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Perspective

Behavior needs neural variability

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SUMMARY

Human and non-human animal behavior is highly malleable and adapts successfully to internal and external demands. Such behavioral success stands in striking contrast to the apparent instability in neural activity (i.e., variability) from which it arises. Here, we summon the considerable evidence across scales, species, and imaging modalities that neural variability represents a key, undervalued dimension for understanding brain-behavior relationships at inter- and intra-individual levels. We believe that only by incorporating a specific focus on variability will the neural foundation of behavior be comprehensively understood.

The ability to adapt our behavior to a multitude of ever-changing external and internal demands (despite a limited neural and behavioral toolset) forms a basis for the extraordinary cognitive capability and efficiency of human and non-human animals. For example, consider a cyclist on their daily commute to work as the upcoming traffic light suddenly switches from green to yellow. If the streets are empty and the cyclist feels fit, then they may speed up and clear the crossing just before the light turns red. However, if the streets are crowded and the cyclist's legs are tired, they may instead choose to stop and wait for the next green light. How does the brain enable flexible adaptation to these different contexts and task demands and allow for choosing the optimal alternative? How does the formation and execution of such complex, adaptive behavior relate to the processing and integration of information in the brain? Here, we propose that the ability to adapt cognitive processes emerges through the capacity of the brain to dynamically adjust neural activity from moment to moment—that is, through neural variability (Figure 1).

From single-cell spiking on the order of milliseconds (Harris and Thiele, 2011) to ensemble activity measured by blood oxygenation level-dependent (BOLD) fMRI over seconds (Garrett et al., 2013a), neural activity is highly variable across time at a variety (perhaps all) of temporal and spatial scales (Fox and Raichle, 2007; Ringach, 2009). This variability has traditionally been regarded as a nuisance or as measurement noise. However, recent investigations of neural variability continue to paint a different picture. Variability-based approaches outperform traditional methods when brain-behavior relationships are probed (Cohen and Maunsell, 2009; Garrett et al., 2011, 2013a, 2015; Waschke et al., 2019). It is no longer debated that variability is likely present at every level of nervous system function (Faisal et al., 2008; Garrett et al., 2013a). Here, we argue how and why these different aspects of neural variability are behaviorally relevant.

We first outline recently developed methodologies to define and quantify specifically the temporal variability of neural activity in neural recordings (from single-unit activity to BOLD fMRI). We then show that neural variability not only captures inter-individual (even "trait-like") differences in the overall adaptive capacity of the brain but also that variability tracks available resources, sensory information, and task demands within an individual ("states"). Despite strong initial evidence for the behavioral relevance of neural variability, its precise functional role remains unclear at present. Hence, we also propose different experimental designs to probe distinct sources of neural variability that aim at maximizing sensitivity to intra- or inter-individual differences in behavior. By summarizing apparent differences and communalities of variability-based approaches between invasive animal work and non-invasive human cognitive neuroscience, we also aim to bridge methodological and conceptual gaps between fields.

CONCEPTUALIZING AND MEASURING NEURAL VARIABILITY

To foster investigations into the behavioral role of various approximations of neural variability, we highlight three primary and complementary "families" of temporal neural variability measures typically used in the field: variance-based, frequency-based, and information theory-based measures (see Figure 2). To facilitate the understanding and implementation of these families of measures, we also point to key publications

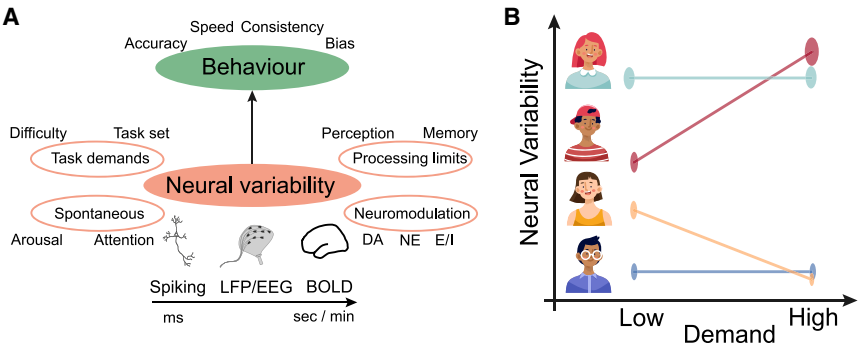

Figure 1. Dimensions and relevance of neural variability for behavior

(A) Neural variability on different temporal and spatial scales (milliseconds to minutes, neurons to ensembles) varies with task demands, individual processing limits, spontaneous arousal and attention states, and neuromodulatory activity (DA, dopamine; E/I, E/I balance; NE, noradrenaline), while affecting different aspects of behavior.

(B) Variability of brain activity can differ between individuals within or across tasks (perhaps representing a trait), or variability may differentially shift within individuals (states) due to, for example, changing task demands.

that provide methodological details and examples of specific methods, as well as online resources and commonly used software packages (see Table 1). Of note, depending on the experimental design used, all approaches highlighted below are theoretically capable of detecting both strictly task-related and task-unrelated neural variability when probing associations with behavior.

Variance-based measures

The simplest measure of neural variability is the time series variance or standard deviation (square root of the variance), representing the distributional width of a neural time series (Figure 2B). Variance measures are applied in different ways across neuroscience/neuroimaging disciplines, including single- and multi-unit activity (e.g., to estimate the Fano factor), invasive and non-invasive electrophysiology using electro- and magnetoencephalography (EEG, MEG), and standard deviation of the fMRI-BOLD signal (SD_{BOLD}) or mean squared successive differences (the first derivative of the time series; von Neumann et al., 1941).

Frequency-based measures

Neural variability is also commonly analyzed in the frequency domain by calculating spectral power over a wide range of frequencies. As the data transformation from the time to frequency domains is lossless via the Fourier transform, oscillatory power is mathematically nothing more than frequency-specific variance (with the total power being equivalent to the overall time series variance). Importantly, spectral analysis assumes that brain signals consist of sinusoidal waveforms. Under the (still contentious) assumption that oscillations are a primary, theoretically driven "filter" via which to understand brain function, such methods are commonly applied to all types of neural recordings in the field. For example, it is typical to calculate a time-resolved estimate of oscillatory power over a wide range of frequencies. Low-frequency power (~2–10 Hz) has been used widely as an approximation of neural variability in local field potential (LFP) and MEG/EEG signals (Harris and Thiele, 2011; Pachitariu et al., 2015; Reimer et al., 2014). It is typically interpreted as an inverse measure of cortical desynchronization and tracks noise correlations (see below) in cortical neurons (Cui et al., 2016; Ecker et al., 2014; Pachitariu et al., 2015). In addition to mere low-frequency power, the steepness of the power spectrum (1/f spectral exponent; see Figure 2C and Table 1) has been shown to track variations in the balance of excitation and inhibition (E/I; Gao et al., 2017), which in turn is closely linked to neural variability on fine timescales (Harris and Thiele, 2011; Kanashiro et al., 2017). Detrended fluctuation analysis (DFA) represents a closely related approach (He, 2011; Linkenkaer-Hansen et al., 2001) to quantify aperiodic activity in neural activity based on power-spectral density estimates and relates to changes in E/I balance as well as behavior (Hardstone et al., 2012; Pfeffer et al., 2018). Crucially, however, because the use of frequency-based methods does not guarantee that "true" oscillations exist in recorded data, other methods are required, which define oscillations as deviations from a linear 1/f power spectrum of non-periodic signals (Donoghue et al., 2020; Kosciessa et al., 2020a; Wen and Liu, 2016; Whitten et al., 2011).

Information theory-based measures (entropy)

Furthermore, neural variability can be quantified by calculating the entropy measures of a neural time series. In general, time series entropy estimates the "information content" in a given signal by analyzing the distribution of temporal patterns that occur in the data (Shannon, 1948). Although several different forms of entropy are used in the field (Keshmiri, 2020; Takahashi, 2013), in general, signals with a repetitive structure (e.g., stationary signals, rhythmic fluctuations) will have low entropy, and less predictable (or random) signals will exhibit high entropy (see Figure 2D). Unlike measures of time-domain variance, entropy does not rely on distributional assumptions, and it does not impose a sinusoidal signal waveform, as assumed by spectral analysis. Thus, entropy is theoretically complementary to these metrics. One common measure is multi-scale entropy (MSE), which allows the estimation of signal irregularity on both shorter and longer timescales (Costa et al., 2002). Importantly, a host of previously noted confounds in the estimation of MSE have recently been addressed and corrected for within a modified version of MSE (Kloosterman et al., 2020; Kosciessa et al., 2020b). Promisingly, methods also exist that attempt to disentangle the impact of overall variance from detectable patterns in the time series. For example, permutation entropy (PE; Bandt and Pompe, 2002) ranks the time series before pattern estimation to avoid variance confounds, while weighted PE (WPE; Fadlallah et al., 2013) re-weighs PE estimation by the overall

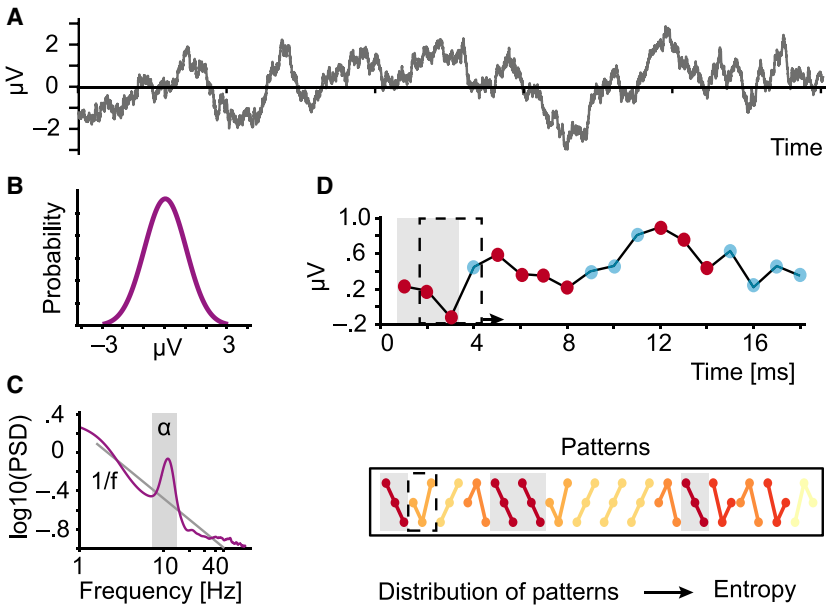

Figure 2. Overview of methods to quantify neural variability

(A) Exemplary time-series of neural activity in microvolts (LFP/EEG).

(B) Variability can represent the distributional width of the time- series (e.g., signal variance, standard deviation [SD]).

(C) Oscillatory and non-oscillatory estimates of variability can be quantified by analyzing the power spectrum. The shaded area denotes the range of human alpha oscillations, and the fitted line indicates the 1/f spectral exponent.

(D) Illustration of the general rationale used to calculate entropy (top). Snippets of data are divided into patterns of a certain length, and those patterns are compared throughout the signal. A more regular time series will show pattern repetitions (bottom, e.g., red pattern; 4/16 possible matches). The less often patterns repeat (i.e., the more uniform the pattern distribution), the higher the entropy estimate.

distributional width in the recorded signal (see Waschke et al., 2017, 2019).

Estimating shared sources of variability

When trying to understand how temporal variance reflects behavior, it is also typical to examine how such variability is shared in the spatial domain across cells, cell ensembles, and/or brain regions. Doing so allows neuroscientists to unpack the extent to which temporal variability is either reflecting a local or a distributed brain process. When recording spiking from many neurons at the same time (e.g., Jun et al., 2017), noise correlations reveal the extent to which trial-to-trial variability of neural responses is shared across cells and repetitions of the same stimulus, while all other external factors are kept constant (Shadlen and Newsome, 1998). This is quantified by counting the number of spikes in response to stimuli (after spike sorting; see Table 1), followed by computing the Pearson correlation between spike count distributions of pairs of neurons. Other approaches to quantify shared variability include mutual information (to unpack shared from "local" entropy; Vakorin et al., 2011) or dynamic functional connectivity (dFC); an expression of the extent to which time-series correlations are stable across moments (Bassett et al., 2011; Cabral et al., 2017; Lurie et al., 2020).

A word on the direction of variability effects

It is important to note that the choice and interpretation of variability measures summarized in Table 1 strongly affect the direction of observed effects. For example, reduced noise correlations, indicating lower temporal neural variability, often coincide with a pronounced reduction in spike coherence specific to low frequencies (~5 Hz; Harris and Thiele, 2011; Mitchell et al., 2009). Hence, the time domain variance of single-cell neural activity is indeed lower, pointing to decreased variability. However, the same cell will display a lower autocorrelation compared to a state during which ~5 Hz fluctuations in spiking persist. Quantified using time series entropy, this would suggest higher temporal variability. Thus, depending on definition and measurement granularity, decreased noise correlations can also be taken as a sign of increased neural variability.

It is also important to note that different variability measures do not necessarily trace back to the same generating neural mechanism. For example, although the variance of BOLD time series and the spectral exponent of LFP recordings may very well be driven by a common neural process that is in turn linked to task requirements or resources, there is no available evidence for such a mechanism at present. Furthermore, different variability measures may display interrelationships that are complex and can only be discerned through dedicated experimental designs and by combining different imaging techniques that provide complementary insights (e.g., EEG/fMRI). Hence, until there is evidence that explicitly links separate variability measures to common neural processes or describes their relationship, we argue that researchers should constrain their interpretation of "variability" effects to the specific measure used.

Here, we are not primarily concerned with advocating for an absolute direction of neural variability effects per se, but rather we focus on the role of different types of neural variability for understanding behavior at inter- and intra-individual levels. Similarly, we do not focus on the important distinction between neural and measurement-related sources of variability (see Garrett et al., 2010, 2013a, 2017), as others have also recently done in detail (Uddin, 2020).

FROM NEURAL VARIABILITY TO BEHAVIOR

With these families of temporal neural variability measures in mind, we evaluate the evidence that neural variability matters for understanding behavior at both inter- and intra-individual levels (see Figure 1).

Table 1. Overview of common measures to quantify neural variability

Measure family	Example measure	Neural signal	Overview	Resources
Variance-based measures	time series variance	all types	variance (or SD) of neural activity across time (Cohen and Maunsell, 2009; Garrett et al., 2013a)	VarTbX (https://github.com/LNDG/vartbx); in-built functions of most programming and analyses platforms (R, Python, MATLAB)
	Fano factor	spiking	variance divided by the mean (or "mean-matched") across conditions before variance estimation (Churchland et al., 2010)	In-built functions of most programming and analysis platforms
Frequency-based measures	spectral power	LFP, MEG/EEG, BOLD	(time-resolved) estimates of oscillatory power, more commonly in low frequencies (e.g., 2–10 Hz), computed using Fourier-based methods (Pachitariu et al., 2015)	Fieldtrip (Oostenveld et al., 2011): https://www.fieldtriptoolbox.org/; Python MNE (Gramfort et al., 2013): https://mne.tools/stable/index.html; BrainStorm (Tadel et al., 2011): https://neuroimage.usc.edu/brainstorm/
	1/f exponent	LFP, MEG/EEG	separation of oscillatory and aperiodic activity by analyzing peaks and steepness of power spectra; typically not time resolved, but estimated from data sections (e.g., single trials)	FOOOF (Donoghue et al., 2020): https://github.com/fooof-tools/fooof; eBOSC (Kosciessa et al., 2020a): https://github.com/jkosciessa/eBOSC; IRASA (Wen and Liu, 2016): https://github.com/raphaelvallat/yasa/
Information-theoretic measures	MSE	LFP, MEG/EEG, BOLD	irregularity of time series at different temporal scales; based on recurring patterns (Costa et al., 2002; Kosciessa et al., 2020b); also, time resolved and for sparse data (Grandy et al., 2016)	mMSE (Kloosterman et al., 2020; Kosciessa et al., 2020b): modification of original MSE, controlling power-related, scale-specific biases in estimation (https://github.com/LNDG/mMSE; https://www.fieldtriptoolbox.org/example/entropy_analysis/)
	WPE	LFP, MEG/EEG	time-resolved irregularity of time series using symbolic patterns; amplitude information re-introduced by weighting with variance (Bandt and Pompe, 2002; Fadlallah et al., 2013)	see code within Waschke et al., 2019
"Shared" variability	noise correlations	spiking	correlation of post-stimulus spike distributions (across trial) between pairs of neurons (Cohen and Kohn, 2011)	spike sorting: KiloSort (Pachitariu et al., 2016); Spyke (Swindale and Spacek, 2014); SpyKING Circus (Yger et al., 2018)
	dFC	MEG/EEG, BOLD	time-resolved functional connectivity estimates based on correlations between time series of different brain regions (Hutchison et al., 2013)	GIFT: https://trendscenter.org/software/gift/; DynaConn (Sakoğlu et al., 2010); CONN (Whitfield-Gabrieli and Nieto-Castanon, 2012)

BOLD, blood oxygenation level dependent; dFC, dynamic functional connectivity; EEG, electroencephalography; LFP, local field potential; MEG, magnetoencephalography; MSE, multi-scale entropy; SD, standard deviation; WPE, weighted permutation entropy.

Inter-individual differences in neural variability are behaviorally relevant

A host of studies across multiple neuroimaging modalities and task types now support the link between inter-individual differences in neural variability and behavior.

In the electrophysiological domain, McIntosh et al. (2008) examined relations between signal variability and behavior using EEG in a sample of 8- to 33-year-olds on a face-recognition task. The authors found that MSE was associated with higher face-recognition accuracy and more consistent reaction time responses. In a sample of 6- to 41-year-olds, Misić et al. (2010) examined MSE on MEG data and a working memory task using face stimuli, and found that higher MSE was moderately correlated with lower response-time variability and higher accuracy. In a sample covering the adult lifespan, Waschke et al. (2017) showed that higher pre-stimulus WPE yielded biased perceptual decisions, independent of participant age. Voytek et al. (2015) also showed that steeper EEG-based 1/f slopes were typical of younger, more accurate, and faster, more stable responders on a visual working memory task (Figure 3A; Voytek et al., 2015). Importantly, a recent study was able to demonstrate the compensation of age-related declines in working memory performance by boosting neural variability in the form of low-frequency oscillations (likely steepening the spectral exponent) through non-invasive brain stimulation (Reinhart and Nguyen, 2019). Several studies using fMRI also demonstrate a positive link between behavior and temporal neural variability on task. For example, previous work indicates that a higher SD of the BOLD signal reflects higher accuracy and faster, more stable response times on a host of tasks spanning perception, internally and externally oriented attention, working memory, and task switching in younger adults, older adults, or across both age groups (Armbruster-Genç et al., 2016; Garrett et al., 2011, 2013b, 2014; Grady and Garrett, 2018; Guitart-Masip et al., 2016; see Figures 3B and 3C for examples). Notably, dedicated studies investigating the inter-individual relationship between behavior and neural variability in non-human animals remain extremely rare (but see Avitan et al., 2020 and Honegger et al., 2019 for examples of between-animal differences in behavior alone).

Various other sources of inter-individual differences should be taken into account when aiming to understand the link between different aspects of neural variability and behavior. Representing the most examined source to date, human development across the lifespan has been increasingly linked (along with cognition) to temporal neural variability in intracranial EEG (iEEG), MEG/EEG, and fMRI data using different variability metrics (Garrett et al., 2013a, 2014; McIntosh et al., 2014). Several studies show that from childhood to young adulthood, MSE (McIntosh et al., 2008; Misić et al., 2010) increases, while the 1/f spectrum flattens (McIntosh et al., 2008) and BOLD variability reduces (Nomi et al., 2017). From young to older adulthood, WPE increases on average with age (and is directly correlated with 1/f flattening), while the across-trial SD of WPE decreases (Figure 3D; Waschke et al., 2017). Furthermore, the 1/f exponent continues to flatten (Figures 3E and 3F; Dave et al., 2018; Kosciessa et al., 2020a; Voytek et al., 2015; Waschke et al., 2017), short-scale sample entropy increases while long-scale entropy decreases (McIntosh et al., 2014; Sleimen-Malkoun et al., 2015; Wang et al., 2010), and $BOLD_{SD}$ reduces in a distributed set of cortical areas across a host of different cognitive and sensory tasks (Garrett et al., 2011, 2013a). These various findings underscore that chronological age offers a crucial inter-individual difference variable that helps to contextualize the relation between neural variability and behavior.

Attempts have also been made to link neural variability to diseases such as autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), schizophrenia, dementia, traumatic brain injury, congenital blindness, and epilepsy (Dinstein et al., 2015; Garrett et al., 2013a; Nomi et al., 2017; Yang et al., 2014). However, almost no links between behavioral performance and disease-related changes in neural variability have been reported to date (see Raja Beharelle et al., 2012 for a rare example). Extensive future research is thus needed to establish such associations.

Inter-individual neural variability as a "trait-like" representation of behavior

Beyond marking individual differences on a single task, neural variability may even link to behavior in a "trait-like" way, spanning different tasks and behavioral measures. For example, Grady and Garrett (2018) showed that negative associations between SD_{BOLD} and both $mean_{RT}$ (see Figure 3C) and SD_{RT} were similar across four different tasks, within and across young and older age groups. Garrett et al. (2011) also reported that older, slower, and more inconsistent performers expressed lower cortical SD_{BOLD} on three different tasks (Figure 3B). Furthermore, multiple studies indicate that the level of neural variability itself is correlated across different tasks. For example, Dave et al. (2018) showed that 1/f exponents from EEG spectra were highly and positively correlated across two different lexical tasks (see Figure 3E), and Misić et al. (2010) found that associations between MSE and speeded behavior were invariant to the inversion of stimuli during face processing. This work suggests that relations between neural variability and behavior may be trait-like.

BEHAVIORALLY RELEVANT INTRA-INDIVIDUAL "STATES" OF NEURAL VARIABILITY

Neural variability also clearly fluctuates over time within individuals (McGinley et al., 2015a; Okun et al., 2010), providing a basis for conceptualizing intra-individual "states" of neural variability (see Figure 4). Different neural variability states not only relate to ensuing behavioral performance but also may be co-determined by fluctuations in situational constraints. Below, we summarize arousal-related links to both behavior and neural variability. We then reflect on the impact that attention, complex task demands, and behavioral strategies may exert on variability states. Finally, we examine variability modulation on the state level ("meta-variability") as a unique, behaviorally relevant trait, and outline its connection with dopaminergic activity.

Arousal states, behavior, and neural variability

Arousal typically refers to the overall level of physical and mental "alertness." Arousal has long been suspected to influence behavior following an inverted U-shaped relationship (Yerkes

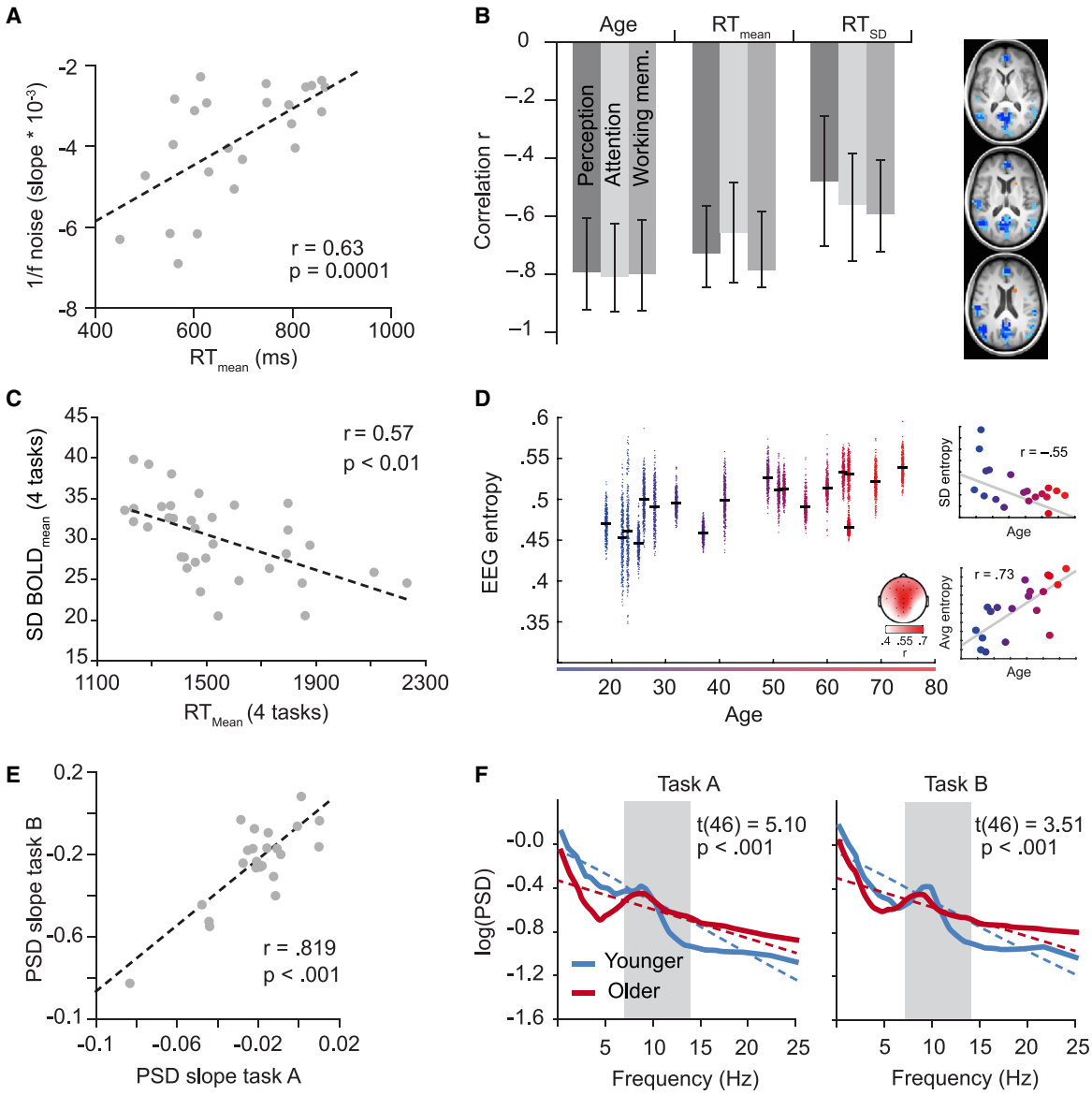

Figure 3. Inter-individual differences in neural variability relate to behavior and age

(A) Lower PSD slopes (flatter EEG spectra) are related to slower performance in a working memory task (occipital electrodes; adapted from Voytek et al., 2015).

(B) BOLD variability represents an age- and performance-related trait that generalizes across multiple tasks. Bar graphs (left panel) represent correlations of SD_{BOLD} with age, average RT, and individual SD of RT, respectively, for 3 different tasks; older, poorer performers express lower SD_{BOLD} in blue regions (right panel). Adapted from Garrett et al. (2011) to depict the intuitive direction of effects. Error bars represent bootstrapped 95% confidence intervals.

(C) Average BOLD variability relates to performance. Reaction times and BOLD variability levels were averaged across 4 different tasks. Adapted from Grady and Garrett (2018).

(D) Average EEG entropy (WPE) increases with participant age while the across-trial variability of entropy decreases. Colored dots in the left panel represent trial-wise averages from single participants and horizontal bars denote the mean. The panels at right show subject-wise averages of entropy (lower) and across-trial SD of entropy (upper). All data from electrode Cz (re-plotted from Waschke et al., 2017).

(E) Individual EEG PSD slopes are highly correlated across tasks (re-plotted from Dave et al., 2018).

(F) Power spectra are flatter in older (red) adults compared to younger adults (blue) across different tasks. Lines represent linear fits (excluding the gray alpha range; adapted from Dave et al., 2018).

and Dodson, 1908). Variations in arousal likely trace back to fluctuations in noradrenergic (NE) activity from the locus coeruleus (LC), which projects to most areas of the brain (Sara, 2009). Non-invasively, NE-related variations in arousal can be measured by fluctuations in pupil dilation, which track LC NE activity (Aston-Jones and Cohen, 2005; Joshi et al., 2016). At a behavioral level, arousal affects performance across species and task types. In simple sensory tasks, mice and humans display optimal performance following periods of intermediate arousal (Figure 4A; McGinley et al., 2015a; Neske et al., 2019; Waschke et al., 2019). McGinley et al. (2015b) found that mice performed more accurately during intermediate arousal, and

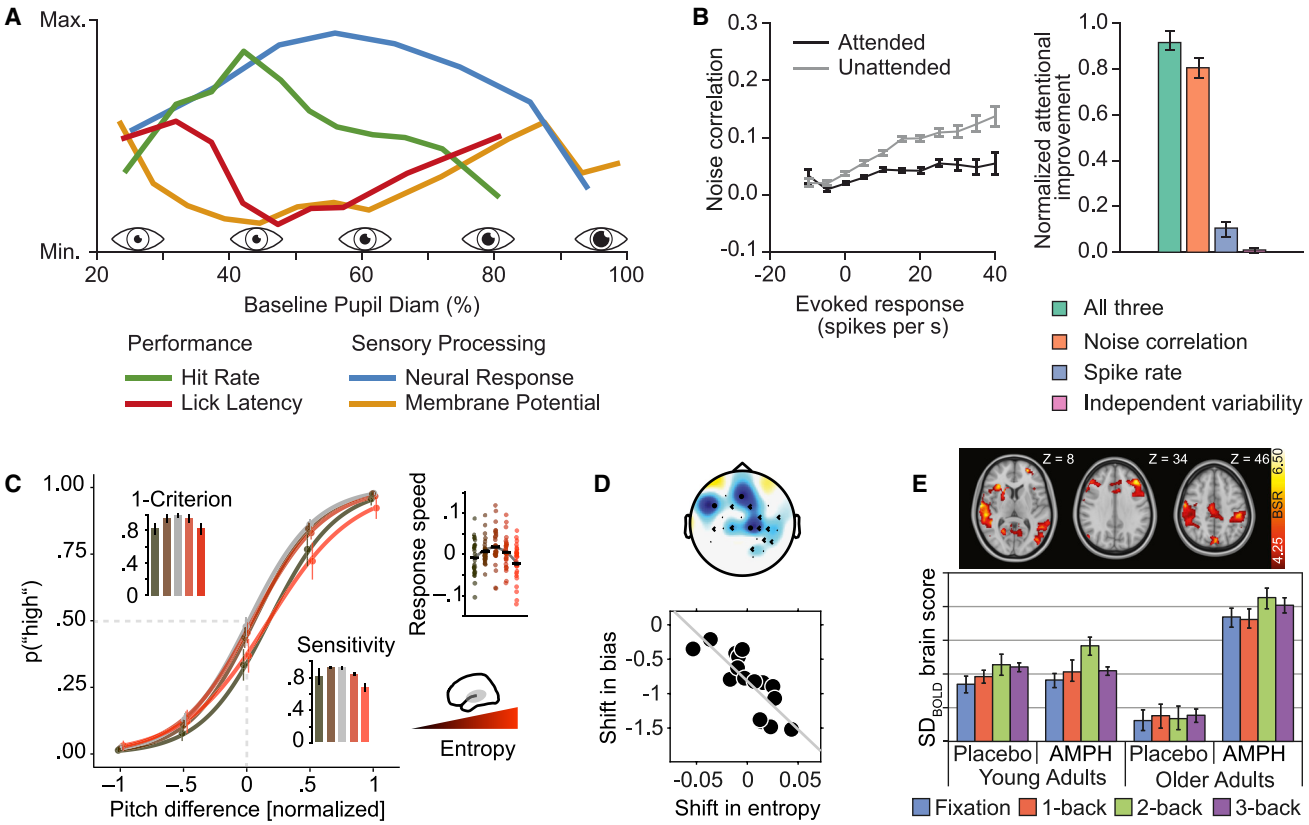

Figure 4. Neural variability "states" are behaviorally relevant

(A) In mice, behavior is most accurate (green) and fastest (red) following intermediate arousal (pupil dilation). Similarly, neural responses (blue) and membrane depolarization (orange) are maximized during such states. Adapted from McGinley et al. (2015a).

(B) Noise correlations in monkey visual cortex decrease during selective attention (left panel). Attention-related behavioral improvements are primarily explained by noise correlations (right panel; adapted from Cohen and Maunsell, 2009). Error bars represent standard error of the mean (SEM).

(C) Psychometric functions as a function of human auditory cortex EEG entropy (brown to red), displaying unbiased decision making following intermediate desynchronization (gray bar, upper left). Responses are fastest following intermediate desynchronization (right; re-plotted from Waschke et al., 2019). Error bars represent SEM.

(D) Liberal-conservative shift in decision bias (through instruction) correlates with shifts in EEG entropy. Spatial topography of correlations (top). Blue indicates negative correlations; black dots indicate electrodes involved. Average correlation (bottom). Subjects with a greater shift in entropy achieve a greater liberal decision bias shift (more negative criterion) (adapted from Kloosterman et al., 2020).

(E) SD_{BOLD}-related brain scores from fixation and n-back conditions under placebo and amphetamine for older and younger adults. SD_{BOLD} increases with memory load, but this increase is more pronounced within younger adults. SD_{BOLD} increases under amphetamine are specific to older adults. Error bars represent bootstrapped 95% confidence intervals. Axial slices of thresholded effects are shown in the upper panel (adapted from Garrett et al., 2015).

Waschke et al. (2019) demonstrated higher perceptual sensitivity during intermediate arousal states in humans. Arousal also exerts an influence on performance in more complex (memory) tasks (Podvalny et al., 2019). Finally, the association of pupil-linked arousal and behavior also appears to hold in complex decision-making tasks, during which participants' performance varies as a function of arousal (van Kempen et al., 2019). While the exact shape of the relationship remains to be specified (linear versus quadratic), the link between arousal and behavior generalizes across different domains from simple sensory processing to more abstract decision making. However, how does arousal link to neural variability?

Arousal (measured by time-resolved pupil dilation) is tightly linked to reductions in low-frequency power, both in non-human animals (McGinley et al., 2015a, 2015b; Neske et al., 2019; Reimer et al., 2014) and humans (Dahl et al., 2020; Meindertsma et al., 2017; Waschke et al., 2019). In addition to LC NE activity and its cortical projections (the LC-NE system), cholinergic activity from the basal forebrain also affects arousal and is linked to pupil size (Reimer et al., 2016). Both NE and cholinergic activity affect neural excitability and suppress the generation of synchronous activity in lower frequencies (McCormick, 1992; McGinley et al., 2015a). Thus, arousal-related reductions in low-frequency power likely trace back to increases in both NE and cholinergic activity. A recent study found that arousal was correlated both with temporal BOLD fluctuations across large parts of the brain and with LFP-defined measures of arousal (Chang et al., 2016). Thus, arousal-related fluctuations in brain activity may materialize similarly in both electrophysiological recordings and BOLD fMRI.

Sensory-evoked firing rates and cortical gain (the amount of neural output per unit of sensory input) in non-human animals are highest following intermediate arousal states, suggesting

optimal sensory processing (Figure 4A; McGinley et al., 2015a, 2015b; Neske et al., 2019). Similarly, sensory-evoked activity in human EEG increases with pre-stimulus arousal (Dahl et al., 2020; Gelbard-Sagiv et al., 2018), and arousal has been shown to boost neural gain (Lee et al., 2018). Overall, arousal not only serves as a link to a variety of different variability measures but it also represents a general driver of variation in sensory processing and behavioral performance.

Attention invokes neural variability states that affect behavior

Attentional state may also determine fluctuations in neural variability. The selective allocation of attentional resources to one sensory domain or stimulus feature results in a topographically specific reduction of noise correlations in non-human animals (Cohen and Maunsell, 2009; Mitchell et al., 2009; Rabinowitz et al., 2015), which has been linked to increases in task performance (see Figure 4B; Cohen and Maunsell, 2009, 2010). Visual discrimination learning and performance within individual animals is also closely tracked by attention-related reductions in noise correlations (Ni et al., 2018). Although future studies are needed to test the behavioral relevance of attention-related variability modulation in more complex task settings, these findings illustrate a tri-fold link between attention, neural variability, and performance in non-human animals.

At the level of LFPs (largely representing postsynaptic activity; Buzsáki et al., 2012), selective attention manifests in a reduction of low-frequency power (~2–10 Hz), a phenomenon often called "desynchronization" (Fries et al., 2001; Harris and Thiele, 2011; Mitchell et al., 2009). A similar attention-related reduction in low-frequency power occurs in human EEG recordings (also dominated by postsynaptic activity) in the 8- to –12-Hz (alpha) range, often paralleled by increases in high-frequency power (e.g., Wyart and Tallon-Baudry, 2009). Such variability changes appear specific to cortical areas relevant to the currently attended sensory domain (Kloosterman et al., 2019; Liu et al., 2014; Rajagovindan and Ding, 2011). Crucially, human behavioral performance benefits from attention-related decreases in low-frequency power. This link holds across different sensory modalities, including vision (Myers et al., 2014; Rajagovindan and Ding, 2011), audition (Wöstmann et al., 2019), and somatosensation (van Ede et al., 2011, 2012; Haegens et al., 2011, 2012). Similar findings have been reported for working memory (van Ede et al., 2016). In addition, attention also fluctuates spontaneously, and one way in which these attentional fluctuations may affect performance is via changes in pre-stimulus neural variability, an effect previously shown to affect response bias in humans (Figure 4C; Waschke et al., 2019). Finally, such attention-related modulations of neural variability have also been reported for human fMRI signals and are linked to performance (Garrett et al., 2013b; Grady and Garrett, 2018). Taken together, the selective allocation of attentional resources tightly links to neural variability, which in turn relates to behavioral performance across species, imaging techniques, and tasks. What are the viable neural pathways by which attentional states could yield changes in states of neural variability?

Potential neural mechanisms underlying attention-related shifts in variability

There exist different potential neural processes via which selective attention can link to neural variability. According to a prominent account, selective attention may be realized by thalamocortical and cortico-cortical feedback connections that affect local inhibitory activity (Zagha and McCormick, 2014; Zagha et al., 2013). Specifically, projections from the prefrontal cortex (PFC) to the thalamus carry information about the currently attended modality and alter thalamic activity (Marton et al., 2018; Nakajima et al., 2019; Wimmer et al., 2015). Tasks that involve directed attention yield robust increases in SD_{BOLD} (relative to rest; Grady and Garrett, 2018), and topographically, these task-related increases in SD_{BOLD} are not limited to classic sensory regions, but also include hub regions of functional and structural connectivity such as the thalamus (Garrett et al., 2013b; Grady and Garrett, 2018).

Attention-dependent glutamatergic projections from the thalamus to sensory cortical areas have been proposed to affect changes in the E/I balance (Harris and Thiele, 2011; Wimmer et al., 2015). Noise correlations are also sensitive to fluctuations in the E/I balance, as shown in modeling and experimental studies (Cardin, 2018; Renart et al., 2010; Shew et al., 2011; Zhou and Yu, 2018). Mesoscopic changes in neural variability (e.g., in LFP or MEG/EEG) in the context of selective attention may too be reflective of alterations in E/I balance in sensory cortices. As outlined above, selective attention coincides with decreases of low-frequency MEG/EEG power (e.g., Haegens et al., 2011), potentially paralleled by a power increase in higher frequencies (Wyart and Tallon-Baudry, 2009). This 2-fold alteration in oscillatory power represents a pronounced change in neural variability and could be conceived of as a flattening of the power spectrum. The 1/f spectral exponent has been shown to approximate E/I balance (Gao et al., 2017; Waschke et al., 2019). Thus, attention-related fluctuations in neural variability may depict topographically specific changes in E/I balance that are potentially realized via thalamo-cortical projections.

Of note, the neural mechanisms that implement the selective allocation of attentional resources may differ from the ones highlighted above. The fronto-parietal attention network has been suggested to coordinate attentional sampling via low-frequency neural oscillations (Fiebelkorn and Kastner, 2019), potentially also affecting neural variability downstream. Regardless of the exact neural manifestation, fluctuations in attention likely coincide with variability in sensory-evoked activity (Helfrich et al., 2018; Nandy et al., 2017; Saenz et al., 2002)

Sensory input shapes variability states

Neural variability may also reflect the "richness" of sensory information (i.e., the amount of perceivable sensory input). Processing more feature-rich stimuli requires increased neural resources, potentially resulting in more dynamic brain activity during stimulus processing (Hermundstad et al., 2014; Młynarski and Hermundstad, 2018). A recent fMRI study showed that the ability to upregulate brain signal variability in response to more feature-rich visual input predicted more accurate, faster, and less variable behavioral performance across a series of different cognitive tasks (Garrett et al., 2020). Converging evidence from

computational and animal work (spiking, membrane potentials) also suggests that the degree of perceived sensory input (in turn, providing a form of "perceptual uncertainty") can be encoded by neural variability (Orbán et al., 2016); the authors showed that single neuron responses become more distinct when processing different features of higher-contrast stimuli. We presume that this should also entail that V1 population-level (across cell) response variability across different types of stimuli ("signal variability") will be upregulated with increasing visual contrast. In general, it is likely that if natural images are processed, then a multitude of different features will elicit a multitude of neural responses for which specificity will increase with visual contrast (i.e., richness of input). Hence, more feature-rich images should entail higher variability of visual cortex activity overall (Garrett et al., 2020). Although both studies suggest promising links between stimulus richness and neural variability, given the differences in recording and modeling techniques between Orbán et al. (2016) and Garrett et al. (2020), future research is needed to test whether both results trace back to a common mechanism. Regardless, these initial studies suggest that neural variability during sensory processing scales with the richness of sensory input and that the tightness of this scaling may represent an upper limit for behavioral performance.

How do higher-order demands and strategies influence variability states?

In addition to arousal, attention, and the complexity of sensory input, neural variability also reflects higher-order demands that arise from one's environment or task. Such demand-dependent alterations in neural variability may reflect the upregulation of computational resources in a given task, at least until processing limits are reached. For example, the low-frequency power of LFP recordings in monkeys has been shown to decrease with memory load during encoding, while high-frequency power increased, which is evidence for spectral flattening with memory load (Kornblith et al., 2016). In humans, intracranial EEG recordings have also revealed memory load-related power decreases in dorsolateral PFC (DLPFC; Brzezicka et al., 2019). Similarly, widespread decreases in low-frequency MEG/EEG power (Haegens et al., 2014; Tran et al., 2016) and increases in high-frequency power (Rouhinen et al., 2013) have been reported with increasing attentional load, pointing to a flattened spectrum during high cognitive demand.

Memory load-dependent increases in human MEG/EEG high-frequency power (Palva et al., 2011; Rouhinen et al., 2013) and EEG entropy (Grundy et al., 2019) during cognitively demanding tasks have also been found to predict behavioral performance. Similarly, load-dependent increases in high-frequency MEG/EEG power have been linked to visual working memory performance (Honkanen et al., 2015). Furthermore, low-frequency power decreases in DLPFC can be predictive of inter-individual differences in memory performance (Brzezicka et al., 2019). These findings are in accordance with recent evidence from an fMRI study in which SD_{BOLD} was found to scale with working memory load (Figure 4E; Garrett et al., 2015). In fact, demand-related upregulation of BOLD variability appears to be a hallmark of performance and cognitive flexibility (Armbruster-Genç et al., 2016; Garrett et al., 2013b; Grady and Garrett, 2014). Thus, topographically specific patterns of neural variability across different imaging techniques are sensitive to the current level of cognitive load or demand and relate directly to behavioral performance.

In addition to task demands, inter-individual differences in behavioral strategies may be reflected in the momentary level of neural variability and in ensuing behavior. For example, externally induced changes in response criterion (liberal versus conservative) via altered instructions and feedback schemes have been found to be associated with variations in pre-stimulus alpha power (Kloosterman et al., 2019). Furthermore, a recent study reported that greater shifts in the response criterion (from a more conservative to a more liberal response mode) were reflected in heightened post-stimulus EEG entropy (Figure 4D; Kloosterman et al., 2020). These findings illustrate that different response tendencies or strategies may manifest in altered patterns of neural variability during pre- and post-stimulus periods, suggesting a potential top-down source of variability modulation that affects behavior (Iemi et al., 2017; Kloosterman et al., 2019).

Could intra-individual modulation of neural variability states ("meta-variability") also serve as a behaviorally relevant trait?

As outlined above, the up- and downregulation of brain signal variability reflects demands and resources within a given individual. Promisingly, the degree of within-subject variation in neural variability measured across time, tasks, demands, and responses in turn has also been shown to distinguish individuals from one another (Garrett et al., 2015; Kloosterman et al., 2020; Waschke et al., 2017). It has remained unclear, however, whether the degree to which an individual expresses such meta-variability reflects a behaviorally relevant trait. Initial evidence by Garrett et al. (2020) showed that a greater ability to upregulate BOLD variability in V1/V2 as a function of the richness of visual input yielded faster, more consistent, and more accurate performance across 8 different offline cognitive-behavioral paradigms ranging from response inhibition to working memory. The authors argued that higher performers may do well because they appropriately modulate bottom-up allocation of processing resources (indexed by neural variability), in line with the richness of sensory input, allowing them to encode key distinctions in their environment. Although this study only used passive viewing of pictures, it is also conceivable that individuals could have top-down control over the modulation of neural variability to adapt to momentary demands in the environment. Dedicated experimental research will be needed to disentangle bottom-up from top-down influences on variability modulation, and to test the generalizability of meta-variability traits across imaging modalities and pinpoint neural substrates.

Dopaminergic associations between meta-variability and behavior

In addition to noradrenaline and E/I balance, dopamine (DA) also plays a crucial role in the modulation of neural variability. To date, DA remains the only system that has been probed with the joint goal of manipulating neural variability and behavior concurrently. In general, DA is thought to shift brain activity between system stability and flexibility (Bäckman et al., 2010; Cools, 2011; Li

et al., 2001). Computational modeling suggests that adding white noise to DA-depleted neurons can boost relatively impoverished stimulus detection performance (Li et al., 2006). At millisecond and second timescales, DA release also operates via shorter- and longer-term facilitation and depression (i.e., "kick-and-relax" dynamics; Day et al., 2007; Montague et al., 2004) that affect subsequent DA-dependent spike dynamics. Notably, DA-deficient mice exhibit a dearth of phasic bursting activity, which can be restored via DA agonism (Paladini et al., 2003). In line with the contention that brain signal variability can index a healthy neural system (Garrett et al., 2013a), animal models indicate that trial-to-trial variability in DA release appears to increase, rather than decrease, with increasing task proficiency (Owesson-White et al., 2008). This fundamental work has prompted the idea that DA may also affect *in vivo* brain signal variability and its cognitive correlates in humans. For example, Garrett et al. (2015) found that low-dose amphetamine (a potent DA agonist) boosted SD_{BOLD} and the speed and stability of reaction times concurrently in (task-naive) older adults undergoing a working memory task (Figure 4E). Alavash et al. (2018) showed that greater L-DOPA-driven increases in BOLD variability reflected faster reaction times compared to placebo. The DA system thus represents a promising first step in the effort to elucidate neurochemical mechanisms underlying intra-individual links between neural variability and behavior.

FURTHER CONSIDERATIONS IN THE STUDY OF NEURAL VARIABILITY-BEHAVIOR ASSOCIATIONS

The special case of variability quenching

In contrast to much of the work profiled in this article, which examines neural variability across time within experimental trials or blocks of trials, several studies report an intra-individual reduction of across-trial neural variability in response to sensory stimulation, a phenomenon called variability quenching (Churchland et al., 2010). In non-human animal studies, spiking variability (typically estimated using the Fano factor; see Table 1) is commonly calculated for each time point and across trials. However, a variety of other approaches, highlighted above, estimate "moment-to-moment" variability across time points within and across trials. Studies examining variability quenching rarely display strong, stable relationships with inter- or intra-individual performance, if behavior is reported at all (Churchland et al., 2010; Ito et al., 2020; Ponce-Alvarez et al., 2015). In two studies that examined behavior comprehensively, one showed no associations between EEG quenching and behavior (Arazi et al., 2017a), while another study showed that although post-stimulus quenching of across-trial EEG variability did relate to perceptual performance, this effect was entirely attributable to the pre-stimulus period (Arazi et al., 2017b). It is beyond the scope of this Review to discuss the various potential reasons why different variability metrics within versus across trials may indicate different directions of variability change upon stimulus presentation; here, we simply wish to highlight what has been a general lack of behaviorally relevant effects of variability quenching in the literature to date.

On the specificity of neural variability-behavior associations

As outlined above, different estimates of neural variability are linked to intra- and inter-individual differences in behavior. However, a statistical association between neural variability and behavior does not necessarily imply a causal chain of neural processes. In the context of correlated intra- and inter-individual differences in neural variability and behavior, at least three basic scenarios are conceivable. Behaviorally relevant differences in neural variability within and between individuals may capture neural processes that (1) reflect specific, time-locked aspects of the current task (e.g., stimulus onset; Cohen and Maunsell, 2009); (2) index experimental conditions in general (e.g., aggregated condition-wise differences in rest versus task; Grady and Garrett, 2018), or (3) are not directly related to the task, but nevertheless affect behavior (e.g., spontaneous arousal states; McGinley et al., 2015a). In addition, neural variability may represent processes inaccessible to researchers for different reasons, including measurement techniques, analysis approaches, and generative models, but nevertheless relate to behavior. The degree to which these sources of neuro-behavioral correlation can be dissociated hinges on the precision of recorded neural activity and on the definition of task-related (versus task-unrelated) neural activity. It is thus crucial to disentangle these various sources wherever possible when linking neural variability to behavior. The following section describes a series of complementary ideas regarding experimental design and interpretation of results.

THE WAY FORWARD

Having surveyed the existing evidence above, here, we outline several points that may buttress future efforts toward better understanding inter- and intra-individual associations between neural variability and behavior. First, we highlight experimental considerations for probing associations between neural variability and behavior. Second, we point out gaps in our understanding of how neurochemical activity may shape variability and behavior and suggest novel approaches to bridge these gaps. Finally, we outline promises of and remaining challenges for the field, arguing for a deliberate focus on neural variability to better understand the neural foundation of behavior.

Experimental considerations when probing neural variability as a basis for behavior

The basic principles of experimental design for variability-focused versus other approaches are generally comparable. For example, controlling and accounting for potentially confounding variables (e.g., low-level stimulus features, cognitive load) represents an obvious prerequisite in the investigation of any neurobehavioral correlation. However, neural variability-based approaches require additional considerations, which we briefly discuss and provide suggestions on below.

First, it should be clearly specified which aspect of intra- or inter-individual differences in neural variability shall be investigated. On the one hand, if the impact of task-unrelated neural variability on behavior is investigated, then it is advisable to sample a wide range of spontaneous variability states during

constant task conditions (McGinley et al., 2015b; Waschke et al., 2019). On the other hand, if task-related changes in neural variability are of interest, then conditions should be varied within individuals while controlling for changes in spontaneous, task-unrelated brain states (Garrett et al., 2011, 2015). Hence, in both cases, it is advisable to record available proxy measures of spontaneous brain states such as pupil-linked arousal, either to be analyzed specifically or as a potential cofounder for which to control. Overall, we advocate the use of within-subject paradigms, which not only provide the ability to estimate different variability states but also allow for the investigation of inter-individual differences in neural variability within and across tasks (they may also constitute stable trait-like features; Garrett et al., 2020).

Second, it is crucial to choose *a priori* a specific variability measure based on the exact research question and temporal and spatial scale of interest and then to adapt the task design and analyses to specific considerations for the chosen measure. If non-oscillatory aspects of neural variability on the scale of milliseconds will be analyzed, then WPE and MSE of LFP or EEG recordings represent suitable measures (Fadlallah et al., 2013; Kosciessa et al., 2020b; Waschke et al., 2019). While single-trial WPE time courses can be estimated using a moving window approach, this is not possible for all slower temporal scales of MSE for which across-trial concatenation results in an aggregated entropy time series (Grandy et al., 2016). However, if your research question is rooted in single-trial-related insights of slow entropy processes, then adequate single-trial durations are required. Regardless, before estimating any variability measure, it is essential to account for non-neural sources of variability (e.g., subject movement, eye blinks and microsaccades, vascular reactivity [for BOLD]) whenever possible (Garrett et al., 2010, 2017; Uddin, 2020).

Third, to further specify the links between distinct aspects of neural variability and behavior, more comprehensive parameterizations of behavior are required than have often been used in the literature to date. For example, behavioral performance can be partitioned into sensitivity and bias using classical signal detection theory (SDT; Green and Swets, 1989), but also dissected further into estimates of evidence accumulation or decision boundaries with the help of drift-diffusion modeling (Ratcliff and McKoon, 2008). As evidenced by first results in non-human animals (Churchland et al., 2011) and humans (Kloosterman et al., 2019, 2020), such finer-grained compartmentalizations of behavior into different aspects of evidence accumulation via modeling approaches such as drift diffusion, time-dependent scaling, or attractor models provide unique insights into how perceptual performance and neural variability are linked. It is also largely unstudied to date how computational models of reinforcement learning may relate to variability, providing another fertile avenue for future research (e.g., can neural variability "encode" choice stochasticity, learning rates, or prediction errors during learning?).

Toward more in-depth probes of candidate mechanisms

The establishment of mechanisms underlying associations between neural variability and behavior remains in its infancy. As noted above, DA represents the only system that has been probed with the joint goal of manipulating neural variability and behavior concurrently (Alavash et al., 2018; Garrett et al., 2015). Other neurochemical candidate systems (NE and E/I balance) have an evidence-supported role in modulating neural variability and behavior separately, but evidence for joint changes between NE or E/I balance, neural variability, and behavior is still lacking. In the case of LC-NE-related arousal, associated changes in neural variability, sensory processing, and performance have been reported to follow highly similar slopes on average, intuitively suggesting a common underlying mechanism (McGinley et al., 2015a). A crucial role of neural variability in this context would imply that arousal is associated with changes in neural variability, which in turn affect sensory processing and bias behavioral performance. Although these joint associations have often been implied, they have not yet been empirically quantified. Future experiments or re-analyses of existing datasets are required to test whether arousal-related changes in neural variability affect behavior in a direct or indirect manner (e.g., through altered sensory processing).

Similarly, although the involvement of alterations in E/I balance may represent a key mechanism for attention-related changes in neural variability and performance, evidence for these joint associations is also lacking. Despite direct links between attention-related changes in neural variability and behavior (Cohen and Maunsell, 2009; Haegens et al., 2011), the involvement of altered E/I levels in this association has not been tested directly. Future studies could use novel approximations of E/I (e.g., 1/f exponent) in connection with attentional manipulations and multimodal imaging (e.g., EEG, fMRI) or direct recordings in non-human animals. Magnetic resonance (MR) spectroscopy is also viable for estimating baseline E/I levels in humans and could be combined with pharmacological interventions of excitatory (glutamate) versus inhibitory (GABA) systems. Initial work in organoids shows promise, indicating that E/I balance yields maximum entropy in the system, which is reduced during pharmacologically induced hyper- and hypo-excitable regimes (Shew et al., 2011). Finally, dedicated work is required to establish the specificity of these different candidate neurochemical mechanisms (DA, NE, E/I), especially given the known interactions between them (El Mansari et al., 2010; Guiard et al., 2008).

Promises and remaining challenges

Across species, methodologies, temporal, and spatial scales, this diverse body of evidence suggests that neural variability holds remarkably rich information about the internal and external constraints under which an agent operates. While "neural" variability needs to be carefully separated from technical and measurement-related sources of noise (Uddin, 2020), neural variability may represent a core signature of (1) how stimuli become neurally encoded, (2) how this "bottom-up" sensory information interacts with "top-down" task demands, and (3) how decisions are formed.

Conclusions regarding the behavioral relevance of neural variability have thus far hinged explicitly on the precise metric and experimental design that researchers used to quantify neural variability. Simple statements regarding "more or less variability" create confusion as to what was estimated. First, we need to specifically probe associations and trade-offs between

variance-, frequency-, and information theory-based measures (Kosciessa et al., 2020b) to better understand how and why neural variability-related behavioral effects continue to emerge in cognitive neuroscience. Second, it is essential to investigate the potential existence of individual dynamic repertoires of neural variability using highly controlled experimental manipulations of task and input complexity.

Furthermore, the majority of existing studies examining temporal neural variability have taken essentially a "localized" approach, estimating different variability metrics within cells/electrodes/sensors/voxels/regions. As such, we need to better decouple local from distributed sources of neural variability to understand their respective behavioral relevance. Initial efforts have shown that temporal variability exhibited within a brain region may be largely due to shared sources of moment-to-moment variance across networked regions (Doiron and Litwin-Kumar, 2014; Garrett et al., 2018; Vakorin et al., 2011). However, few studies have examined inter- and intra-individual links between local/distributed sources of neural variability and behavior, providing a clear target for future work.

Interestingly, the idea that neural variability may index "uncertainty" continues to gain ground in the field. This is especially true within the context of sensory perception (Beck et al., 2008; Ma et al., 2006; Orbán et al., 2016). Here, the general idea is that neural responses may be probabilistic (Bayesian) in form, and the more clear and reliable sensory input that a neuron receives (i.e., higher sensory evidence/lower uncertainty), the narrower the probability distribution should be in response to a particular stimulus ("noise variability"). Responses of single neurons should also be more variable (differentiated) across different stimulus features ("signal variability"). In this way, different forms of neural variability may jointly reflect perceptual uncertainty. Crucially, links between neural variability and uncertainty have also recently been abstracted to higher levels of analysis beyond perception. For example, Kosciessa et al. (2020c) showed that EEG-based time series entropy upregulated parametrically (within-person) with increasing state uncertainty (i.e., uncertainty over relevant stimulus features), while perceptual input was held constant. Future work could thus jointly examine these various levels at which uncertainty may be encoded by neural variability, and how such sources may trade off, within and beyond the domain of sensory perception.

Finally, although the association between neural variability and behavior is clear, it remains unknown whether variability really "causes" behavior. Exploiting neural variability in future studies as a key variable will require researchers to manipulate neural variability and behavior more precisely. A relatively simple and tractable route in human research is to deploy task designs that drive neural variability through the magnitude (e.g., demand) and direction (e.g., internal, external) of resources that the neural system is deploying, particularly at the intra-individual level. Manipulation may also be achieved through direct interference in neural circuits (e.g., optogenetic stimulation; see for example, Nandy et al., 2019, but also see Jazayeri and Afraz, 2017) or via drug agonism/antagonism of candidate neurochemical systems (e.g., DA, NE, glutamate/GABA) beyond the very sparse work done to date (Alavash et al., 2018; Garrett et al., 2015).

Conclusions

The temporal variability of brain activity represents a key, undervalued dimension for understanding brain-behavior associations. We believe that only by incorporating a specific focus on variability will the neural foundation of behavior be comprehensively understood, and theoretically driven, targeted investigations of neural variability using dedicated analysis tools and designs will prove essential in this effort. In the end, neuroscientists must grapple with the possibility that behavior may emerge because of neural variability, not just in spite of it.

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AUTHOR CONTRIBUTIONS

L.W., J.O., and D.D.G. conceived the main perspective. L.W., N.A.K., J.O., and D.D.G. wrote, edited, and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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