambda_e \int EPSP^2 dt + J_i \lambda_i \int IPSP^2 dt$$

where μ_v denotes the mean of the membrane potential, σ_v^2 its variance, J the strength of incoming spike pulses and λ their rate of arrival. The indices e and i refer to excitation and inhibition respectively, and E(I)PSP stands for excitatory (inhibitory) postsynaptic potentials due to the arrival of a single pulse.

The equations above show that the variance of the membrane is proportional to the square of the postsynaptic potential amplitude and both excitatory and inhibitory (E/I) inputs increase the variance, even when μ_v is zero (i.e. E/I balance). Alternative proxies of E/I ratio obtained through analysis of *in-vitro* and *in-silico* neuronal avalanches (142), have also supported that neural entropy can be maximal in a balanced state. Synchrony in excitatory and inhibitory input can further increase the variance unless excitatory and inhibitory inputs are themselves correlated with each other.

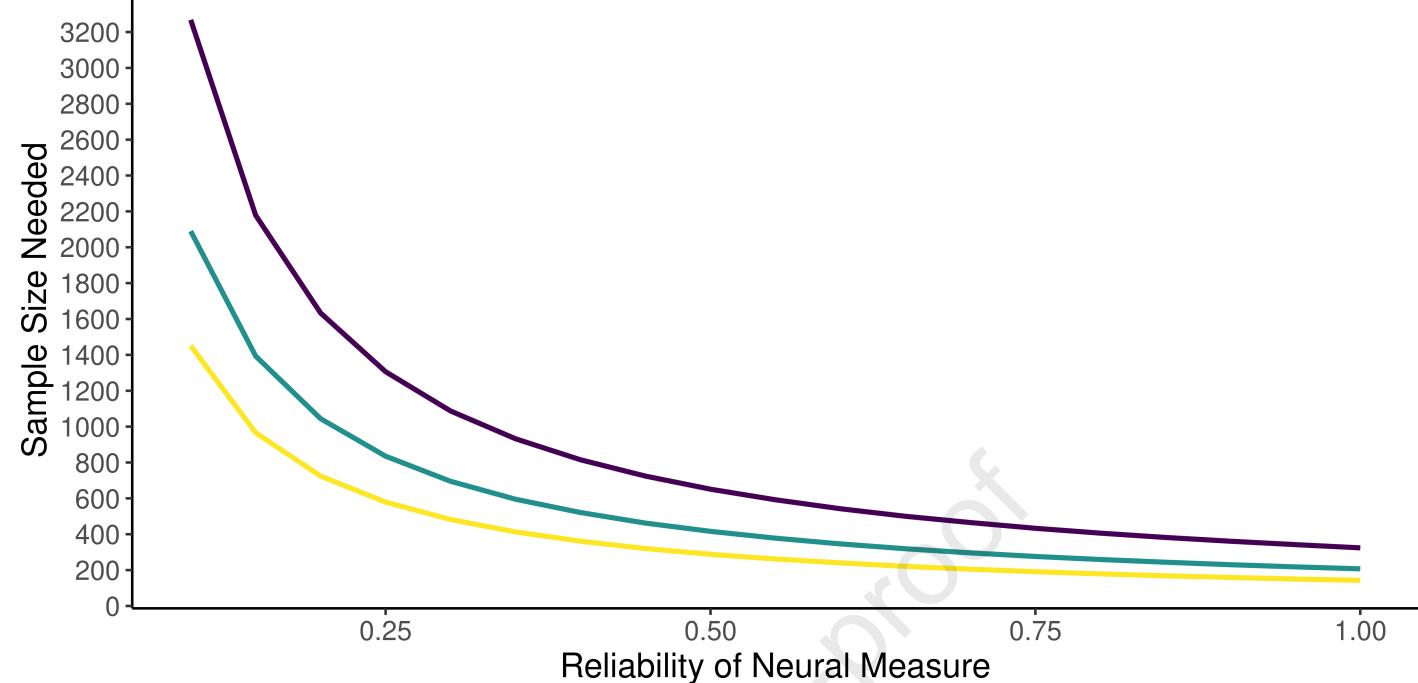
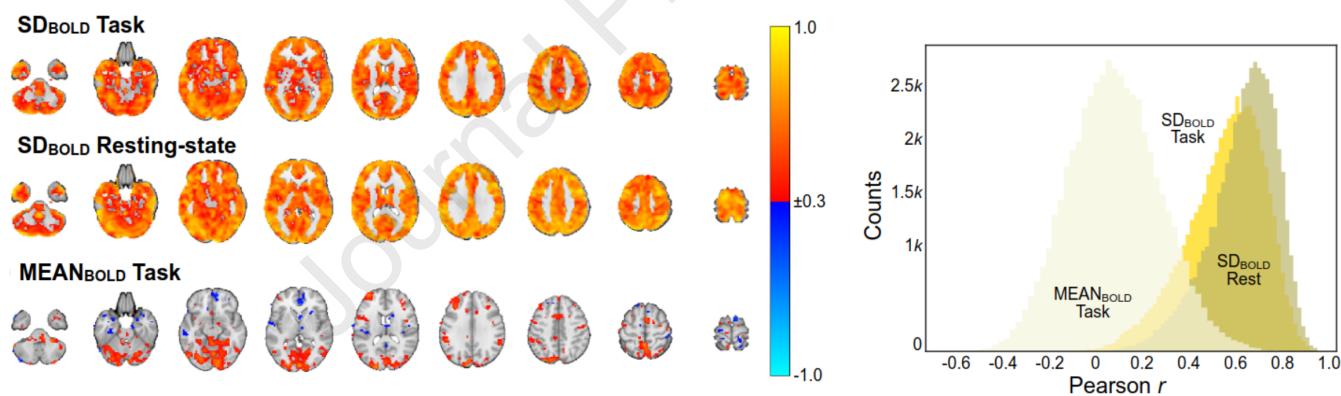
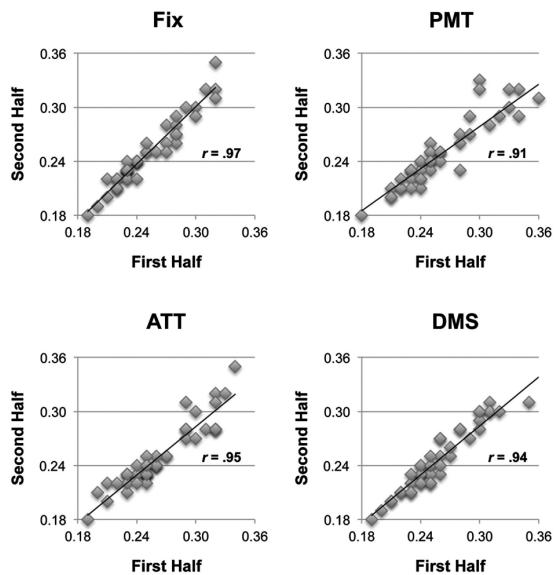
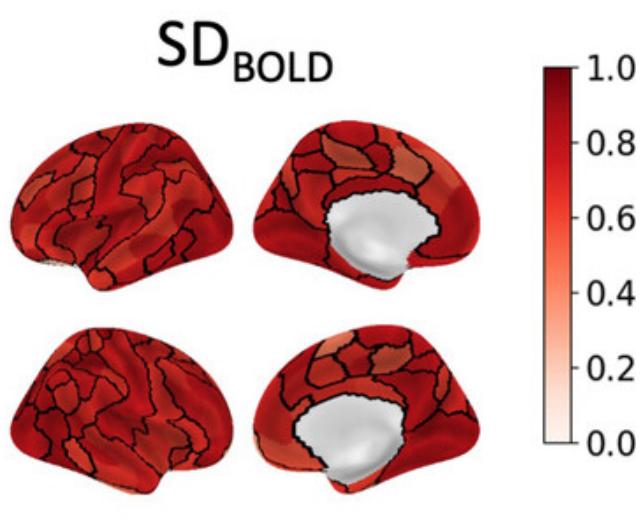
NV is also largely shaped by EI balance and neuronal excitability (143), and by extent neuromodulators also contribute to NV. With regards to its stimulus-induced reduction, multiple mechanisms have been proposed, primarily investigated under the framework of recurrent network dynamics using computational models. Computational models have suggested that a clustered network connectivity structure (**Figure 4, left**) can enable a network to reduce variability when exposed to stimuli (22). An emerging theme from this work has been the explanation of both trial-by-trial and ongoing variability in terms of (winnerless) competition between cell clusters exhibiting multistable dynamics (21,144,145). Ongoing temporal variability is produced by different attractors dominating the network's activity at different times, while the stimulus-induced reduction is reflecting a 'pinning down' to specific attractors due to the afferent input. This framework can also accommodate variability at multiple timescales (including fast moment-to-moment and slower trial-by-trial dynamics) by virtue of multiple hierarchically organized clusters of different sizes (21). More recent work has focused on the role of inhibitory interneuron populations, particularly their spatial arrangement (146), subtypes (23), and input structure (23,24) in mediating realistic variability dynamics (**Figure 4, left**).

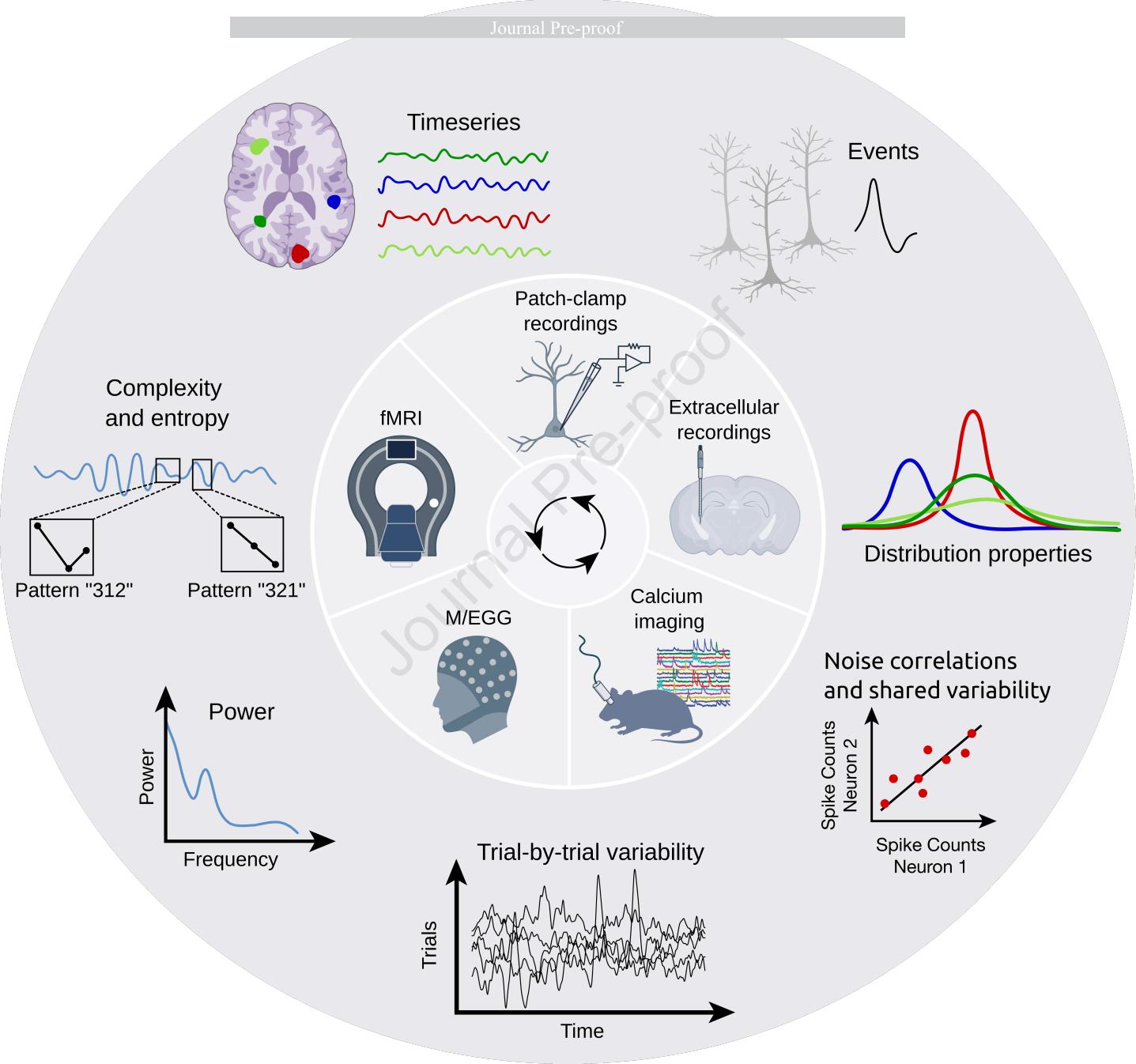
A further consideration that arises at the level of populations is the cross-trial shared variability among neurons. While this has long been believed to limit information transmission, computational (147) and experimental (148) studies capitalizing on powerful recording methods, such as calcium imaging and high-density microelectrodes (**Figure 2**), have pointed to the presence of neural codes that achieve a trade-off between efficient and robust information transmission.

A

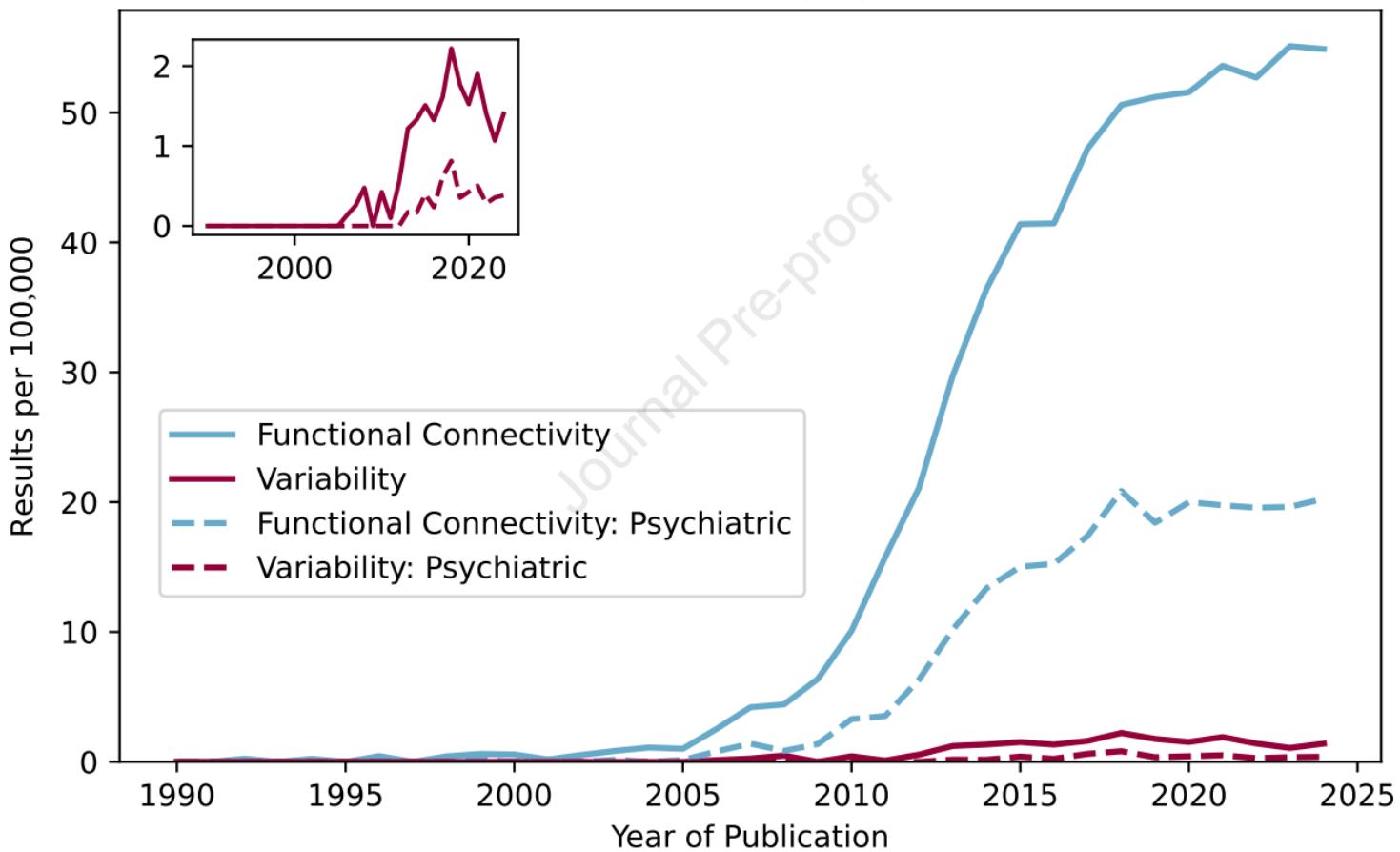
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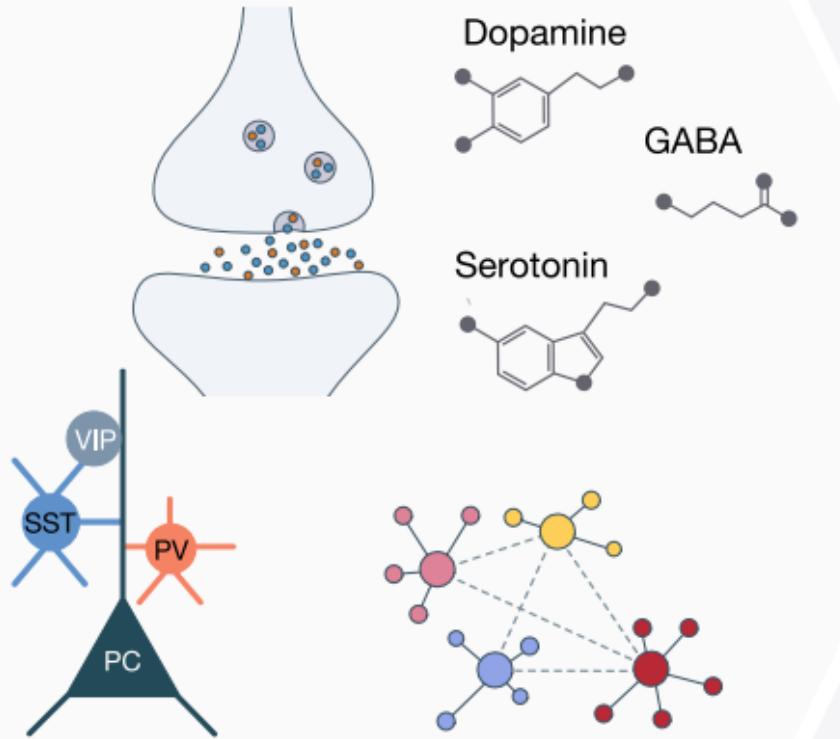
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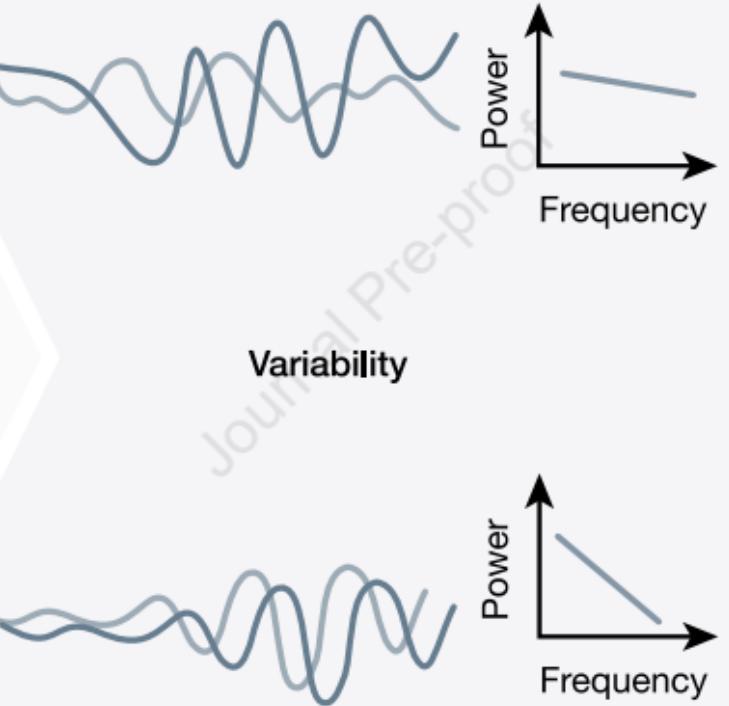
Trends in Neuroimaging Research



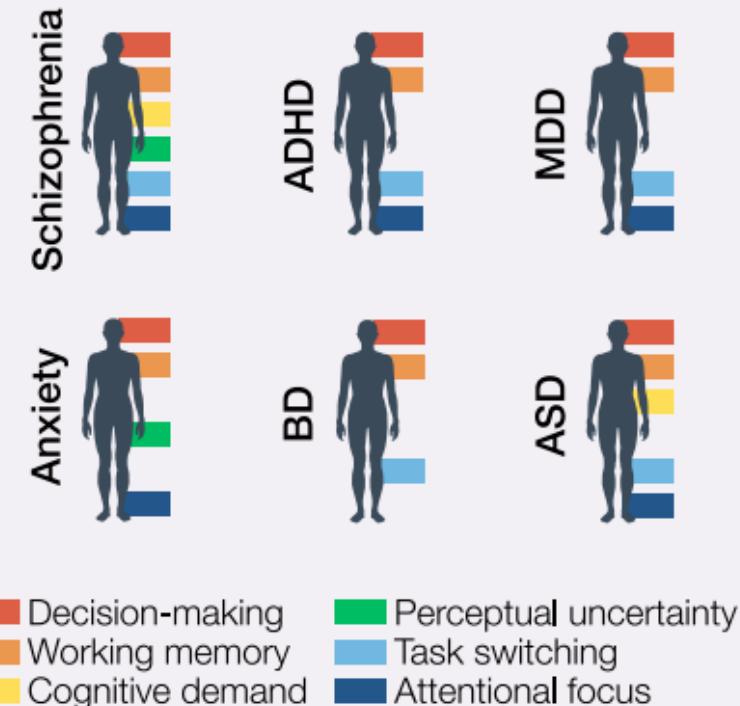
Microscale mechanisms of variability



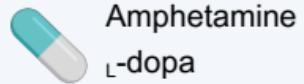
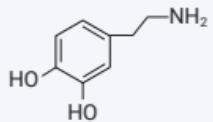
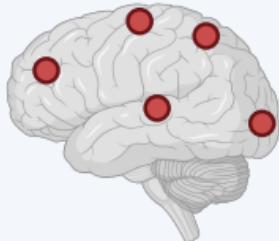
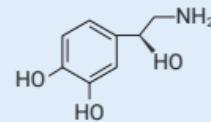
Macroscale variability of neural signals



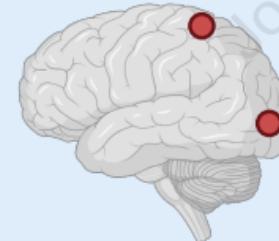
Disrupted variability and cognition in psychiatric disorders



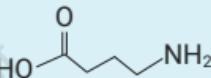
Pharmacological modulation of neural variability

A**Dopamine**Amphetamine
L-dopaGarrett et al., 2015
Alavash et al., 2018**B****Noradrenaline**

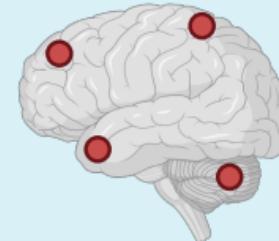
Atomoxetine



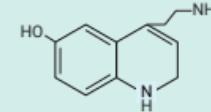
Pfeffer et al., 2018

C**GABA**

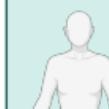
Lorazepam



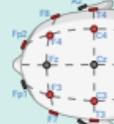
Lalwani et al., 2021

D**Serotonin**

LSD



Psilocybin

Murray et al., 2024
Tagliazucchi et al., 2014

