OPINION

The benefits of noise in neural systems: bridging theory and experiment

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Abstract | Although typically assumed to degrade performance, random fluctuations, or noise, can sometimes improve information processing in non-linear systems. One such form of 'stochastic facilitation', stochastic resonance, has been observed to enhance processing both in theoretical models of neural systems and in experimental neuroscience. However, the two approaches have yet to be fully reconciled. Understanding the diverse roles of noise in neural computation will require the design of experiments based on new theory and models, into which biologically appropriate experimental detail feeds back at various levels of abstraction.

There is substantially increased interest in the sources and impact of stochastic biological noise in the nervous system, stemming both from new experimental methods for identifying it and from a growing body of modelling work demonstrating its functional consequences. Recent reviews have defined noise in terms of variability that results from "random or unpredictable fluctuations and disturbances"[1], and they describe stochastic resonance as one example of the potential benefits of noise[1,2]. Here, we take a closer look at the divergence between experimental and theoretical approaches to studying stochastic resonance. We propose a unifying framework that reconciles these two approaches and advocate the use of the term 'stochastic facilitation' to describe all biologically relevant noise benefits in the nervous system, including stochastic resonance.

The term 'stochastic resonance' was introduced in the early 1980s in the statistical physics community[3–5]. Within this field, the term has a very specific definition — in this article it is referred to as classical stochastic resonance. In this paradigm, the presence of a weak periodic input to a non-linear dynamical system cannot be inferred from the response of the system in the absence of noise (FIG. 1a). Classical stochastic resonance is observed when the presence of additive noise allows the input signal to be detected based on a calculation of the output signal-to-noise ratio from the spectral content (power spectral density) of the response. Typically, the signal-to-noise ratio exhibits a single peak as the power of the noise is varied. By the mid 1990s, however, the concept had spread to many other scientific fields and the definition had broadened considerably[6].

The last decade has seen a growing body of experimental and biologically detailed modelling work on stochastic resonance in the neurosciences[7–15], but we are of the opinion that because these approaches typically focus on classical stochastic resonance, they have not yet been fully reconciled with advances in theoretical work. Increased understanding of the functional roles of noise in *in vivo* neural information processing will require new experiments to be developed in close conjunction with new theoretical approaches. Although these new approaches should be liberated from the classical description of stochastic resonance, it is important that they are constrained by biologically appropriate modelling.

Theoretical work on stochastic resonance, whether classical or otherwise, has rarely diverged from the statistical physics discourse[3–6,16–20]. As a result, an abstract model is chosen and stochastic resonance is said to be observed with respect to an output of the model if its statistical signal processing performance improves according to an arbitrary metric as various levels of stochastic noise are added[6]. This approach tends to neglect the biological appropriateness of key factors such as the signal, the noise, the model and the neural processing role of the system. The characteristics of the system's processing[21–23] (for example, encoding, transforming, feedback inhibition, coincidence detection and gain control) should inform the choice of models and metrics to help to ensure that any theoretical enhancement of performance does convey true benefits in biological terms.

Systemic failure to consider biological appropriateness and broader definitions of stochastic resonance highlights the importance of two-way dialogue between theoreticians and experimentalists. Stochastic noise is ubiquitous in neural systems[1,2,24] and its potential roles in facilitating information processing deserve greater attention.

For progress to be achieved in this field, however, the dichotomous approaches of researchers with different backgrounds must be reconciled using a common approach. One obstacle has been historical semantic baggage, and we believe it is timely to advocate using a new term, stochastic facilitation (FIG. 1b), as a descriptor for all research into the constructive roles of biologically relevant noise in the nervous system, including stochastic resonance — see below and FIG. 2.

We also propose a unified framework for studying stochastic facilitation in future experimental and modelling approaches. This framework emphasizes the importance of beginning every study with a concrete

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and precise hypothesis regarding the computational role of a specific neural system, thus encouraging divergence from classical stochastic resonance and simultaneously embracing biological appropriateness. We anticipate that an increased intersection between theoretical ideas and experimental approaches will lead to substantial progress in understanding the constructive roles of stochastic noise in the brain.

Why 'stochastic facilitation'?

There are several reasons why we advocate the term stochastic facilitation. First, the term stochastic resonance is problematic in several ways. Pinpointing which phenomena

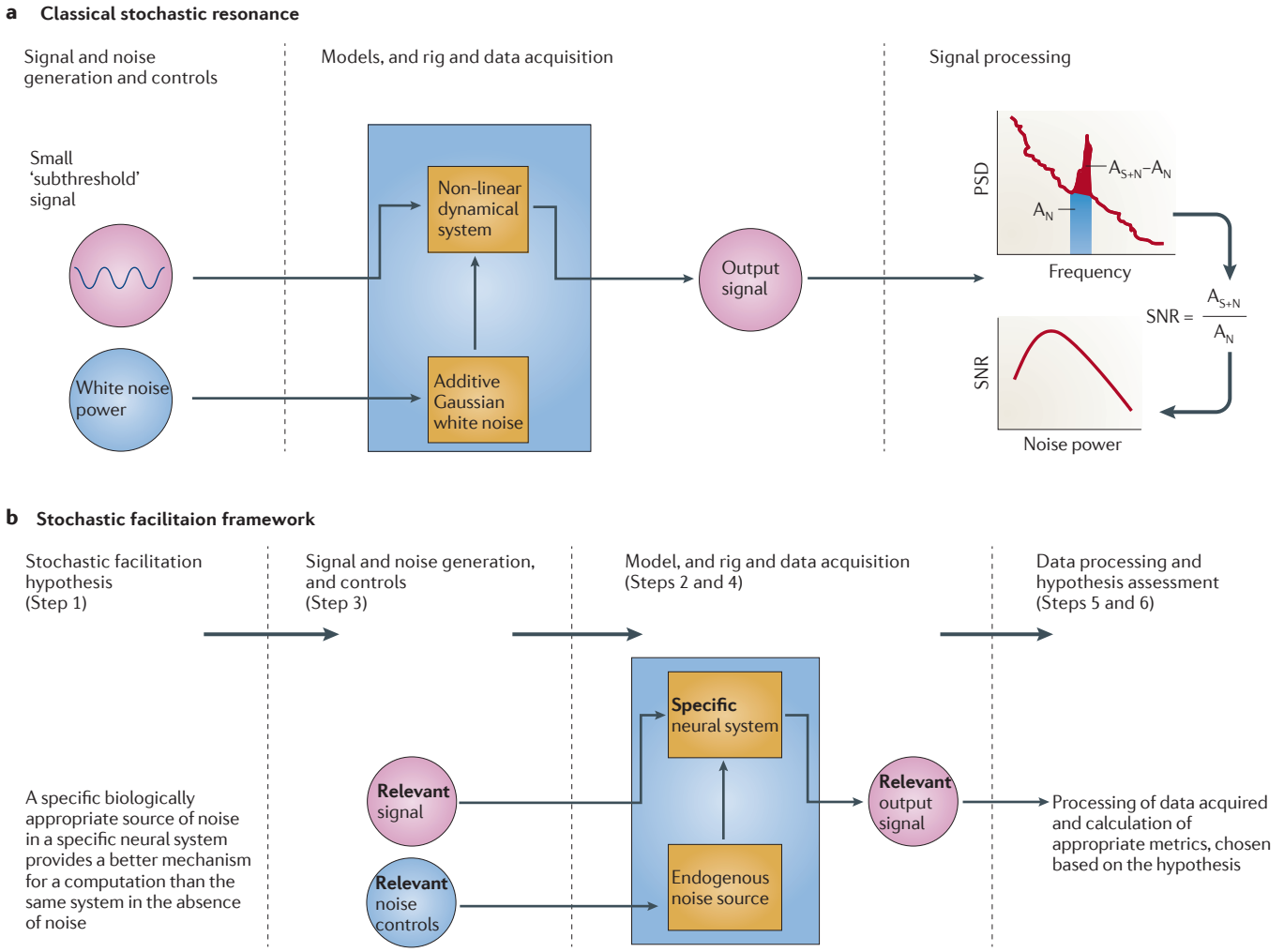

Figure 1 | **Classical Stochastic resonance versus stochastic facilitation. a** | The necessary conditions for classical stochastic resonance[5]. A weak periodic signal is assumed to be an input to a non-linear dynamical system, such that its presence cannot be inferred from the response of the system in the absence of noise. In many cases, the signal is labelled as 'subthreshold'. Classical stochastic resonance is said to be observed when noise allows the input signal to be detected statistically, with the quality of that detection measured by output signal-to-noise ratio (SNR), based on the spectral content (power spectral density (PSD)) of the response[4]. Typically, the SNR exhibits a single peak as the power of the noise is varied. Non-classical variations of stochastic resonance have discarded the requirements of periodic signals and SNR[6], and weak subthreshold signals have been shown to be unnecessary for a simple network of neurons[8,9]. **b** | A six-step scheme for studying stochastic facilitation in neural systems. First, a hypothesis concerning the positive role of stochastic biological noise in facilitating signal processing or a computational task of a specified neural system is stated (step 1). Next, a neural preparation — or mathematical or computational model — that can be stimulated by inputs relevant to the hypothesis and produce output responses that can be measured is specified (step 2). Then hypothesis-relevant input signals (if necessary for the hypothesis) and noise that can be generated and introduced into, or deleted from, the experimental material or model are chosen (step 3). Once the input signals and noise (or its suppression) that are selected in step 3 are introduced into the experimental rig or simulation of the model, the relevant output data are acquired (step 4) and processed (step 5). Finally, the hypothesis from step 1 is assessed based on step 5 (step 6). In many past studies of neural-system stochastic resonance, these steps have been followed in a different sequence. Typically, the neural system was chosen for study and performance was measured by output SNR, as a function of noise power — which requires the signal to be periodic. Often the output was defined solely in terms of the times of action potentials, and the SNR was based on the output PSD of the resulting stochastic point process. Rather than first stating a hypothesis regarding a computational role, the choice of SNR as a metric imposed an implied hypothesis; that the computational role of the neural system is to produce a sequence of action potentials when a sinusoidal input current at a specific frequency is introduced into the system and to produce a statistically distinct pattern of action potentials when it is absent. Moreover, the full computation, which is to determine if the noisy periodic signal is present, cannot be completed by the neural system. In the approach we advocate, the hypothesis of step 1 should instead be stated first and investigated using only relevant, biologically appropriate signals and metrics.

should be labelled as stochastic resonance is not trivial because of the multiple evolving definitions in theoretical work[6]. Moreover, the word resonance is misleading, because in its broad sense, stochastic resonance describes a noise-induced peak in performance that may have nothing to do with frequency resonance[6]. The term stochastic facilitation would remove this confusion and yet is sufficiently general to encompass all previous definitions of stochastic resonance and its qualitative essence.

Notwithstanding the above semantic issues, stochastic resonance stands apart from other identified constructive roles for noise in that all existing definitions require identification of an input signal and an output signal[6]. This immediately associates the concept with notions of information processing and computation, as in engineered signal processing systems. Consequently, stochastic resonance is often described as paradoxical or counter-intuitive, because in engineered electronic systems noise is naturally seen to be only detrimental to quality. However, in a biological context, the effect is hardly counter-intuitive when thought of as the benefits of randomness, as with other constructive roles of noise in which inputs and outputs need not be readily identifiable[6]. As depicted in FIG. 2, the term stochastic facilitation encompasses all constructive roles for noise, including stochastic resonance, and would no longer be associated with any paradoxes.

The most interesting unresolved scientific questions about stochastic facilitation are those concerning whether, or when, biologically relevant noise is exploited to benefit neural systems, and if so, precisely how this occurs. Classical stochastic resonance tends to focus on signal detection, but more broadly, stochastic resonance is concerned with signal processing. With regard to the more general concept of stochastic facilitation, however, there are many possible choices for a computation that might be relevant to a neural system, and that do not necessarily require identification of an input signal or an output signal[25].

Nonetheless, in this article we devote our attention to stochastic resonance as a special case of stochastic facilitation in neural systems, in which input–output information processing is facilitated by random variability that originates from biological noise, although we acknowledge that randomness can, and does, play a facilitative part in many other areas of biology, such as foraging, evolution and learning. We do this to highlight that although stochastic resonance has

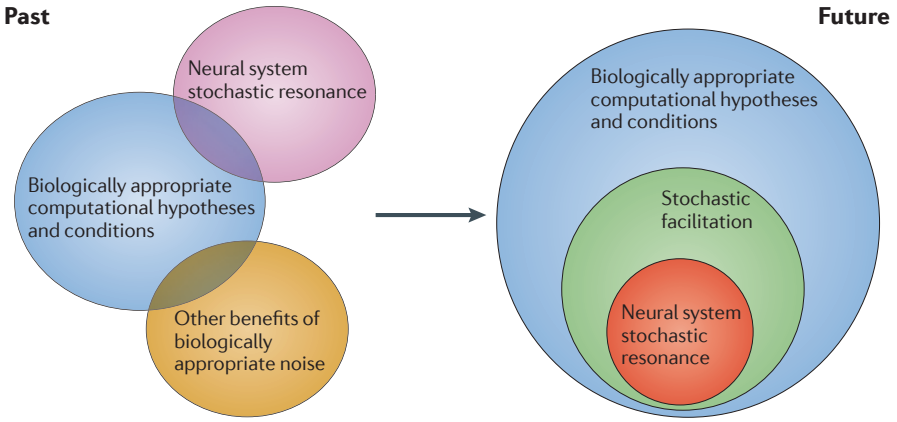

Figure 2 | **The future of stochastic facilitation research.** In the past, most research on stochastic resonance in neural systems has been at odds with biologically appropriate hypotheses and conditions such as the input signal and noise. Stochastic resonance has also been considered in isolation from other benefits of randomness that do not exhibit input–output processing. Our proposed definition of stochastic facilitation and unified framework would encompass stochastic resonance as a subset of all possible constructive roles for biologically appropriate noise in neuroscience, and all such research would be based on biologically appropriate computational hypotheses and conditions.

been reported in neurobiological experiments[8–12,14,15,26–49] (TABLE 1; see supplementary information S1 (table)) and models (TABLE 1 ; see supplementary information S2 (table)), these studies have rarely embraced the much richer set of conditions that are allowed by broader theoretical definitions in combination with biologically appropriate hypotheses, thus precluding the cross-application of ideas and tools.

The need for computational hypotheses

Observation of stochastic facilitation in neural function first requires the identification of a constructive computational role for endogenous biological noise. One goal of computational neuroscience is to determine the information processing properties of the nervous system[50–55]. Typical approaches describe functional and biologically realistic neurons (and neural systems) and generate formal models that capture the essential features of a biological system at multiple spatial and temporal scales. These computational models are used to frame hypotheses that can be directly tested by biological and/or psychological experiments.

The findings from classical stochastic resonance cannot be reconciled easily with this definition of computational neuroscience. Experiments have often involved adding exogenous noise to neural systems, rather than aiming to control or reduce endogenous noise. Observed improvements in performance due to exogenous noise do not provide evidence for *in vivo* stochastic facilitation. Many modelling studies have been published in the physics literature, as their purpose was to establish underlying principles, not to model specific existing systems. Often, the neural models that were used were not biologically appropriate in terms of their physiology as the focus was often on simplified models for which mathematical tractability was potentially feasible, thus allowing verification or prediction of simulation results. This has meant that aspects such as multiple-scales, neuron topology and geometry, the role of protein and chemical coupling, and network architecture have been largely excluded from study, as mathematical tractability is unlikely in these contexts. Although model simplification aids the examination of general hypotheses, the specification of a hypothesis and an associated conceptual model should ideally precede simplification of a mathematical or computational model[56].

Crucially, because classical stochastic resonance mandates that performance must be measured using output signal-to-noise ratio, the question of a neural system's function in the context of a framed hypothesis and an associated conceptual model concerning the nature of the computation, are aspects that have been conspicuously underdeveloped. Over 30 years ago, Marr and Poggio argued that computation in complex systems, such as the brain, must be understood at different levels of description[50,57] — namely, the nature of a computation, algorithms and representations for performing the computation, and physical mechanisms that implement algorithms.

The problem with defining stochastic resonance in terms of signal-to-noise ratio is that this implies the nature of the computation — that a neural system encodes a periodic signal's frequency in such a manner that spectral analysis is required to detect the presence of this frequency (FIG. 1a). This computation cannot, however, be fully implemented by the neural system, as its physical output does not represent the result of the computation. Additional mechanisms are required to achieve the computation by processing the neural output.

Our definition of stochastic facilitation allows for arbitrary computational

Table 1 | **Representative experimental and modelling studies of stochastic resonance (in chronological order)**

Approach	System, or level of organization	Technique, or level of detail *	Signal and noise	Result‡	Function *in vivo* or proposed computation	Ref
Experimental studies	Shark multimodal sensory cell	Extracellular recording	Ramped temperature, and electrical current changes and intrinsic noise in neurons	Information-transmitting spikes generated, allowing dual coding of temperature and electrical fields	Water temperature and depth sensing, and prey detection	28
	Cricket cercal receptor — innervating interneurons	Intracellular recording	23-Hz sinusoidal and 5–400-Hz broadband modulation of air current, and 5–400-Hz white noise-modulated air currents	SNR (23-Hz signal) and mutual information (broadband signal) enhanced by noise	Predator avoidance	29
	Human muscle spindle afferents in arm	Extracellular recording	0.5-Hz sinusoidal rotation of arm and random stretching of tendon	SNR of afferent firing at signal frequency enhanced by noise	Movement sensation	30
	Whole human brain	EEG	5-dB sensation level, 1000-Hz and 500-Hz pure tones and broadband acoustic noise	Neural synchrony within (40-Hz transient response) and between (θ, α and γ frequency bands) brain regions enhanced by noise	Auditory processing	49
Modelling studies	Neuron	Single compartment	Sinusoidal signal and Ornstein–Uhlenbeck noise process	Interspike interval histogram at period of forcing enhanced by noise	Transmit frequency of input signal	90
	Molecules	Not applicable	Periodic signal and white noise	SNR maximized by noise	Ion channel signal transduction	80
	Network	Single compartment	Aperiodic random signal and Ornstein–Uhlenbeck δ-correlated noise	Aperiodic stochastic resonance demonstrated by calculation of input–output correlation coefficient	Sensory neuron encoding of input signal in spike train	91
	Neuron	Detailed compartmental	Simulated synaptic release for both signal (simultaneous) and noise (correlated)	SNR, interspike interval histogram and spectral power amplification enhanced by noise	Response to synaptic input events	7
	Network	Single compartment	Periodic pulse train signal and irregular spikes from CA3 neuron models	SNR of CA1 neurons enhanced by noise; stochastic resonance in CA1 neurons used to recall encoded pattern	Memory recall in hippocampus	88
	Molecule and neuron	Single compartment	Aperiodic random signal and a stochastic ion channel noise source	Calculations of mutual information exhibited suprathreshold stochastic resonance	Estimation of a graded signal	92,93
	Neuron	Single compartment	20-Hz sinusoid; white noise	Noise enables phasic neurons to respond to low frequency inputs	Encode the instantaneous slope of an analogue input current into a spike rate	14

EEG, electroencephalography; SNR, signal-to-noise ratio. *'Level of detail' refers to models of individual neurons, or neurons within networks. ‡'Noise' in the Result column of this table refers to a non-zero but intermediate level of added or endogenous noise.

hypotheses, but these would usually be targeted at the level of physical mechanisms. It is likely that observations of stochastic facilitation in the brain can be explained in terms of the randomness arising from stochastic biological noise enabling the operation of a mechanism that implements a computational task. Clearly, there could be a diverse range of neural mechanisms in which this dependence of 'algorithm implementation' on noise could occur.

One example is that subthreshold membrane potential oscillations, whose frequency varies with water temperature in shark multimodal sensory cells, trigger spikes that transmit this information to the shark's brain only in the presence of noise[28]. Thus, the shark's algorithm for detecting rates of temperature change, based on the relationship between subthreshold oscillations and temperature, requires noise for its implementation. A second example, in the broader sense of stochastic resonance, is that repetitive spiking in models of single neurons driven just above their spiking-threshold input current can be inhibited by the presence of noise, as shown by a series of theoretical studies[58,59]. This effect was dubbed 'inverse stochastic resonance'[60]. If it could be shown *in vivo* that the removal of biologically relevant noise diminishes inhibition of spiking under these conditions, it could provide evidence that a computation requiring such inhibition utilizes noise for its implementation.

By contrast, stochastic facilitation is not best associated with the algorithmic level of description, except when the randomness inherent in noise potentially has a necessary role, which could occur when the nature of a computation involves assessing probabilities[61] or when an algorithm requires a randomization step, such as in foraging behaviour.

The principle underpinning our proposed unified framework is that studies of stochastic facilitation should begin with an explicit computational hypothesis. Given that a large proportion of prior work on stochastic resonance focuses on single neurons, this means attributing some well-defined notion of computation to a single neuron. Although individual neurons or isolated networks are frequently treated as input–output devices in experiments and simulations, and many computational roles can be suggested based on observed dynamics in this context[22,53], it is often unclear whether such roles can be directly related to integrative brain functions like behaviour, memory and cognition.

Nevertheless, we place a deliberate emphasis on the necessity for a computational hypothesis to be stated when studying stochastic facilitation, whether or not there is evidence supporting that hypothesis, because this is still indicative of progress beyond classical stochastic resonance.

Hypotheses regarding stochastic facilitation need not be associated only with computation in single neurons — however computation might be defined — but can be observed across many levels of organization. As highlighted by Churchland and Sejnowski, there is a hierarchy of structural levels of organization[62], each with a characteristic spatial size scale: central nervous system (1 m), systems (10 cm), maps (1 cm), networks (1 mm), neurons (100 μm), synapses (1 μm), and molecules (1 Å–100 nm). They point out that because there is organized structure at each level, there are many levels at which computational algorithms are implemented by neural mechanisms[62]. We now provide an overview of existing evidence for stochastic facilitation in neurobiology that has been labelled as stochastic resonance, with an emphasis on studies that provide evidence for the breadth in levels of organization.

Stochastic resonance in neural systems

Evidence from experiments. The experimental evidence for stochastic resonance in neural systems is diverse, although there are relatively few publications compared with the number of publications from modelling work. A wide range of neural systems has been studied at a wide range of size scales, from complete organisms (crayfish, paddlefish and humans) to slice preparations, and covering a wide range of *in vivo* functions, from sensory reception to memory (TABLE 1; supplementary information S1 (table)). Signals have typically been comprised of artificial sinusoids and noise has usually been comprised of random modulations, of the same stimulus dimension as the signal. Data collection techniques have been more uniform, mostly extracellular recordings for non-humans and electronencephalography (EEG) and magnetoencephalography (MEG) for humans. Many studies describe the effects of noise on signal-to-noise ratio at the signal frequency (classical stochastic resonance) or the correlation of neural output with input, although some more interesting measures have also been used, such as coherence or synchronization, vowel coding, reflex output, heart rate and neural entrainment, and evoked potentials, which are more closely related to the putative function of the system studied. Researchers have often tried to simulate natural signals such as water movements, air currents or electric fields generated by predators or prey, limb movements, sounds, lights or touches. Often, the human studies have used simple stimuli, such as modulated lights, sounds or touches, whose processing is well understood in other experimental contexts (see BOX 1 for a more detailed description of two representative experimental studies at very different levels of organization).

Box 1 | Examples of experimental evidence of stochastic resonance

One early experiment[29] demonstrated stochastic resonance in the cricket cercal system, which detects changes in air currents caused by predators or conspecifics. Intracellular recordings were made from single afferent nerve fibres from interneurons connected to the cercal receptors. The receptors were stimulated with naturalistic air currents that were modulated either at a single frequency or at multiple frequencies in the range of those caused by predator attack, and with noisy (broadband) air currents as would occur in a natural environment. Fourier analysis was used to extract the signal-to-noise ratio from the spike train, and information transmission between the stimulus and the spike train was computed for broadband signals. Both the signal-to-noise ratio and mutual information showed a maximum at intermediate (non-zero) levels of the added noise, with the former indicating classical stochastic resonance and the latter indicating stochastic resonance in the broad sense.

More recently, stochastic resonance-modulated synchronization in the human brain was described based on an electroencephalography (EEG) experiment[49]. EEG detects synchronized neural oscillations and synchronization in neural models is enhanced by low levels of added noise. Thus, it was proposed that acoustic noise would enhance the 40-Hz transient auditory response and also the consequent interactions between brain regions. In the experiment, subjects detected occasional intensity deviants in a stream of near-threshold pure tones. Broadband acoustic noise was added to the stimuli in the left ear but not to those in the right ear. Independent component analysis was used to identify independent signals localized to specific brain regions, and wavelet analysis was used to extract the amplitude and phase of the signals in specific frequency bands. Synchronization within brain regions (40-Hz response) and between brain regions (in θ, α and γ bands) was enhanced by an intermediate (non-zero) level of added noise. This happened for both the noise added to the stimuli (left ear) and for the noise and stimuli combined in the brain (right ear)[42,45].

Box 2 | **Examples of models that exhibit stochastic resonance**

A canonical example of classical stochastic resonance is its occurrence in the output signal-to-noise ratio estimated from simulations of the Fitzhugh–Nagumo neuron model when stimulated by a small sinusoidal current whose amplitude is corrupted by a wide-band random noise current[84]. The Fitzhugh–Nagumo model[85–87] simplifies the Hodgkin–Huxley model: one differential equation models the evolution of the membrane potential, including any action potentials, and the second replaces all the gating equations. Stochastic resonance was demonstrated in the model by numerically solving the equations and estimating the power spectral density of the resulting action potential timings for a range of values of input noise power[84]. The resultant plot of signal-to-noise ratio versus noise power displayed a characteristic stochastic resonance curve, with a peak signal-to-noise ratio at a non-zero noise power. The (implied) computational hypothesis in any study of this type is that the computational role of the neuron being modelled is to produce a sequence of action potentials when a sinusoidal input current at a specific frequency excites the cell, such that the power spectral density at the signal frequency in the spike sequence is greater than that at non-signal frequencies or that at the signal frequency in the absence of a signal. The spectral processing part of the computation cannot be completed in the neural system itself.

Classical stochastic resonance has been demonstrated in a much more detailed Level I[22] compartmental model of neocortical pyramidal neurons in layer VI of cat cortex[7]. Signal and noise were introduced through currents generated by realistically spatially distributed AMPA synapses (>16,000) and GABA synapses (>3,300). Synaptic background activity, based on intracellular recordings and modelled by independent Poisson synaptic release, comprised the noise, and a simultaneous release every 100 ms from additional AMPA dendritic synapses comprised the signal (similar to a 10-Hz sinusoid). In addition to classical stochastic resonance, the detail of the model that was used allows for a wide variety of additional computational hypotheses, with the concomitant possibility of unexpected stochastic facilitation. For example, layer IV neurons project to the thalamus, and it is possible that synchronization between them and thalamic neurons could be increased by the synaptic background activity, in turn increasing information transmission between cortex and thalamus.

Recently, stochastic resonance has been contrasted in tonic and phasic neuron models[14]. Realistic single compartment neuron models were designed to mimic real auditory brainstem neurons. Uniquely, this study described specific and different signal encoding roles for phasic (bandpass filtering) versus tonic (frequency encoding) neurons, with a concomitant difference in the form of stochastic resonance they exhibited: classical stochastic resonance in tonic neurons and 'slope-based' stochastic resonance in phasic neurons. Slope-based stochastic resonance refers to the noise-enhanced ability of phasic neurons to encode input signals with an intensity slope below their usual slope threshold. It would now be important to demonstrate slope-based stochastic resonance in auditory brainstem neurons.

Lastly, a biologically realistic example of neural network stochastic resonance was described in a model of a hippocampal system responsible for memory encoding and recall[88]. Single compartment models of hippocampal CA1 pyramidal neurons received weak afferent input from entorhinal perforant path fibres and noisy afferent input from similar models of numerous CA3 pyramidal neurons. Network stochastic resonance was demonstrated in that the output signal-to-noise ratio of the CA1 neurons to weak sinusoidal input was maximized for an intermediate CA3–CA1 synaptic strength, indicating an intermediate level of CA3-induced noisy membrane fluctuations in the CA1 neurons. The distribution of CA3–CA1 synaptic strengths can encode patterns in memory, and thus the resulting stochastic resonance effect can be exploited to implement memory recall.

Biologically realistic and unrealistic models. Whereas models of individual neurons (and neuronal networks) vary vastly in their balance between abstraction and details, the entire spectrum can lead to important new insights into computation[22]. Five levels of abstraction detail have been identified for single neurons[22] — detailed compartmental, reduced compartmental, single compartment or point neuron, cascade and black box. Stochastic resonance has been observed in numerous theoretical studies of single-neuron models across all of these levels (TABLE 1; supplementary information S2 (table)). It is therefore clear that the stochastic resonance phenomenon should not be associated with a particular level of model detail (see BOX 2 for examples of modelling work in both neuron and network level models).

The classical definition of stochastic resonance specifies that an input signal to a system must be periodic and that the system's performance should be measured by output signal-to-noise ratio, whereas the evolution in the definition of stochastic resonance used non-periodic (aperiodic) signals[29,31,63] and measures other than signal-to-noise ratio, both experimentally and in models (TABLE 1; supplementary information S2 (table)). In many cases however, the choice of signal was the primary concern, and performance metrics were chosen based on this. In some cases, simple hypotheses were stated, such as that neurons are channels that should communicate input spike trains, in the sense that a spike train that arrives at a neuron should be reproduced precisely by the neuron's own spikes[64]. This is not realistic, in that neurons do not simply relay spikes from one point to another. Indeed, they perform a substantial amount of computational integration in their dendrites, typically integrating inputs from thousands of other neurons in producing their own spike train. Moreover, they are influenced by slow extracellular currents and often participate in many interleaved neural circuits. Lastly, electrical fields that are generated by ion flow within and around neurons can affect other nearby neurons directly[65].

Based on what has been achieved to date, we believe there is considerable scope for new biologically appropriate hypotheses to be investigated in conjunction with biologically appropriate models of neural systems and noise sources.

The future of stochastic facilitation research

Building realistic models with realistic noise. There are many different sources of stochastic biological noise in the CNS[1,24] (TABLE 2), but there have not been exhaustive studies of all possible sources with respect to stochastic facilitation. Although some of the sources listed in TABLE 2, such as network connectivity and synaptic barrages, might be argued to be not necessarily stochastic, they certainly can be modelled as stochastic variables in the context of their impact on specific computational mechanisms. Clearly not all variability is a sign of exploited noise. Nonetheless, the lesson from past stochastic resonance research is that it can be worthwhile to at least consider whether observations of random noise or background fluctuations may be evidence of a source of biological randomness that is potentially exploited *in vivo* for stochastic facilitation.

Building realistic models of course requires that we apply simplification judiciously, especially when considering the level of detail, neuron type (for example, excitatory, inhibitory or bursting), synaptic activity and any neuron-to-neuron connections. We emphasize that model simplification must be based on the proposed computational goal of the system. Sufficient model elements must be included so that the required

Table 2 | **Biologically relevant sources of noise that may contribute to stochastic facilitation**

Noise Source	Description	Refs
Thermal noise	Also known as Johnson noise, thermal noise arises from random thermal agitation of charge carriers in electrical conductors, and appears as fluctuations in membrane potentials.	24
Stochastic molecular diffusion	Molecular interactions during calcium signalling in dendritic spines is inherently stochastic owing to diffusion, with potentially important consequences for synaptic plasticity.	94
Crosstalk noise	Spillover of synaptic vesicles to adjacent neurons can lead to unpredictable variability, as potentially could ephaptic coupling, whereby the electric field produced by adjacent neurons may cause changes in their membrane potentials.	1,65
Synaptic neurotransmitter release	Both the number of neurotransmitter molecules released from synaptic vesicles and the number of activated postsynaptic receptors seem to be random variables, and thus lead to stochastic variability in action potential generation.	53,95–97
Short-term plasticity	Several interacting effects can mean that even spikes that arrive regularly at axonal terminals may lead to irregular postsynaptic events. These effects include facilitation, adaptation, depression and recovery as well as the stochastic release of neurotransmitters from vesicles.	95,98–100
Ion channel gating and membrane noise	The stochastic nature of the opening and closing of ion channels is well known. This leads to fluctuations in neuron membrane potentials, and in turn affects action potential generation.	10,53,101,102
Synaptic barrages	Pyramidal neurons can have many thousands of synaptic connections with other neurons, and the numerous input events from these can lead to the neuron's membrane potential being in a state of increased or decreased, or fluctuating, conductance. This can have profound effects on the neuron's spiking properties.	103
Diversity owing to stochastic gene expression	Intrinsic biophysical properties vary over populations of neurons and have been shown to benefit neural coding. The notion that this kind of variability can lead to benefits is sometimes called diversity-induced resonance.	104,105
Network connectivity	Cortical neurons form connections with many other cortical neurons to form irregularly structured networks.	106
Sensory inputs	Disturbances can be extrinsic (such as background visual clutter) or intrinsic to biological transduction mechanisms.	107
Motor noise	Movements induced by muscle fibres are subject to variability through several mechanisms.	1

computations can be realized completely in the neural system. The choice of additional elements could be based on mathematical or numerical tractability, elegance, symmetry, completeness or other considerations. The noise source should also help to determine which model elements are essential. Although noise can often be modelled simply as a series of samples from a probability distribution with associated correlation times, as has been done most often in physics approaches, it may also be necessary to model a noise generation mechanism. For example, modelling the intrinsic dynamics of ion channels provides realistic noise in a simulation of the effects of noise on multiplicative computations within a neuron[66]. Another study of stochastic resonance in which the noise source was modelled in a biophysically realistic fashion examined neurons that are under constant bombardment by a barrage of synaptic inputs[7].

Biologically appropriate signals. New kinds of stochastic facilitation might be observed when biologically appropriate input and output signals are defined within the context of a computational hypothesis. For example, whereas the output signal in stochastic resonance work is often a sequence of action potentials in response to an input current, other signals for a computational process might be biophysical entities, such as neurotransmitters from synaptic vesicles, or calcium currents. Another possibility is to define a computation in terms of the intervals between action potential initiations at the soma of a neuron (the input) and their arrival times at an axon terminal (the output). A third possibility is an external sensory input, such as sound pressure waves that enter the transduction mechanisms of the inner ear. Constructive roles for biologically relevant noise have already been studied based on the currents induced in inner hair cells[34] or action potentials in primary afferent auditory nerve fibres[20,67,68] as output signals, with the computation being transduction and encoding of a sound wave.

Stochastic facilitation may not require an input signal. Stochastic resonance has historically been defined relative to input and output signals and information processing. However, stochastic resonance has recently been identified in a model of emergent synchronization of whole brain functional networks[69], in which it is not clear what model features might be labelled as an input signal. Although the lack of signal means that calling this effect stochastic resonance redefines the term — indeed, this type of effect is known as coherence resonance[70,71] in statistical physics and has consistently been described as a different kind of noise-enhanced effect from stochastic resonance — there would be no such ambiguity associated with calling it stochastic facilitation. The computational hypothesis about the constructive role of noise might be that it is important for a network to oscillate at 0.1 Hz for one range of noise levels and not to oscillate outside of that range.

Distinguishing signal and noise. It is often very difficult to distinguish signal from noise[72]. In engineered communication systems, information-carrying signals can seem to be as random as a noise source, and this should also be expected *in vivo*. Because signal can only be defined in conjunction with a well-defined computational hypothesis, defining the assumed nature of the computation helps to mitigate this problem. Conversely, although many sources of noise never act as signals, the input signal for one computation may well be considered noise for a different computation. To complicate matters, although it is often assumed that a signal is independent of any noise source,

this may not always be a good assumption[73]. The problem of deciding what is noise and what is signal is even greater in experimental work, owing to other systematic forms of noise measurement. This means that falsifying hypotheses about stochastic facilitation will be very challenging. Our framework does not provide solutions for this problem; what we hope is that it will encourage a much richer, more creative pool of hypotheses and generate new experiments and models that help elucidate constructive roles for noise.

Bridging theory and experiment

To aid the cross-application of ideas and analytical methods between experimentalists, modellers and theorists, we propose the following more formal definition of stochastic facilitation for the neurosciences:

Stochastic facilitation is observed within a specific neural system if a proposed computational goal is better achieved in the presence of random fluctuations originating from stochastic biologically relevant noise than in their absence.

We also propose a common framework for future experimental and computational neuroscience approaches for addressing stochastic facilitation. This framework consists of six sequential steps (FIG. 1b) that will help researchers to make biologically appropriate choices with regard to stimulation and analysis for a given concrete hypothesis. Typically, studies of stochastic resonance in neural systems are dictated by the classical definition of stochastic resonance[5], which predetermines potentially inappropriate choices for stimulation and analysis in steps 3, 5 and 6 (FIG. 1b), because it imposes a restrictive computational hypothesis for step 1 that cannot be implemented solely by the neural system. To assess whether stochastic facilitation occurs, a biologically appropriate computational role of a neural system needs to be identified or proposed first, along with a biologically relevant indicator of performance.

Conversely, in computational studies the model in step 2 and the noise in step 3 (FIG. 1b) are often chosen with little regard to specific biologically realistic neural systems. For example, classical stochastic resonance was often studied in the context of single point neuron models. Although these neurons simulate the dynamics of real neurons[74,75], they are too simple to capture details of neuron topology, biophysics and kinetics that could manifest noise benefits in variables other than action potentials. The physics approach aims to discover fundamental principles that are inferred at a level of analysis that predicts the existence of stochastic resonance in neural systems generally, whereas the neuroscience approach aims to discover basic mechanisms that are actually realized in specific neural systems of living organisms.

Confirmation of a stochastic facilitation hypothesis requires performance to be measured in normal conditions, as well as in conditions under which the noise level is reduced, in order to conclude that biologically relevant noise provides a benefit. Experimentally changing the properties of biologically relevant noise and measuring the resulting efficacy of the computation is clearly very difficult in most circumstances. Nevertheless, it is possible. For example, recent experiments have found that correlations in input noise into retinal ganglion cells allowed a computation to be more precise; removing the correlations in the noise — but not the noise — was found to cause a decrease in the precision of coding[76]. We now present some studies in which noise might be modified experimentally and stochastic facilitation hypotheses could be applied, perhaps leading to new or alternative conclusions.

As a first example of the approach that we advocate, we consider the study of Mazzoni *et al.*[77] Their model simulates some aspects of the structure and function of the V1 region of visual cortex as it receives inputs from the lateral geniculate nucleus (LGN) of the thalamus. The authors showed that it can account for transmission of information about an external stimulus in the presence of 'external' noise from the LGN to V1 through synchronous activity in two specific frequency channels. The computational goal of the LGN is assumed to be to faithfully transmit the information that it receives about the spatial and temporal distribution of light on the retina to V1, where visual features such as oriented edges are detected and located relative to each other. A relevant measure of performance of this goal is the total mutual information between the LGN-generated noisy signal and the resultant V1 activity integrated across spatial location, time slices and frequency channels. This model can be studied in the context of stochastic facilitation by reducing the noise or removing it from the LGN signal altogether. Another approach would be to introduce V1-specific noise, for example, from synaptic bombardment, and manipulate the amount and nature of that noise. We speculate that either approach could affect the LGN–V1 mutual information, and that eliminating all noise could substantially decrease it, thus indicating that the noise is necessary for the successful achievement of the computational goal.

Experimental verification would require placing extracellular recording electrodes (polytrodes) in LGN and V1 areas of monkeys while they are immobilized but awake[78]. The monkeys would be trained to look at a computer monitor that presents various visual stimuli, such as gratings or movies. The challenging part of the experiment is to determine which inputs to LGN and V1 are signal and which are noise, or at least to determine a way to suppress the noise that is added to the signal by the LGN and V1 neurons. This might be accomplished by blocking a subset of synapses resulting from pyramidal–interneuron circuits in V1 or by suppressing metabotropic synapses (likely to be modulatory) but leaving ionotropic synapses (likely to be driving) unaffected. A decrease in mutual information between LGN and V1 neurons would confirm that synaptic noise of a particular type is necessary for the normal computational function of this network.

> "Stochastic facilitation is observed within a specific neural system if a proposed computational goal is better achieved in the presence of … stochastic biologically relevant noise than in its absence."

A series of papers by Bezrukov and Vodyanoy established that external electric noise (artificially generated) can facilitate transduction of weak sine wave signals through the alamethicin channel in a lipid bilayer[79–81]. This work was accomplished using the physics discourse (FIG. 1a), including the choice of artificial noise with a Lorentzian power spectrum (constant amplitude for low frequencies and then a drop-off of power as the square of the frequency for higher frequencies), and signal-to-noise ratio in the output power spectrum as a performance metric. Of particular interest was the fact that this is a non-dynamical and threshold-free system. A sophisticated model was proposed to account for this experimental finding, including a mathematical expression that predicted the dependence of the signal-to-noise ratio on noise level.

On activation by transmembrane potentials, voltage-dependent ion channels have a variety of functions, including muscular contraction, excitation of neurons, upregulation of gene expression and release of hormones or neurotransmitters. A fair amount is known about these functions, but it is unknown whether any function *in vivo* depends on the presence of random fluctuations in the transmembrane potential. Following the approach outlined in FIG. 1b, a first experiment would be to attempt to reduce the electric noise under more natural conditions for a specific example of a voltage-gated ion channel and to measure the performance of the relevant function under this condition. Clearly, the performance metric would depend on the function studied — for example, the force of muscular contraction, amount of gene expressed or amount of hormone or neurotransmitter released, or the dependence of these quantities on other variables. Modelling would then have to concentrate on a mechanism for this effect. Some elements of the Bezrukov and Vodyanoy model could possibly be adapted but this is not guaranteed, especially as their model concentrated on derivation of an expression for the signal-to-noise ratio in the output power spectrum for a noisy sine wave input.

A final study to which our approach could be applied is one carried out by Ward and colleagues (BOX 1), in which stochastic resonance-modulated synchronization of the whole human brain is described[49]. They showed that adding near-threshold broadband acoustic noise to a brief weak pure tone stimulus resulted in an increase in both local (40-Hz transient EEG response) and global (between brain regions showing a 40-Hz response) synchronization. Moreover, at a higher level, the added noise also increased synchronization with respect to a weak stimulus to the contralateral, isolated and noise-free ear, implying that the noise received by the other ear propagated throughout the auditory system and beyond. Although Ward and colleagues cited and briefly discussed a model of noise propagation in the brain[82], they did not develop that model to explain their own findings. Again, although the performance metric was unique in this study (synchronization within and between brain regions, also studied in models previously) these models were not addressed directly except to predict the general effects of the noise. Lastly, although the natural function of the auditory system, detection and discrimination of sounds was addressed in this study, the noise was added artificially and exogenously as in most previous studies.

From our point of view, a first step would be to model the phenomenon of noise-modulated synchronization in response to sensory stimuli that was reported by Ward and colleagues based on the previous models of neural networks and cross-modal stochastic resonance. Presumably, these models would assume endogenous sources of neural noise and its variation over time and brain regions. Informed by these modelling exercises, experiments could then be designed that would predict the effects of decreasing neural noise by altering neurotransmitter function, possibly as in the first example we discussed, or increasing it directly by means of transcranial magnetic stimulation, for example. Additionally, measurements of internal neural noise need to be developed and employed to test the models' predictions that not only does the noise vary over time and brain region, but that the variations affect the functions of the relevant regions, augmenting or interfering with them.

Once such findings are detailed at a biologically realistic modelling level and confirmed experimentally, they could be studied at more abstract levels from a physics approach to reveal further general principles of information processing in non-linear systems. These principles may be quite different from those previously developed based on the classical stochastic resonance definition.

The evolutionary origins of noise

Identifying a constructive role for noise does not answer the question of why a particular stochastically facilitated mechanism might have evolved. It is possible that other mechanisms that could achieve the same computation would perform less well in the presence of noise.

Perhaps noise is unavoidable, owing to biophysics or biochemistry, and the mechanism that works best given this noise is one that does not work if noise is artificially removed[28]. Another possibility is that evolutionary pressures have led to higher levels of random fluctuation, perhaps through a genetic mutation, resulting in a mechanism that implements a computation that did not previously exist, or which previously had inferior performance (for example, REFS 34,83). Experimental evidence for just such a scenario has been described in the fly antennal lobe[11]. This mechanism might be very far from optimal according to engineering theory, but if it led to a fitness advantage for the corresponding gene in the existing niche, then why should it be optimal in that sense? Lastly, it might be worth considering that the randomness that leads to a working mechanism for a computation can be viewed as noise in the context of that computation, whereas it is in fact a signal when viewed in a different context.

In none of these cases is it necessary that the presence of noise results in an optimal mechanism for achieving a computation. What can be said is that the mechanism that actually does exist for achieving a computation would perform less well without the noise.

Conclusion

We have argued that the physics approach that characterizes much of the previous work in stochastic resonance has not exploited all of the possibilities for advancing our understanding of the beneficial role of noise in neural systems. Our proposed framework for investigating stochastic facilitation in neural systems promises not only to elucidate many of the mechanisms already known to neuroscience but also to open exciting new areas. Our understanding of neural systems is still incomplete, and bridging theory and experiment in the study of the constructive roles of biologically relevant noise may lead to similar efforts in other areas of neuroscience.

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Competing interests statement
The authors declare no competing financial interests.

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Beatrice de Gelder, Jack van Honk and Marco Tamietto
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Emotion and the brain: multiple roads are better than one
Luiz Pessoa and Ralph Adolphs
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This correspondence relates to the article:

Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance
Luiz Pessoa & Ralph Adolphs
Nature Rev. Neurosci. **11**, 773-783 (2009)

ERRATUM

From glutamate co-release to vesicular synergy: vesicular glutamate transporters

Salah El Mestikawy, Åsa Wallén-Mackenzie, Guillaume M. Fortin, Laurent Descarries and Louis-Eric Trudeau

Nature Reviews Neuroscience **12**, 204–216 (2011)

On page 209 of the above article, 'Nucleus accumbens[33–35], neostriatum[33–35]' should be listed under 'Terminals' not 'Cell bodies'. The online version of the article has been corrected accordingly.