Variability in neural activity and behavior

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Neural activity and behavior in laboratory experiments are surprisingly variable across trials. This variability and its potential causes have been the focus of a spirited debate. Here we review recent research that has shed light on the sources of neural variability and its impact on behavior. We explain how variability may arise from incomplete knowledge about an animal's internal states and its environment. We discuss the problem of incomplete knowledge both from the experimenter's point of view and from the animal's point of view. Both view points are illustrated through several examples from the literature. We furthermore consider both mechanistic and normative models that explain how neural and behavioral variability may be linked. Finally, we review why variability may confer an adaptive advantage to organisms.

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Introduction

Behavior is variable and often unpredictable. While some external events trigger only one specific behavior, such as a reflex, most external events trigger one out of many possible behaviors in a seemingly stochastic fashion. This behavioral variability is also observed in the laboratory, and can rarely be avoided completely. The colloquial Harvard Law of Animal Behavior sums it up as follows: 'Under carefully controlled experimental circumstances, an animal will behave as it damned well pleases.'

Just as behavior is variable, so is the activity of neurons. This variability is observed in essentially all neural recordings, and even in the absence of behavior. Over the last two decades, many studies have quantified neural variability during the performance of well-controlled behavioral tasks. These studies have thereby opened the door to explore the relationship between neural and behavioral variability. Focusing on a sensory area, the pioneering work by Britten and colleagues showed that neural activity and behavioral choice covary on a trial-by-trial basis, even if the stimulus is constant [1]. This early work suggested that random fluctuations in the processing of sensory stimuli could be at the origin of behavioral variability. More recent work has rekindled interest in this topic, showing that the answer is more elusive than originally thought, and highlighting the flexible nature of neural variability across task conditions and behavioral states.

Here, we review recent research that addresses the relationship between neural and behavioral variability. We focus on studies of perceptual decision-making and consider three different, but related aspects of the problem: What is the origin of the observed neural variability? How does neural variability impact behavior? Finally, what are the functional or adaptive roles that neural variability may play?
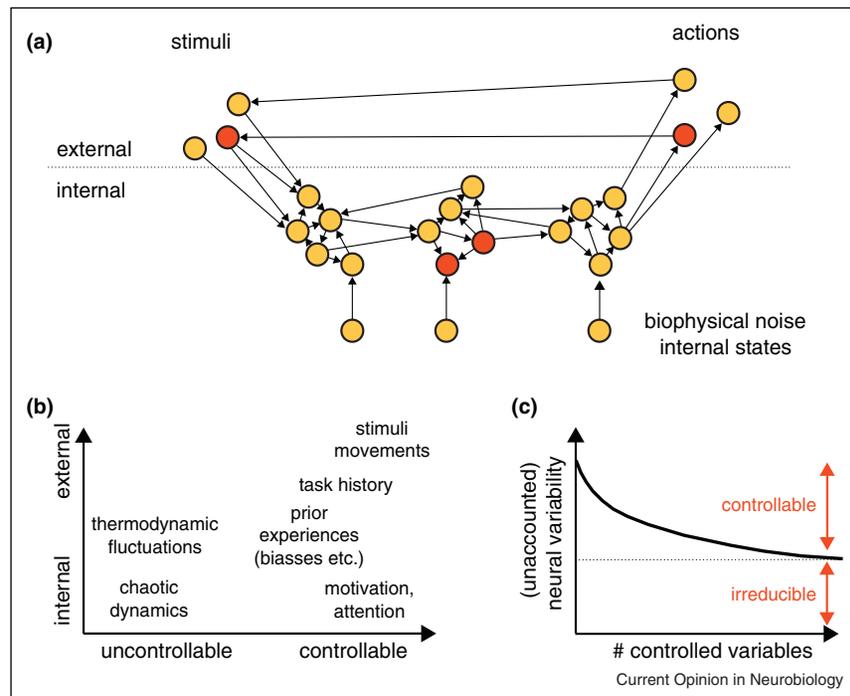
Sources of neural variability

In the classical, reductionist approach, we seek to explain changes in some target variables (say, neural activity) by changes in some other variables (say, an external stimulus). In any particular neurophysiological experiment, not all factors that influence the targeted neural activity can be controlled or monitored. Unknown influences range from thermodynamic fluctuations in the state of ion channels to the various internal states of an organism. Since we lack access to these unknown or 'hidden' variables, any change in their value across trials will show up as random variability (or 'noise') in the neural activity. Since neural activity is influenced by many variables, identifying these hidden variables and locating their sources is one of the hard problems of systems neuroscience.

One way of thinking about this problem is to split the variables into those that are found within the brain (internal) and those that are found outside of it (external), see Figure 1a. We then define *external variability* as any variability in neural activity that arises from a lack of knowledge or control over environmental variables that affect neural activity. These include uncontrolled stimulus dimensions or unobserved movement parameters. *Internal variability* is generated by any internal variables of the brain, such as neural activity in unobserved brain areas, or membrane voltage fluctuations etc.

Another way of thinking about this problem is to arrange potential sources of variability by our ability to monitor or

Figure 1

Sources of variability in the brain. **(a)** In a typical neurophysiological experiment, we monitor some of the animal's sensory observations, some of its movements, and a subset of its neurons (red circles). Of course, activity in any one part of the brain is influenced by many other sources, both internal and external to the brain (yellow circles). These sources or 'hidden' variables create variability in the experimental observations that the observed variables cannot account for. Since most of the observed and hidden variables influence each other, pinning down the actual sources of variability is a hard problem. Note that the figure is schematic, there are likely to be millions or billions of variables involved. **(b)** We sort the hidden variables along two axes. One axis refers to whether they are external or internal to the brain. The other axis denotes their controllability, that is, to what extent they are accessible to experimental control or monitoring. Even though many variables may be deemed controllable, real-world experiments cannot monitor all of them because of practical constraints. **(c)** As more and more control is exerted in an experiment, and more and more variables are being observed, the variability in neural activity that is unaccounted for can only decrease.

control them. For instance, any variability in neural activity caused by the random movement of ions across cell membranes may be considered uncontrollable. On the other hand, variability caused by more global variables, such as the motivational or attentional states of an animal, could, at least in principle, be monitored. Naturally, the border between what can or cannot be controlled is somewhat arbitrary, and changes with the advent of each new experimental technique. Nonetheless, we find it useful to order sources of variability along such an imagined axis.

The two axes of variability thus defined are illustrated in Figure 1b. If most of the variability was due to controllable variables, then most of the variability could potentially be explained by a more refined definition of the external environment and the animals' internal states. In this case, variability could largely be reduced to experimental and measurement problems. If most of the variability was due to uncontrollable variables, then variability in neural activity would be irreducible (Figure 1c).

Controllable sources of variability

In the classic experiments of Britten and colleagues, monkeys were trained to discriminate the overall direction of motion of a random dot pattern [1,2]. More specifically, the behaviorally relevant information was provided by the fraction of dots moving in a coherent direction. However, many distinct patterns of random dot motion are compatible with a given motion coherence, and neurons in cortical area MT are extremely sensitive to these fine-grained dot patterns, especially at low coherences [3]. Consequently, identifying the stimulus with the motion coherence introduces external variability into the activity of MT cells. Although the magnitude of this extra variability has not been thoroughly investigated, preliminary accounts suggest that it could be as much as 30% of the total at low coherences (de la Rocha, *et al.* (2012). *Soc. Neurosci. Abs.* 38, 175.11). More generally, when animals are trained to discriminate sensory stimuli across particular dimensions, the 'stimulus' is usually identified with those dimensions. However, neurons might be sensitive to other, behaviorally irrelevant

dimensions. If the stimulus changes along these dimensions from trial to trial, and these changes are ignored by the observer, then neural activity will appear variable.

A related source of controllable external variability could arise from sensory-motor couplings. For instance, neurons in the olfactory bulb respond to odors with precisely timed spikes when responses are aligned with respect to the sniff cycle [4,5]. When the responses are aligned at the odor onset, spike times become a lot more variable [4]. Such coupling of sensory responses to the motor system may also bridge different modalities. Recent work has shown, for instance, that visual responses in mice [6] and flies [7] are strongly modulated by locomotion. Moreover, sensory-motor couplings may appear in unexpected brain areas, such as the prefrontal cortex, where neurons have been found to be selective to subtle variations in head position [8].

Variability can also be introduced in experiments due to an animal's recent past experiences. The performance of an animal often depends on different aspects of the history of a given experiment, such as past rewards, choices, or stimuli [9–11]. Ignoring this history of past trials introduces external variability into the experiment. Marcos and colleagues recently reported that trial history has a strong effect on the variability (but not the mean response) of single dorsal premotor neurons in an arm reach countermanding task [12]. The variability of neural activity in a given trial increases with the number of previous trials containing a stop signal.

In short, whenever we observe more variables or control an animal's behavior better, neural variability can only decrease. The reverse is also true. When we do not know the external inputs or the animal's behavior, neural variability will increase. An example is 'spontaneous activity', which is defined as brain activity in the absence of discernible external inputs or behavior, and is typically highly variable. Given the previous arguments, one would expect neural activity that is conditioned on a particular stimulus or action to be less variable than during the spontaneous condition, as recently reported [13,14]. A conservative interpretation of these results (see below of for an alternative interpretation) would be that the experimenter has increased control over one of the factors affecting neural activity at stimulus onset.

In the examples above, the sources of variability were external to the animal. Are there controllable sources of variability generated internally? One example is the so-called 'brain state', that is, the global dynamics of brain activity. The brain state alternates between periods of cortical activation and inactivation across the sleep-wake cycle, but also within each phase of the cycle [14]. Recent work has shown that this brain state modulates neural variability. During cortical activation, for instance, sensory responses in cortex are more reliable than during cortical inactivation [15,16]. Furthermore, correlations between neurons' activities decrease [15,17•]. Even though the brain state is an internal variable, it can be easily and quickly measured, since it is associated with large-scale differences in brain activity [18].

Neural variability also depends on attention. Sensory responses in area V4 [19–21] and area V1 [22] become less variable and less correlated across cells when an animal pays attention to the stimulus rather than when attention is paid elsewhere. Consistent with these findings, attention has also been found to suppress collective low-frequency fluctuations in cortical circuits [14,23]. However, attentional modulations can also increase variability (Figure 2; see also below). A previous study found highly correlated activity in V1 during a curve-tracing task between sites strongly modulated by attention, and almost uncorrelated activity between sites not modulated by attention [24]. The relationship between attention and neural variability is therefore complex and may depend on how reliably attention is deployed across trials. Is there any hope of measuring an internally generated attentional signal on a trial-by-trial basis? The advent of large-scale population recordings is making this possible, and methods to produce single trial estimates of attention [25] or decision variables [26] have already been proposed.

In summary, not only external, but also internally generated variables have a significant impact on neural variability. If they can be monitored on a trial-by-trial basis, they potentially lower the observed variability.

Uncontrollable sources of variability

The strong coupling of widely different spatial and temporal scales in biological systems in general, and in the nervous system in particular, generates sources of variability that are difficult to control. One obvious example are microscopic fluctuations of small structural components of neurons, such as ion channels or the synaptic machinery involved in vesicle release [27]. Although the precise impact of this microscopic noise on neural variability remains unclear, it can, in principle, be propagated to the cellular or organismic level through various non-linearities such as spiking thresholds.

An additional, but more subtle source of variability could be the dynamics of neural circuits. Strongly connected recurrent network models can operate in chaotic regimes, for instance, if excitation and inhibition balance each other dynamically [28,29]. Similarly, recurrent circuits of firing-rate neurons can be chaotic if the distribution of synaptic weights is sufficiently wide [30,31]. Such chaotic networks can change their states dramatically

Figure 2
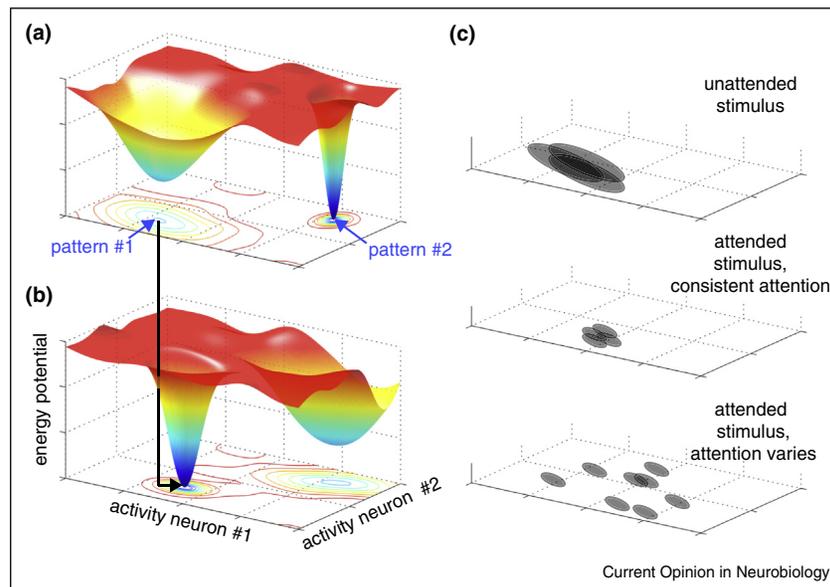
Effects of attention on neural variability. **(a)** The stability of a neural activity pattern (for visualization, only the activity of two neurons is plotted) is schematically represented by the shape of an 'energy function' evaluated at that pattern. The network dynamics moves activity patterns toward the nearest minima of the energy function. Stable patterns are found at the bottom of valleys, where moderate noise levels do not significantly change the activity pattern. Unstable patterns are located on the top of hills, and metastable patterns are those where the energy function is approximately flat. A sensory stimulus may reduce variability by stabilizing a particular pattern (deepening the valley around that pattern). Attention may stabilize the pattern even further. Here, two sensory stimuli are presented, activating patterns 1 and 2, and the stimulus activating pattern 2 is being attended to. **(b)** Here, the stimulus activating pattern 1 is being attended to. Attention changes both the average activity in pattern 1 (black arrow) as well as the size of its well, thereby limiting the effect of noise. **(c)** Stability is represented as a contour (ellipse) of the energy function at a given height above the activity pattern, representing how far the pattern would move under moderate noise. Top. Trial-to-trial variability when the stimulus is unattended. Middle. When the effect of attention is consistent across trials the overall trial-to-trial variability is reduced [20,21]. Bottom. If the effect of attention varies substantially across trials, the overall trial-to-trial variability can increase [24].

when being perturbed. Consistent with these predictions, recent *in vivo* experiments show that cortical circuits are quite sensitive to weak perturbations [32–34].

We emphasize, however, that the moment-to-moment state of single neurons may vary strongly while global network properties, such as the average instantaneous population activity, vary only weakly. The relationship between the two depends on the extent to which the activity of different neurons covaries. These covariations are typically quantified as neuronal correlations. When neural activity is uncorrelated, single cell variability can be averaged out and has no impact on the mean population activity [35]. Similar results hold for asynchronous networks which display correlations that, on average, decay inversely proportional to the network size [17•,36]. Using a normative approach, Boerlin and colleagues have recently shown that networks with qualitatively similar features can accurately represent multiple time-varying signals [37•]. In both types of networks [17•,37•], subtle negative correlations emerge which guarantee an accurate representation at the population level. Such weakly correlated network states are not only of theoretical interest, as several recent studies have shown

that local cortical circuits can operate in regimes where the population-averaged correlation is very low [17•,38–40].

The dynamics of recurrent networks with certain types of *structured* connectivity, however, can generate coordinated temporal fluctuations in the activity of populations of cells. For instance, sufficiently strong positive feedback can lead to the appearance of multiple stable states [41], but if the amount of positive feedback is weaker, such states become metastable, and neurons display coordinated transient fluctuations [42]. This type of collective variability is typical of large networks operating close to a 'critical point' [36,42], that is, a region of parameter space where a transition between qualitatively different dynamical regimes occurs. However, other mechanisms for generating such coordinated fluctuations are possible [43,44].

Importantly, the amount of collective variability generated by a local recurrent circuit can be modulated by external inputs. Sensory, or top-down inputs, such as attention, can increase the stability of a metastable activity pattern, thereby decreasing variability (see

Figure 2a,b). This provides an alternative explanation [31,42] for the decrease in variability observed at stimulus onset [13], and also for the seemingly contradictory effects of attention on neural variability [20,21,24] (Figure 2c).

More generally, if neural circuits live in this meta-stable regime, small external or internal signals can lead to transitions between population patterns that correspond to well-defined perceptual or cognitive states of the animal [45,46]. This property may have an adaptive role by enabling behavioral flexibility. Thus, signal amplification in circuits governed by transient collective dynamics might be important for understanding variability in behavior. Although this type of variability would mostly qualify as uncontrollable and irreducible, impending experimental techniques may improve the degree to which the underlying phenomena can be monitored.

## Neural versus behavioral variability: normative approaches

In the same way that the experimenter needs to determine which variables affect neural activity, neural circuits need to properly allocate responsibility to the diverse influences that can change their synaptic inputs. In solving this inference problem, the brain may use processing strategies that appear inefficient or suboptimal, as recently proposed by Beck and colleagues [47•]. Ideally, neural circuits should retain the relevant aspects of their complex and high-dimensional inputs (the 'signal') and filter out all irrelevant aspects (the 'noise'). However, the process of extracting the relevant information may allow some of the irrelevant input variability to leak into the circuit's output (Figure 3) and to potentially alter behavior [47•]. As a corollary, the neural variability that the experimenter measures might not be what actually constrains the accuracy of behavior.

In the random dot motion example we considered above, the variability present in the neural activity is reduced after the experimenter notices that MT neurons respond faithfully to microscopic patterns of motion [3], but such responses are still noise from the point of view of the task, and should be ignored. Similar arguments apply to the firing rate modulations of sensory neurons due to attention. Their behavioral impact will depend on whether downstream targets can assign responsibility to the appropriate causal influences.

What about the neural variability induced due to sensory-motor couplings? While the variability generated by such sensory-motor loops may pose a problem for experimenters, it is unlikely to have a large impact on the nervous system, as the motor and sensory components of

Figure 3
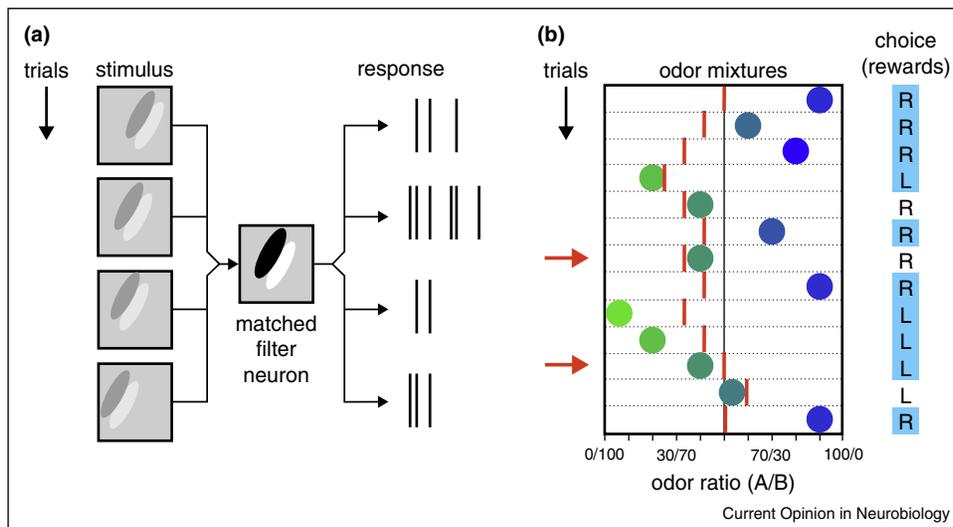
Variability in neural activity and behavior arising from suboptimal strategies. **(a)** If a neuron uses a matched-filter algorithm to identify the orientation of a visual stimulus, then its response will be highly sensitive to variations in the spatial location of the stimulus While visual neuroscientists are well aware of this problem, it serves to illustrate that uncontrolled parameters may affect the measured variability of neural activity. Neural systems themselves may suffer from similar problems if they fail to take such external noise into account, that is, if they use an incorrect inference algorithm to process the signal [47•]. (In this example, a correct inference algorithm would take shift-invariance into account.) **(b)** In an olfactory categorization task, the animal needs to determine which of two odors (A or B) dominates in a mixture of the two. Here the experimenter determines the category boundary (set at a ratio of 50:50 with respect to the physical odor concentrations), but this boundary is an unknown and hidden variable for the animal. Many aspects of the animal's behavior can be accounted for if one assumes that its internal estimate of the category boundary is constantly updated, depending on the choice and reward in the last trial [52•]. A consequence of this (suboptimal) behavioral strategy is that the animal's choices may be different in two identical trials (red arrows).

active sensing have evolved in parallel and are likely to behave as functional units.

Relevant or irrelevant aspects of the inputs can only be defined with respect to a particular goal. Thus, the optimal way to process the inputs requires knowledge of the contingencies that relate the input with an appropriate action. This is a problem particularly in studies of behavior in laboratory settings, in which task contingencies are set by the experimenter and can be quite unnatural and hence difficult to learn by the animal. In most perceptual decision-making tasks, variability in choice for difficult stimuli is assumed to be due to uncertainty about the stimulus, or 'noise' in the respective sensory system (see below). In agreement with this assumption, performance typically increases with stimulus sampling duration [48,49,50[••]] However, this speed-accuracy trade-off is not observed when rats perform an odor categorization task [51,52[•]]. Rather, behavioral variability in this task may arise from a constant updating of the (unknown) category boundary based on the outcome of previous trials [52[•],53]. Since the actual category boundary is fixed by the experimenter, this strategy is suboptimal. The constant adjustments of the category boundary then transforms variability in the random ordering of trials into variability of choice for a given stimulus (Figure 3b).

Why do animals behave 'suboptimally'? Survival requires organisms to deal with difficult inference problems. An animal's efficiency in solving these problems depends critically on the many constraints it faces. For highly restricted inference problems, one can often determine an optimal solution. Many behavioral tasks pose such restricted problems from the point of view of the experimenter. However, the animal faces a far broader inference problem, whose exact nature and constraints are mostly unknown. Its behavior (or neural activities) may seem suboptimal when compared against the idealized scenario, but a serious assessment of the animal's inefficiency is currently impossible.

Neural versus behavioral variability: mechanistic approaches

The relation between neural and behavioral variability was first quantitatively characterized in the context of the classical random dot motion discrimination task, with the remarkable observation that trial-to-trial fluctuations in the activity of single neurons in monkey area MT evoked by stimuli of the same coherence were correlated with behavioral choice [1], a tendency referred to as choice probability (CP). This relationship between neural variability and choice was formalized in the influential model of Shadlen and colleagues, sometimes called the standard model of perceptual decision-making [54,55[••],56]. Within this model, the decision variable is given by a linear weighting of the (stochastic) activity of pools of sensory

neurons and the choice is taken as the sign of the decision variable (Figure 4a).

Because choice in the model depends on pooling activity across sensory neurons, the relationship between neural and behavioral variability depends critically on neural correlations. Such 'noise' correlations are typically positive and moderate in size in primate visual cortex [57], and without them, one does not expect to see significant choice probabilities at all, unless decisions rely on only a handful of neurons [54,55[••],56]. Although CP was originally interpreted as measuring the causal involvement of a single neuron with choice, it was later pointed out that neurons can display significant CPs and have no causal influence on choices, as long as they are correlated with other neurons with significant CPs [56].

The precise relationship between the correlation structure of a neural population and set of population CPs under the standard model of decision making was recently elucidated by Haefner and colleagues [55[••]] (Figure 4a). The authors made the striking observation that the choice probability is simply given by the product of the neuron's noise covariance matrix with the neuron's read-out weights, that is, their eventual contribution to the decision variable. While this formula is difficult to test experimentally, since it requires measuring the activities of the complete sensory population, the brain's deviation from an optimal linear read-out model can be easily tested. Under the assumption of optimality, each neuron's CP value will reflect the ratio between the neuron's sensitivity (its 'neurometric threshold') and the overall sensitivity of the animal (its 'psychometric threshold') [55[••],58]. This relation is easily testable experimentally, which should help to elucidate to what extent the standard model with an optimal decision read-out is correct.

Because CP measures a correlation between neural variability and choice, it is possible that the causal link might be from the behavior to the neural activity and not the other way around, as is typically supposed. In a recent study, Nienborg and Cumming suggested that a large fraction of the measured CPs may have a top-down origin [59[••]]. The authors recorded neurons in area V2 of monkeys performing a depth discrimination task. Using psychophysical reverse correlation methods [60], they showed that, whereas the influence of the stimulus on choice declined throughout the trial (a result consistent with previous findings [61]), the correlation between neural variability and choice tended to grow and saturate. This pattern is difficult to reconcile with an exclusively sensory origin for the choice-related modulation, and instead suggests a top-down origin. Furthermore, the choice-related modulation was shown to act as a multiplicative gain on the neuron's tuning curves, suggesting that the top-down signal might be attentional in nature.

Figure 4
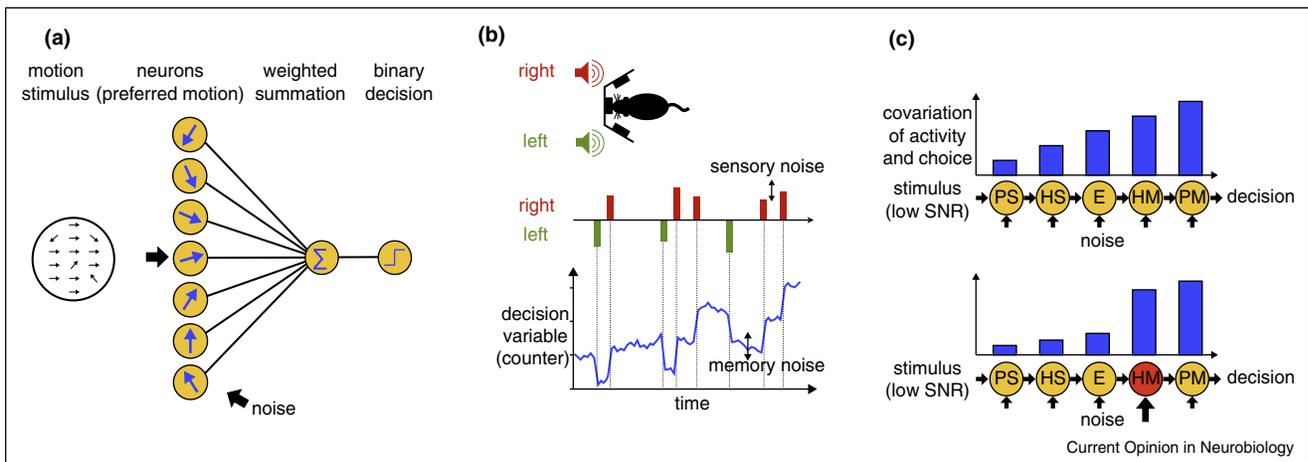
(a) The standard model of perceptual decision-making, based on a monkey that needs to discriminate the direction (left versus right) of a random dot motion pattern [54]. Sensory neurons in monkey area MT vote with their firing rates for the perceived direction of motion. Their responses are then weighted, summed, and passed through a binary decision function. Ideally, the weight of a neuron reflects how much information it conveys about the axis of left-right directions. In this model, behavioral variability mainly arises through noise introduced in the responses of the individual neurons. (b) An auditory version of the random dot motion discrimination task [50]. Here, a rat listens to two trains of click sounds, one coming from the right, one from the left, and has to determine which train contains more clicks. The authors consider a model in which a decision variable or counting process (lower panel) adds or subtracts the clicks arriving from the right or left (central panel). Here, noise can influence the final decision at two stages, both at the sensory stage, by varying the impact of each arriving click, and at the counting stage, by perturbing the decision variable. (c) In a less constrained model of the brain, we may presume that noise can be introduced at many stages of processing (PS, peripheral sensory area; HS, higher-order sensory area; E, executive area; HM, higher-order motor area; PM, peripheral motor area). If the stimulus is uninformative, that is, if the stimulus has a very low signal-to-noise ratio, then peripheral sensory areas are only weakly correlated with the decision, if at all, whereas motor areas will be highly correlated. If the same amount of noise is introduced in each area, then the covariation of activity and choice (or 'choice probability' in two-alternative-forced-choice tasks) will increase linearly from sensory to motor areas. If one of the areas involved has a strong amplifying effect, or if it adds a lot more noise into the processing, then it causes a strong jump in choice covariation. The respective area therefore has the strongest influence on the decision, and the sudden jump identifies it as the 'decision-maker' [63]. Here we only illustrate feedforward examples, but the framework can also be applied to systems with feedback.

Recent modeling work shows that bottom-up and top-down components of CP have different signatures at the level of the time-course of CP throughout the trial, a prediction that is consistent with CPs measured from monkey MT (de la Rocha, *et al.* (2012). *Soc. Neurosci. Abs.* 38, 175.11).

While previous models of behavior have usually relied on finding qualitative parallels with coarse aspects of behavior, Brunton and colleagues recently went the next step. Studying a perceptual decision-making task in which rats had to count sound pulses, they rigorously teased apart the relative contribution of different noise sources to behavior [50••]. The model that best fits the animal's choices had little noise in the memory of the counting process, but significant noise in each pulse's contribution to the running count, thereby suggesting a sensory origin for the observed variability (see Figure 4b). These results are in agreement with the observations of Osborne and colleagues, who studied structure of eye movement errors during a pursuit task, and similarly concluded that most of the behavioral variability has a sensory origin [62].

The more general problem of which noise sources primarily influence a decision was first investigated theoretically for several simplified network models by Koulakov *et al.* [63], focusing on decision-making in the absence of sensory information. The authors showed that the relative contribution of each brain area to a decision depends on how much noise each of the brain areas contributes (or amplifies), and how the respective areas are connected. Loosely speaking, the system that generates or amplifies variability the most, has the highest impact on decision-making (Figure 4c).

The functional roles of behavioral variability

Is variability a bug or a feature? Variability may be a feature if it provides adaptive benefits to the organism. A simple case of such adaptive benefits at the behavioral level is exploration. The need to explore new possibilities may benefit from a stochastic strategy. In the theory of reinforcement learning, for instance, the tradeoff between exploring something new or exploiting the already known is handled probabilistically [64,65]. Since all environments change over time, animals can rarely rely on a purely exploitative, and thereby deterministic, behavioral strategy.

Still, an optimal agent that runs through the same perceptual decision-making task day after day would

eventually learn that task contingencies do not change, and then switch to a deterministic strategy. However, animal behavior rarely becomes completely deterministic. One reason is that, although the task does not change, the animal's natural environment changes all the time, and the animal's behavioral strategies may be adapted to this environment. Another possible reason is that animals may rely on simple and less costly behavioral strategies. In fact, animals may use quick-and-dirty strategies to avoid excessive computational costs, which appear suboptimal at the level of the individual. Remarkably, such behavior might appear near optimal when behavioral measures are averaged across individuals [66].

While the benefits of behavioral variability are easy to point out, neural variability may seem like a bug. However, the need to perform probabilistic computations within the nervous system may similarly rely on strategies that require variability. Several studies suggest that the brain performs probabilistic computations. For instance, when integrating two cues, such as an auditory and a visual cue, the relative confidence of their values is taken into account [67]. Rats use estimates of their own confidence to decide on whether or not to wait for a reward [53]. How could such probabilistic computations be implemented at the neural level? Numerical algorithms often rely on random number generators, and several studies suggest that the brain may do the same, when performing probabilistic computations. One attractive proposal posits that neurons do not represent specific values of a given stimulus, but rather randomly switch between representing different stimulus values, so that the time they spend representing each value is proportional to the relative likelihood of that stimulus value [68,69]. This procedure corresponds to generating samples from a distribution, and can in principle be implemented in networks of integrate-and-fire neurons [70]. In turn, downstream networks can run their inference algorithms with those samples. Here, neural variability is a feature introduced to allow neural circuits to perform probabilistic computations, rather than a bug.

Neural and behavioral variability may also be beneficial to learning. In some bird species, young individuals learn a unique characteristic song through trial and error. This process is believed to be mediated by LMAN, a basal ganglia nucleus which actively produces motor variability, as shown by lesion studies [71]. LMAN's involvement in song production decreases as the animal completes learning of the song [72]. In humans, variability in movements can similarly facilitate the learning of motor patterns [73].

Conclusions

The relation between neural and behavioral variability is key to understanding how brains generate behavior. A lot of insight about this relation has been gained during the last decade, and yet it seems as if we merely scratched the surface. In any particular experiment, all of the effects mentioned above are likely to play a role, from uncontrolled environmental variables to noise generated within the nervous system, including contributions linked to specific processing strategies used by the animal.

We think that a deeper understanding of the relationship between neuronal and behavioral variability will require a significant effort to monitor in detail the environment and actions of behaving animals as well as the activity of very large numbers of neurons. We hypothesize that as these methods become established, the relationship between behavior and neural activity will become significantly more deterministic. An interesting challenge will be to establish what proportion of the remaining variability reflects the difficulty of finding efficient information processing strategies in complex environments and what portion is adaptive in nature and required for exploration and behavioral flexibility.

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest
•• of outstanding interest

1. Britten KH, Newsome WT, Shadlen MN, Celebrini S, Movshon JA: **A relationship between behavioral choice and the visual responses of neurons in macaque MT**. *Visual Neurosci* 1996, **13**:87-100.

2. Newsome WT, Britten KH, Movshon JA: **Neuronal correlates of a perceptual decision**. *Nature* 1989, **341**:52-54.

3. Bair W, Koch C: **Temporal precision of spike trains in extrastriate cortex of the behaving macaque monkey**. *Neural Comput* 1996, **8**:1185-1202.

4. Shusterman R, Smear MC, Koulakov AA, Rinberg D: **Precise olfactory responses tile the sniff cycle**. *Nat Neurosci* 2011, **14**:1039-1044.

5. Macrides F, Chorover SL: **Olfactory bulb units: activity correlated with inhalation cycles and odor quality**. *Science* 1972, **175**:84-87.

6. Niell CM, Stryker MP: **Modulation of visual responses by behavioral state in mouse visual cortex**. *Neuron* 2010, **65**:472-479.

7. Chiappe ME, Seelig JD, Reiser MB, Jayaraman V: **Walking modulates speed sensitivity in drosophila motion vision**. *Curr Biol* 2010, **20**:1470-1475.

8. Cowen S, McNaughton BL: **Selective delay activity in the medial prefrontal cortex of the rat: contribution of sensorimotor information and contingency**. *J Neurophysiol* 2007, **98**:303-316.

9. Bulmer MG, Howarth CI, Cane V, Gregory RL, Barlow HB: **Noise and the visual threshold**. *Nature* 1957, **180**:1403-1405.

10. Sugrue LP, Corrado GS, Newsome WT: **Matching behavior and the representation of value in the parietal cortex**. *Science* 2004, **304**:1782-1787.

11. Gold JI, Law CTT, Connolly P, Bennur S: **The relative influences of priors and sensory evidence on an oculomotor decision**

variable during perceptual learning. *J Neurophysiol* 2008, **100**:2653-2668.

12. Marcos E, Pani P, Brunamonti E, Deco G, Ferraina S, Verschure P: **Neural variability in premotor cortex is modulated by trial history and predicts behavioral performance**. *Neuron* 2013, **78**:249-255.

13. Churchland MM, Byron MY, Cunningham JP, Sugrue LP, Cohen MR, Corrado GS *et al.*: **Stimulus onset quenches neural variability: a widespread cortical phenomenon**. *Nat Neurosci* 2010, **13**:369-378.

14. Harris KD, Thiele A: **Cortical state and attention**. *Nat Rev Neurosci* 2011, **12**:509-523.

15. Goard M, Dan Y: **Basal forebrain activation enhances cortical coding of natural scenes**. *Nat Neurosci* 2009, **12**:1444-1449.

16. Marguet S, Harris KD: **State-dependent representation of amplitude-modulated noise stimuli in rat auditory cortex**. *J Neurosci* 2011, **31**:6414-6420.

17. Renart A, de la Rocha J, Bartho P, Hollender L, Parga N, Reyes A
• *et al.*: **The asynchronous state in cortical circuits**. *Science* 2010, **327**:587-590.
This study showed that recurrent networks with balanced excitation and inhibition typically display globally uncorrelated (asynchronous) activity despite large amounts of shared anatomical input. Also provides experimental evidence that cortical circuits can operate in states of negligible population-averaged pair-wise correlation.

18. Rutishauser U, Kotowicz A, Laurent G: **A method for closed-loop presentation of sensory stimuli conditional on the internal brain-state of awake animals**. *J Neurosci Methods* 2013, **215**:139-155.

19. Mitchell JF, Sundberg KA, Reynolds JH: **Differential attention-dependent response modulation across cell classes in macaque visual area v4**. *Neuron* 2007, **55**:131-141.

20. Mitchell JF, Sundberg KA, Reynolds JH: **Spatial attention decorrelates intrinsic activity fluctuations in macaque area v4**. *Neuron* 2009, **63**:879-888.

21. Cohen MR, Maunsell JH: **Attention improves performance primarily by reducing interneuronal correlations**. *Nat Neurosci* 2009, **12**:1594-1600.

22. Herrero J, Roberts M, Delicato L, Gieselmann M, Dayan P, Thiele A: **Acetylcholine contributes through muscarinic receptors to attentional modulation in v1**. *Nature* 2008, **454**:1110-1114.

23. Buffalo EA, Fries P, Landman R, Buschman TJ, Desimone R: **Laminar differences in gamma and alpha coherence in the ventral stream**. *Proc Natl Acad Sci U S A* 2011, **108**:11262-11267.

24. Roelfsema PR, Lamme VA, Spekreijse H: **Synchrony and covariation of firing rates in the primary visual cortex during contour grouping**. *Nat Neurosci* 2004, **7**:982-991.

25. Cohen MR, Maunsell JHR: **A neuronal population measure of attention predicts behavioral performance on individual trials**. *J Neurosci* 2010, **30**:15241-15253.

26. Briggman KL, Abarbanel HD, Kristan WB: **Optical imaging of neuronal populations during decision-making**. *Science* 2005, **307**:896-901.

27. Faisal AA, Selen LP, Wolpert DM: **Noise in the nervous system**. *Nat Rev Neurosci* 2008, **9**:292-303.

28. van Vreeswijk C, Sompolinsky H: **Chaos in neuronal networks with balanced excitatory and inhibitory activity**. *Science* 1996, **274**:1724-1726.

29. Monteforte M, Wolf F: **Dynamic flux tubes form reservoirs of stability in neuronal circuits**. *Phys Rev X* 2012, **2**:041007.

30. Sompolinsky H, Crisanti A, Sommers H: **Chaos in random neural networks**. *Phys Rev Lett* 1988, **61**:259-262.

31. Rajan K, Abbott LF, Sompolinsky H: **Stimulus-dependent suppression of chaos in recurrent neural networks**. *Phys Rev E* 2011, **82**:011903.

32. Brecht M, Schneider M, Sakmann B, Margrie TW: **Whisker movements evoked by stimulation of single pyramidal cells in rat motor cortex**. *Nature* 2004, **427**:704-710.

33. Yang Y, DeWeese MR, Otazu GH, Zador AM: **Millisecond-scale differences in neural activity in auditory cortex can drive decisions**. *Nat Neurosci* 2008, **11**:1262-1263.

34. London M, Roth A, Beeren L, Häusser M, Latham PE: **Sensitivity to perturbations in vivo implies high noise and suggests rate coding in cortex**. *Nature* 2010, **466**:123-127.

35. Zohary E, Shadlen MN, Newsome WT: **Correlated neuronal discharge rate and its implications for psychophysical performance**. *Nature* 1994, **370**:140-143.

36. Ginzburg I, Sompolinsky H: **Theory of correlations in stochastic neural networks**. *Phys Rev E* 1994, **50**:3171-3191.

37. Boerlin M, Machens CK, Denève S: **Predictive coding of
• dynamical variables in balanced spiking networks**. *PLoS Comput Biol* 2013, **9**:e1003258.
Normative formulation of recurrent spiking networks as optimal encoders of time-varying signals. This framework naturally leads to variability at the single cell level despite a very precise representation of the signal in the population activity.

38. Ecker AS, Berens P, Keliris GA, Bethge M, Logothetis NK, Tolias AS: **Decorrelated neuronal firing in cortical microcircuits**. *Science* 2010, **327**:584-587.

39. Gu Y, Liu S, Fetsch CR, Yang Y, Fok S, Sunkara A *et al.*: **Perceptual learning reduces interneuronal correlations in macaque visual cortex**. *Neuron* 2011, **71**:750-761.

40. Miura K, Mainen ZF, Uchida N: **Odor representations in olfactory cortex: distributed rate coding and decorrelated population activity**. *Neuron* 2012, **74**:1087-1098.

41. Amit DJ, Brunel N: **Model of global spontaneous activity and local structured activity during delay periods in the cerebral cortex**. *Cereb Cortex* 1997, **7**:237-252.

42. Litwin-Kumar A, Doiron B: **Slow dynamics and high variability in balanced cortical networks with clustered connections**. *Nat Neurosci* 2012, **15**:1498-1505.

43. Rabinovich M, Huerta R, Laurent G: **Transient dynamics for neural processing (Neuroscience)**. *Science* 2008, **321**:48-50.

44. Murphy BK, Miller KD: **Balanced amplification: a new mechanism of selective amplification of neural activity patterns**. *Neuron* 2009, **61**:635-648.

45. Miller P, Katz DB: **Stochastic transitions between neural states in taste processing and decision-making**. *J Neurosci* 2010, **30**:2559-2970.

46. Durstewitz D, Vittoz NM, Floresco SB, Seamans JK: **Abrupt transitions between prefrontal neural ensemble states accompany behavioral transitions during rule learning**. *Neuron* 2010, **66**:438-448.

47. Beck JM, Ma WJ, Pitkow X, Latham PE, Pouget A: **Not noisy, just
• wrong: the role of suboptimal inference in behavioral variability**. *Neuron* 2012, **74**:30-39.
Thought provoking study articulating the hypothesis that suboptimal processing strategies by the nervous system might generate a significant fraction of the observed behavioral variability.

48. Burr DC, Santoro L: **Temporal integration of optic flow, measured by contrast and coherence thresholds**. *Vision Res* 2001, **41**:1891-1899.

49. Kiani R, Shadlen MN: **Representation of confidence associated with a decision by neurons in the parietal cortex**. *Science* 2009, **324**:759-764.

50. Brunton BW, Botvinick MM, Brody CD: **Rats and humans can
•• optimally accumulate evidence for decision-making**. *Science* 2013, **340**:95-98.
Powerful modeling approach for the dissection of different sources of variability in behavior. Suggests that rats are capable of accurately accumulating sensory evidence for hundreds of milliseconds.

51. Uchida N, Mainen ZF: **Speed and accuracy of olfactory discrimination in the rat**. *Nat Neurosci* 2003, **6**:1224-1229.

52. Zariwala HA, Kepecs A, Uchida N, Hirokawa J, Mainen ZF: **The limits of deliberation in a perceptual decision task**. *Neuron* 2013, **78**:339-351.
•
Thorough behavioral analysis of the possible causes for the lack of a speed-accuracy trade-off in an odor mixture discrimination task in rats. Evidence is consistent with behavioral variability not being significantly constrained by sensory noise.

53. Kepecs A, Uchida N, Zariwala HA, Mainen ZF: **Neural correlates, computation and behavioural impact of decision confidence**. *Nature* 2008, **455**:227-231.

54. Shadlen MN, Britten KH, Newsome WT, Movshon JA: **A computational analysis of the relationship between neuronal and behavioral responses to visual motion**. *J Neurosci* 1996, **16**:1486-1510.

55. Haefner RM, Gerwinn S, Macke JH, Bethge M: **Inferring decoding strategies from choice probabilities in the presence of correlated variability**. *Nat Neurosci* 2013, **16**:235-242.
••
Theoretical study which reveals the relationship between choice probability and noise correlations in the standard pooling model of decision making (ref. [62]). As such, it clarifies the extent to which choice probability can be used to measure the contribution of particular single neurons to behavioral decisions.

56. Nienborg HR, Cohen M, Cumming BG: **Decision-related activity in sensory neurons: correlations among neurons and with behavior**. *Annu Rev Neurosci* 2012, **35**:463-483.

57. Cohen MR, Kohn A: **Measuring and interpreting neuronal correlations**. *Nat Neurosci* 2011, **14**:811-819.

58. Wohrer A, Machens CK: **Percept and the single neuron**. *Nat Neurosci* 2013, **16**:112-113.

59. Nienborg H, Cumming BG: **Decision-related activity in sensory neurons reflects more than a neuron's causal effect**. *Nature* 2009, **459**:89-92.
••
The first study to provide solid evidence against the hypothesis that variability in sensory neurons plays a causal role on choice variability, and in favor of a top-down origin for choice probability.

60. Neri P, Levi DM: **Receptive versus perceptive fields from the reverse-correlation viewpoint**. *Vision Res* 2006, **46**:2465-2474.

61. Kiani R, Hanks TD, Shadlen MN: **Bounded integration in parietal cortex underlies decisions even when viewing duration is dictated by the environment**. *J Neurosci* 2008, **28**:3017-3029.

62. Osborne LC, Lisberger SG, Bialek W: **A sensory source for motor variation**. *Nature* 2005, **437**:412-416.

63. Koulakov AA, Rinberg DA, Tsigankov DN: **How to find decision makers in neural networks**. *Biol Cybern* 2005, **93**:447-462.

64. Sutton RS, Barto AG: *Reinforcement Learning: An Introduction*. Cambridge University Press; 1998.

65. Dayan P, Niv Y: **Reinforcement learning: the good, the bad and the ugly**. *Curr Opin Neurobiol* 2008, **18**:185-196.

66. Daw N, Courville A: **The pigeon as particle filter**. *Adv Neural Inf Process Syst* 2008, **20**:369-376.

67. Ernst MO, Banks MS: **Humans integrate visual and haptic information in a statistically optimal fashion**. *Nature* 2002, **415**:429-433.

68. Hoyer PO, Hyvarinen A: **Interpreting neural response variability as Monte Carlo sampling of the posterior**. *Adv Neural Inf Process Syst* 2003:293-300.

69. Fiser J, Berkes P, Orbán G, Lengyel M: **Statistically optimal perception and learning: from behavior to neural representations**. *Trends Cognit Sci* 2010, **14**:119-130.

70. Moreno-Bote R, Knill DC, Pouget A: **Bayesian sampling in visual perception**. *Proc Natl Acad Sci U S A* 2011, **108**:12491-12496.

71. Ölveczky BP, Andalman AS, Fee MS: **Vocal experimentation in the juvenile songbird requires a basal ganglia circuit**. *PLoS Biol* 2005, **3**:e153.

72. Ölveczky BP, Otchy TM, Goldberg JH, Aronov D, Fee MS: **Changes in the neural control of a complex motor sequence during learning**. *J Neurophysiol* 2011, **106**:386-397.

73. Wu HG, Miyamoto YR, Castro LNG, Ölveczky BP, Smith MA: **Temporal structure of motor variability is dynamically regulated and predicts motor learning ability**. *Nat Neurosci* 2014, **17**:312-321.