State-dependent effects of neural stimulation on brain function and cognition

Claire Bradley[1]✉, *Abbey S. Nydam*[2], *Paul E. Dux*[3] *and Jason B. Mattingley*[1,3]✉

Abstract | Invasive and non-invasive brain stimulation methods are widely used in neuroscience to establish causal relationships between distinct brain regions and the sensory, cognitive and motor functions they subserve. When combined with concurrent brain imaging, such stimulation methods can reveal patterns of neuronal activity responsible for regulating simple and complex behaviours at the level of local circuits and across widespread networks. Understanding how fluctuations in physiological states and task demands might influence the effects of brain stimulation on neural activity and behaviour is at the heart of how we use these tools to understand cognition. Here we review the concept of such 'state-dependent' changes in brain activity in response to neural stimulation, and consider examples from research on altered states of consciousness (for example, sleep and anaesthesia) and from task-based manipulations of selective attention and working memory. We relate relevant findings from non-invasive methods used in humans to those obtained from direct electrical and optogenetic stimulation of neuronal ensembles in animal models. Given the widespread use of brain stimulation as a research tool in the laboratory and as a means of augmenting or restoring brain function, consideration of the influence of changing physiological and cognitive states is crucial for increasing the reliability of these interventions.

A core endeavour of cognitive neuroscience is to understand how brain regions and networks coordinate their activity to give rise to perception, cognition and behaviour. A prominent approach over the past 30 years has been to image the brain in vivo and to correlate patterns of activity with behaviour under specific task conditions[1,2]. A different approach is to perturb circumscribed brain regions directly using non-invasive magnetic or electrical stimulation, with the goal of establishing causal links between local brain regions and the cognitive processes they regulate[3]. Although the latter approach has proven successful, it is clear that variations in ongoing neural activity arising from changing task demands or endogenous network fluctuations can profoundly influence the effects of brain stimulation on neural activity and behaviour (FIG. 1). It is therefore crucial to understand and account for these influences if we are to apply neural stimulation in a principled manner, both for basic discovery and for clinical translation. Conceptual and technical advances in recent years have transformed our understanding of the neural mechanisms of cognition[4] and enabled integration of concurrent brain stimulation and neuroimaging approaches[5,6]. This, in turn, has paved the way for studies investigating the 'state-dependent'[7,8] nature of brain stimulation effects on both behaviour and patterns of brain activity[9,10].

In this Review, we highlight recent work in the field and critically evaluate the concept of state-dependent variations in brain activity and behaviour in response to both invasive and non-invasive brain stimulation, with a focus on endogenous and task-evoked brain activity relating to cognition. Across a number of domains, including conscious state, attention and working memory, we describe how changes in local and global brain activity can influence the effects of concurrent brain stimulation. We focus on findings from two prominent techniques used in humans — namely, transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) — and relate the data in humans to relevant findings from animal models, in which neuronal ensembles are activated via electrical currents applied directly to neural tissue or through optogenetics (BOX 1). While we also touch on the potential importance of state dependence in the clinical realm, a detailed consideration of patient studies is beyond the scope of this Review.

What makes a 'state'?

Our daily mental landscape is filled with a myriad of states, including sleep and dreaming, attending to external objects and events, and engaging in complex thoughts and actions. This diversity in mental states and

[1]*Queensland Brain Institute, The University of Queensland, St Lucia, QLD, Australia.*

[2]*Department of Psychology, University of Toronto, Toronto, ON, Canada.*

[3]*School of Psychology, The University of Queensland, St Lucia, QLD, Australia.*

✉*e-mail: claire.bradley@uq.edu.au; j.mattingley@uq.edu.au*

https://doi.org/10.1038/s41583-022-00598-1

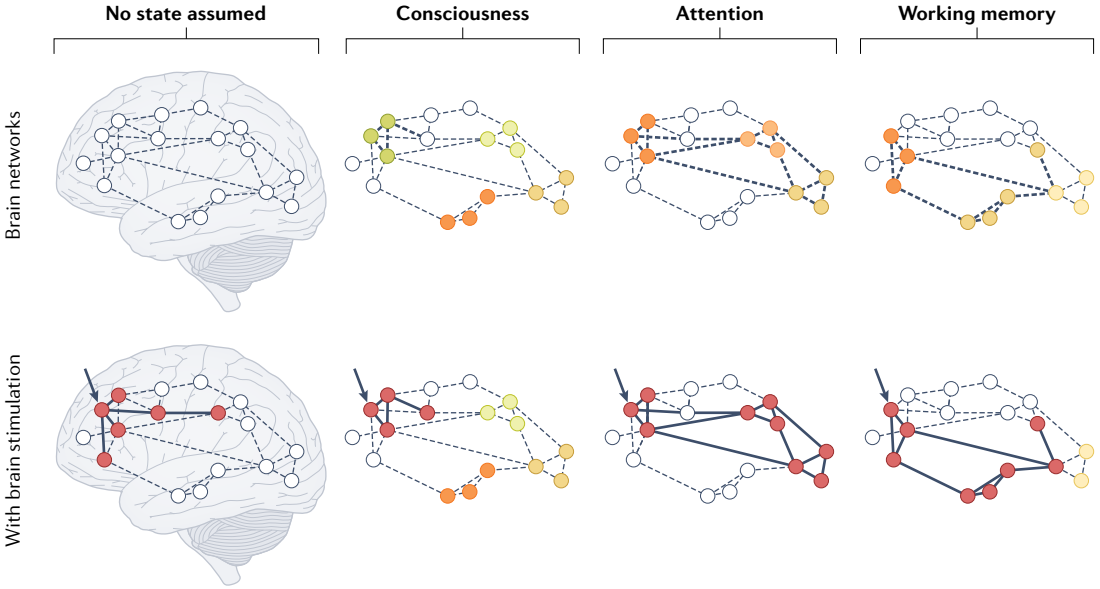


Fig. 1 | **Different cognitive and neural states modify the effects of local brain stimulation.** The brain can be conceptualized as an ensemble of interconnected areas, whose networks are characterized by anatomical and functional connections between nodes (dotted lines between white circles). Stimulation of one of these nodes (black arrow) in a 'resting' brain may disrupt, activate or modulate the excitability of a stereotypical subset of nodes (red circles, full black lines). This subset might be localized within the stimulated area, or could involve more distant nodes (for example, as defined by resting-state network connectivity). The brain is rarely fully 'at rest', however. Instead, it is subject to fluctuating levels of alertness or cognitive engagement, as shown for the three example states we consider in this Review: conscious state, attention and working memory. These different cognitive states are regulated by varying levels of activity in network nodes and by modulation of connections between nodes (thick dotted line between coloured circles), depicted here for illustrative purposes. In turn, stimulation of a single node (black arrow) results in recruitment or disruption of different brain networks (red circles, full lines), depending on the underlying state at the time of stimulation. Note that this theoretical description holds particularly for stimulation techniques that cause neuronal firing (for example, transcranial magnetic stimulation and microstimulation). For techniques that modulate neuronal membrane potential (for example, transcranial electrical stimulation), activity changes may still be passed on to a node's connections via facilitation or inhibition of endogenous neuronal activity. Critically, the specific connections engaged in communication will depend on the current cognitive state and its associated physiological state.

cognitive states is mirrored by a range of correlated neural states. What constitutes a neural 'state' will vary across contexts. Here we follow Zagha and McCormick's definition of a state as "a recurring set of neural conditions that is stable for a behaviourally significant period of time"[11]. This set of neural conditions is often reflected in distinct patterns of ongoing activity but can also be revealed by neural responses to stimuli. Familiar examples include the different stages of sleep, which are characterized by distinct profiles of brain activity[12], or the unique functional networks that emerge during quiet, restful wake[13,14], active exploration of the environment[15] or attentive sensory discrimination[16]. While distinct neural states often correspond with identifiable perceptual, cognitive or motor states, there is not always a simple one-to-one correspondence between the two. Therefore, in evaluation of the different effects of neural stimulation on the brain and behaviour, it is critical to consider 'states' as defined in both neural and behavioural terms.

Broadly speaking, neural activity can be characterized at the level of molecules and cells, microcircuits, local networks or whole brain systems. Correspondingly, methods for capturing activity may focus on patterns of neuronal firing (for example, intracellular recordings and multiunit activity), extracellular electric fields (for example, local field potentials and scalp electroencephalography (EEG))[17] or metabolic activity that is only indirectly related to neuronal activity (for example, functional MRI (fMRI) and optical imaging)[18]. A further important consideration is that fluctuations between distinct brain states vary over vastly different timescales. At one extreme, brain states may change over the course of developmental maturation and normal ageing, or with the slow progression of a disease state such as dementia. Here we focus exclusively on states that vary on a much shorter timescale, from hours (for example, across sleep stages) to hundreds of milliseconds (for example, during shifts of attention or retrieval of items from working memory).

Influencing brain activity

Manipulation of brain activity can be achieved by many means, including behavioural, pharmacological or direct stimulation interventions. In this last class, a rapidly evolving range of options allows invasive and non-invasive stimulation in animals and humans (BOX 1). A detailed account of the mode of action of these techniques is beyond the scope of this Review, but we refer the interested reader to recent reviews on their various applications and mechanisms of action[3,19]. Here

Cognitive states
Finite periods of information processing or mental activity which, in conjunction with their associated neural activity, regulate functions such as attention, learning, memory, thought and reasoning.

Electroencephalography
(EEG). A non-invasive imaging technique that uses electrodes placed on the scalp to record stimulus-evoked or endogenous electrical activity in the brain with millisecond precision.

Functional MRI
(fMRI). A non-invasive imaging technique used to measure changes in metabolic activity in the brain associated with local and distributed fluctuations in the blood oxygen level-dependent signal.

we summarize key concepts underlying the use of two major classes of non-invasive brain stimulation used in humans: TMS and tES.

Transcranial magnetic stimulation as a probe for neural networks. TMS uses electromagnetic induction to excite neurons[20,21]. For every TMS pulse delivered, a short-lived electrical current passing through a stimulation coil produces a magnetic field, which in turn travels through scalp, skull and brain tissue, causing secondary currents in excitable elements. At high intensities, these currents trigger action potentials in neurons. The most direct observation of this effect in humans is the motor evoked potential (MEP), which involves recording the transient muscle contraction following a suprathreshold TMS pulse delivered to the primary motor cortex. Close inspection of descending activity in the spinal cord reveals successive peaks of activity, suggesting that a TMS pulse can directly depolarize corticospinal pyramidal neurons, as well as excitatory and inhibitory interneurons projecting onto pyramidal neurons one or several synapses away[21]. Experiments using pairs of pulses of different intensities, or changing the orientation of the coil and thus modulating intracortical currents, reveal further details of the microcircuitry activated by TMS of the motor cortex[21]. Caution is needed when one is extrapolating these findings to other cortical areas, however. The specific effect of a TMS pulse will depend on the pulse properties (for example, coil orientation and pulse

Box 1 | **Brain stimulation techniques commonly used in human and animal studies**

Several different brain stimulation techniques are commonly used in human and animal studies, and they differ in their degree of invasiveness, spatial range and specificity[3].

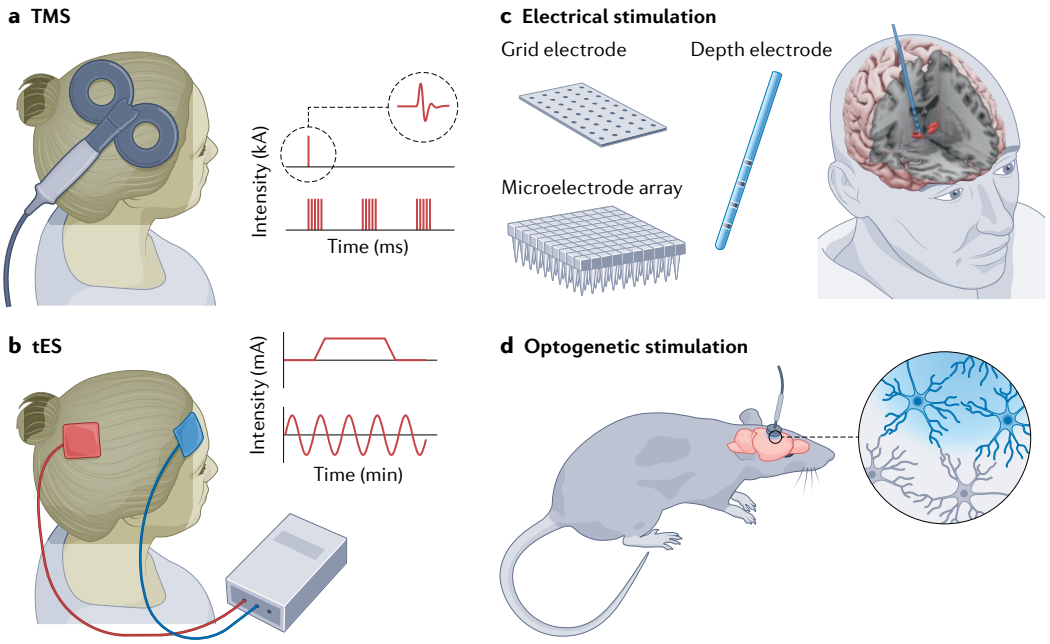
Transcranial magnetic stimulation (TMS; see the figure, part **a**) uses a coil (blue) to create a time-varying magnetic field that can make neurons fire. While single-pulse TMS can be used to probe the excitability of a network or to disrupt its normal function, repetitive TMS — involving different pulse patterns and frequencies — modulates cortical excitability over time and is thought to engage synaptic plasticity mechanisms.

Transcranial electrical stimulation (tES; see the figure, part **b**) delivers a weak electrical current to the scalp between at least two electrodes. Some electrode configurations afford a more focal distribution of current (high-definition tES). The mechanisms of action of tES are debated[40,171,172], but it is generally considered to modulate neuronal resting membrane potential[3] and can lead to long-lasting after-effects on the brain and behaviour.

Electrical currents can also be applied directly to brain tissue (see the figure, part **c**). These invasive methods encompass microstimulation[173] both in animal models and in human patients being treated for neurological disorders. A typical example is deep brain stimulation (DBS)[174] for Parkinson disease, in which depth electrodes are used to deliver continuous high-frequency (for example, 120-Hz) stimulation to basal ganglia structures to reduce motor dysfunction.

In animal models, optogenetic stimulation[175] (see the figure, part **d**) involves selective excitation or inhibition of populations of neurons expressing light-sensitive proteins (opsins) after genetic manipulation. Opsins are activated by laser light delivered through an implanted optical fibre. This technique offers exquisite control over the populations of neurons targeted and the patterns of stimulation.

Collectively, the tools described here are undergoing rapid development, which has enabled new features. For instance, use of two TMS coils to deliver precisely timed pulses to two different cortical regions (corticocortical paired associative stimulation[8]) allows neural plasticity to be manipulated between any two connected areas. Entirely new techniques are emerging which exploit the summation of sound waves (transcranial ultrasound stimulation[176]) and electric fields of varying frequencies (temporal interference[177]), enabling non-invasive targeting of deeper brain structures.



Stochastic resonance
A phenomenon in which the addition of noise to a nonlinear system can, under certain conditions, improve performance or output-signal quality.

Entrainment
The alignment or synchronization of brain activity in response to rhythmic sensory stimuli or brain stimulation, and which may play a role in regulating perceptual and cognitive states.

Oscillations
Wave-like patterns of periodic brain activity in the 0- to ~200-Hz range, often defined in terms of characteristic 'frequency bands' such as delta (0.5–3 Hz), theta (4–7 Hz), alpha (8–14 Hz), beta (15–30 Hz) and gamma (more than 30 Hz).

Plasticity
The capacity of the brain to alter its structure and function, often in response to experience, and which is expressed at different anatomical scales, from individual neurons and synapses to cortical maps and networks.

duration, intensity and shape) and the characteristics of the stimulated area, such as cortical folding (angle of the cortical sheet and the direction and thickness of axons), the distribution of cell types and the patterns of connectivity between units[3,22]. The intensity of stimulation, in particular, has been proposed to shift the overall effects of TMS on behaviour from facilitatory at low intensities to inhibitory at higher intensities[8,23]. Different stimulation intensities may also preferentially recruit different neuronal subtypes[21,24]. In spite of these nuances, an overarching principle is that TMS triggers action potentials and exerts its effects on local microcircuitry as well as through network activity.

The effect of TMS on neural networks can be exploited in different ways. The so-called virtual lesion approach[25] uses TMS, delivered either as a single pulse or in a rapid sequence of several pulses, to disrupt normal neural activity at a specific point during the execution of a task. The nature of this disruption has been hypothesized to involve processes such as inhibition of active neurons, 'noise' injection in all neurons or excitation of task-irrelevant neurons[26–28]. Another approach consists in recording physiological signals during the delivery of TMS, which is then used as a probe to examine reactivity of a neural circuit of interest. For example, MEP amplitudes can reveal the integrity of the corticospinal tract in various neurological disorders[21], or cortical excitability under different experimental conditions[21]. Use of TMS to perturb local brain regions at rest or during a task, and recording of the resulting activity via EEG[29] or fMRI[30], can elucidate the pathways along which neural activity propagates in a network.

Transcranial electrical stimulation as a modulator of membrane potential. tES involves delivering a weak electrical current (typically between 0.5 and 2 mA) over the scalp[31,32]. The current can be continuous (transcranial direct current stimulation (tDCS)) or alternating (transcranial alternating current stimulation (tACS)), or can vary according to a noise distribution (transcranial random noise stimulation (tRNS)). The resulting electric field distribution varies depending on the size, number and position of the electrodes, but it is typically rather diffuse and covers not only the cortex but also the cerebrospinal fluid, skull, skin and nerves, where it may have functional effects[33]. In contrast to TMS, tES is thought to modulate cortical neuronal membrane potentials rather than triggering action potentials. Such effects may indirectly influence spontaneous and evoked neuronal firing rates, as well as the synchronization of firing between neurons. Early experiments that applied currents to the cortical surface of anaesthetized cats revealed that a surface anodal polarization delivered over the motor cortex generally increased neuronal firing rates, whereas cathodal stimulation decreased firing rates[34] — with interesting variations by cell type and location relative to the cortical surface. Similarly, tDCS delivered in humans with the anode over the motor cortex was shown in early work to increase MEP amplitude, whereas cathodal tDCS decreased MEP amplitude[35], leading to the oversimplified view that anodal tDCS is 'excitatory' and cathodal tDCS is 'inhibitory'. This view has since been refined by further human and animal studies, which have shown that tDCS effects depend on a host of factors, including stimulation intensity and duration, electrode montage and the physiology of the stimulated area. The hypothetical mechanisms of tRNS and tACS also involve neuronal membrane potential modulation, potentially leading to stochastic resonance for tRNS[36,37] and to entrainment of oscillations at the frequency of stimulation for tACS. Direct evidence for these has been conflicting[38] but is growing[39–41]. Further research into the mechanisms of tES and their generalization across species[42] will be crucial for the advancement of the field.

Persistent effects over time: plasticity induction. A defining feature of both TMS and tES is that they can be used to trigger changes in behaviour and brain physiology that persist beyond the period of stimulation. For example, delivery of anodal tDCS to the motor cortex for periods as brief as ~10 min causes MEP amplitude increases over a period of ~1 h[43], and brain imaging studies have revealed changes in cerebral blood flow[44] and neurotransmitter concentration[45] that unfold over at least 15 min after tES. While a single TMS pulse causes only transient neuronal activity, delivery of several hundred pulses in succession using so-called repetitive TMS (rTMS) can lead to lasting changes[46]. In this application, the relative timing of pulses is a crucial determinant of any after-effects: low-frequency rTMS (less than 5 Hz) over the motor cortex generally reduces MEP amplitude, whereas high-frequency rTMS (5 Hz or greater, often 10 or 20 Hz) seems to increase MEP amplitude. Special rhythmic patterns of pulses (for example, theta-burst stimulation), or combinations of central and peripheral stimulation such as paired associative stimulation (PAS), can also lead to lasting inhibitory or excitatory changes. Crucially, the history of activity, either from exercise or from successive plasticity paradigms, can reliably reverse the after-effects of motor cortex rTMS. Such apparent reversals of plasticity after-effects are often interpreted in terms of homeostatic processes that prevent 'runaway' excitability changes[47]. Similarities with classical animal experiments, and sensitivity to pulse timing and to various drugs that modulate neuroplasticity, strongly suggest that these long-lasting changes occur because of engagement of synaptic plasticity mechanisms. Other types of plasticity, such as non-synaptic neuronal, glial or vascular changes, may also contribute, but their contributions have barely been explored. The potential for TMS and tES to induce persistent changes makes them attractive as therapeutic tools, and has led to studies in which multiple stimulation sessions are delivered over the course of days or weeks[48,49]. Importantly, our understanding of persistent, 'offline' after-effects of brain stimulation is still relatively divorced from what is known about their instantaneous mechanisms of action, and requires further study.

Activity-dependent effects of brain stimulation. Foundational work investigating the preparation and execution of actions has shown that the ongoing level of activity of a neuronal population determines how

responsive it is to brain stimulation[28]. A striking example comes from delivery of a TMS pulse during mild voluntary contraction of the target muscle, which results in a substantially larger MEP than is observed when the same pulse is delivered at rest[21]. Activity-dependent effects of brain stimulation have also been uncovered in the visual domain. Using an approach known as 'TMS adaptation', which has since been extended across sensory and cognitive domains[50], Silvanto and colleagues exploited the fact that some neurons reduce their activity (that is, 'adapt') when engaged in prolonged activity. TMS pulses were delivered to occipital areas with the goal of inducing phosphenes, immediately after presentation of a coloured adapting stimulus[51]. Phosphenes are usually colourless, but after adaptation, the phosphene took on the colour of the adapting stimulus, suggesting that TMS activated the adapted, less active neuronal circuit. This body of work led Silvanto and Cattaneo to propose an excitability-dependent sliding scale of TMS effects, whereby the facilitatory-to-inhibitory effects of TMS intensity are determined by the current state of stimulated neurons, as controlled, for example, by attention or adaptation[23]. The mix of excitability levels in a neural population at any given time thereby determines the net effect of stimulation on behaviour.

Importantly, while activity dependency or state dependency in brain stimulation studies is a well-accepted concept, the mechanisms underlying it are not well understood. The precise relationship between ongoing activity and neuronal excitability is probably complex[28,52], and current perspectives have yielded opposing predictions. For example, it has been hypothesized that tES may preferentially modulate active networks[53]. Alternatively, because neural activity is generally accompanied by a decrease in membrane resistance, it can be hypothesized that tES may be less effective at modulating membrane potential in active neurons[52]. A more comprehensive understanding of the state-dependent effects of brain stimulation is clearly required, especially at levels of description that are accessible in humans.

In the sections that follow, we present recent work that has investigated how brain stimulation interacts with ongoing brain states relevant to cognition, as illustrated across the domains of consciousness (anaesthesia, sleep and drowsiness), attention and working memory. Where possible, we focus on studies that have directly compared the effects of brain stimulation across different states, and that incorporated brain imaging as an outcome measure.

Conscious state fluctuations

Alterations in conscious state, which occur during anaesthesia and sleep, are characterized by altered subjective experience, a lack of responsiveness relative to wakefulness and widespread fluctuations in neural physiology. Several studies have uncovered differential effects of brain stimulation with fluctuations in conscious state, as we describe herein. Wakefulness is broadly characterized by desynchronization of cortical activity, with the generation of local rapid rhythmic activity in the alpha to gamma range and long-range corticocortical connectivity[15]. By contrast, slow-wave sleep (also known as non-rapid-eye-movement (NREM) sleep) is characterized by large-amplitude synchronized thalamocortical activity in the low-frequency range (0.5–4 Hz), known as slow waves. The cellular and network mechanisms that lead to these alternations have been extensively studied[12,54,55], and point to recurrent shifts in the balance of local excitation and inhibition. Slow-wave-like activity is pervasive in unconscious states, such as those which occur during anaesthesia[56,57] and in disorders of consciousness[58] (but see REF.[59]). A notable exception is rapid eye movement (REM) sleep, during which brain activity displays low-amplitude, fast rhythms reminiscent of wakefulness. REM sleep is also associated with dreaming and reports of vivid subjective experience. Different stages of sleep and anaesthesia are also accompanied by marked changes in fMRI-measured brain connectivity[60,61] and are strong modulators of memory and plasticity[62,63].

Anaesthesia. Our current understanding of the cellular-level effects of brain stimulation has been derived from in vitro studies on slices or with anaesthetized animal preparations (for examples, see REFS[64–68]). It remains unclear to what extent findings from these approaches can be generalized to in vivo studies of awake humans or other animal species, although some recent work has focused on the effects of brain stimulation in awake animals[40,69]. Work in macaques has shown that microstimulation during anaesthesia generally requires higher current intensities than it does during wake to evoke comparable stimulation effects, as measured by haemodynamic changes and microsaccades. Use of fMRI to investigate the network effects of microstimulation targeting the thalamus[70] or the parietal cortex[71] in the macaque has revealed both activations and deactivations at distant sites that are remarkably similar in awake and anaesthetized animals. By contrast, other recent work in macaques has shown that microstimulation of the ventral tegmental area results in haemodynamic network effects that vary considerably with anaesthetic state[72]. In this work, stimulation during the wake state more readily evoked increases in activity, and with a different frequency-dependent profile and spatial distribution, than under anaesthesia. This is consistent with work that combined optogenetic stimulation of the medial prefrontal cortex and fMRI in rodents, which revealed greatly reduced network activation in anaesthetized animals compared with awake animals[73]. More research is needed to elucidate the importance of specific anaesthetic agents and targets of stimulation. The latter is likely to be particularly important since modulation by anaesthesia has been shown to vary across cortical areas[74,75].

A central goal of many brain stimulation studies has been to manipulate brain plasticity and learning[46]. Long-term, high-frequency suprathreshold rTMS (20 Hz) of the frontal cortex in rats leads to distinct (and opposing) outcomes, depending on whether stimulation is delivered while the animal is awake or anaesthetized[76] (FIG. 2a). Among other findings, animals exhibit increased or decreased levels of hippocampal plasticity markers, such as brain-derived neurotrophic

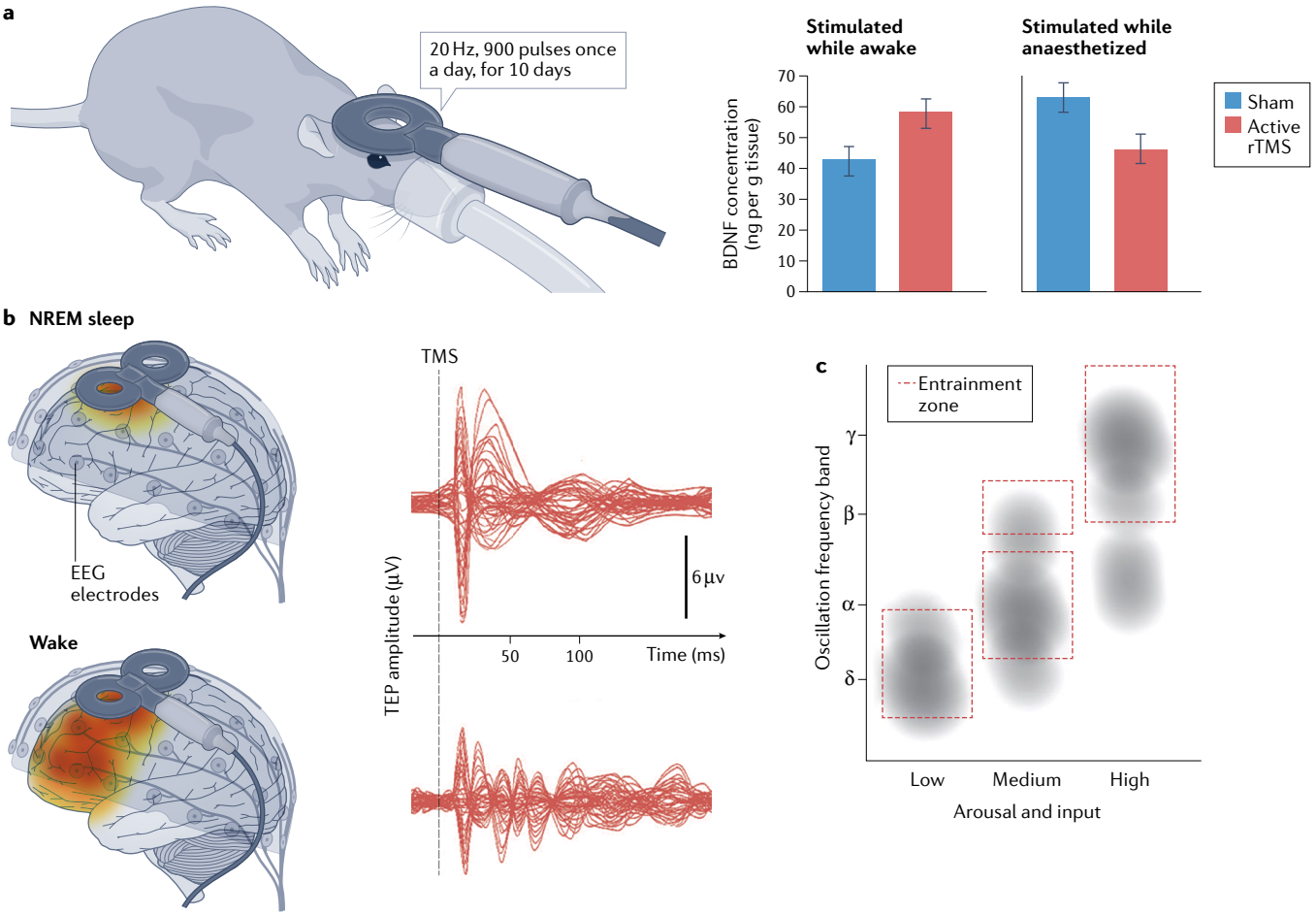


Fig. 2 | **Brain stimulation applied during different states of consciousness yields distinct effects on brain activity. a** | Gersner and colleagues[76] showed that rats receiving daily repetitive transcranial magnetic stimulation (rTMS) for 10 days while awake displayed increased hippocampal brain-derived neurotrophic factor (BDNF) concentration; the opposite was true when rTMS was delivered to anaesthetized animals. A similar pattern was seen for prelimbic cortex BDNF concentration, and for the level of the AMPA receptor GluR1 subunit and its phosphorylated form in the hippocampus (not shown), suggesting modulation of receptor numbers with increased calcium permeability. **b** | Massimini and colleagues[77] recorded electrical brain activity in humans (left panel, red shading) generated in response to a TMS pulse with scalp electroencephalography (EEG) electrodes (small grey circles). The resulting time-varying activity at each electrode (right panel), called 'TMS-evoked potentials' (TEPs), is of larger amplitude, but is more restricted in terms of cortical spread, when TMS is delivered during non-rapid-eye-movement (NREM) sleep (top) versus wake state (bottom). **c** | States of consciousness are generally characterized by different dominant frequencies of oscillatory activity. Modelling work[92] using artificial biophysical networks of neurons can reproduce these oscillatory signatures (shaded grey areas) by modulating 'arousal' (neuronal conductance values as constrained by the acetylcholine-to-noradrenaline ratio) and 'afferent input' (excitatory input, assumed to be highest during active wake). A proxy for periodic brain stimulation is able to entrain oscillatory activity in different frequency bands (dotted rectangles) depending on the network state, with more prominent entrainment at the dominant oscillation band, consistent with the concept of 'resonance'. Part **a** adapted with permission from REF.[76], Society for Neuroscience. Part **b** adapted with permission from REF.[77], AAAS. Part **c** based on data from REF.[92].

TMS-evoked potentials
Evoked changes in electrical potential generated in response to a transcranial magnetic stimulation (TMS) pulse and recorded by electroencephalography, resulting in region-specific changes in neural activity generally lasting ~500 ms.

Effective connectivity
Pattern of interactions between different elements of the nervous system in which the direction of functional communication is causally inferred.

factor, when stimulated while awake or anaesthetized, respectively.

These studies highlight that care should be exercised when one is comparing the effects of brain stimulation between anaesthetized and awake states. Although the precise conclusions probably depend on such factors as the specific anaesthetic agent, stimulation technique and neural target, the direction of stimulation effects on network activity and long-term plasticity markers can be markedly different.

Sleep. In a pioneering study, Massimini and colleagues[77] probed the effects of sleep on brain activity in human participants using single-pulse TMS and concurrent EEG. They found that a TMS pulse delivered to the premotor cortex during NREM sleep profoundly altered TMS-evoked potentials compared with those evoked during wakefulness (FIG. 2b). Specifically, local activity was of larger initial amplitude but declined rapidly and displayed a smaller spatial and temporal spread than TMS-evoked potentials recorded during wakefulness, suggesting a reduction in long-range effective connectivity during NREM sleep. This finding has been replicated in numerous studies[78–80]. Qualitatively similar findings — namely, large amplitude TMS-evoked potentials and lack of sustained propagation to distant regions — have also been identified during general anaesthesia[81,82]. By contrast, TMS-evoked potentials more closely resembling those associated with wakefulness have been observed in conditions involving relatively more reportable

conscious content, such as REM sleep (dreams[83]) and ketamine anaesthesia (vivid hallucinations[84]). These findings highlight that altered states of consciousness have a dramatic impact on the propagation of neural signals across widespread neural networks, in a way that depends on the specific stage of sleep or type of anaesthesia.

Several interventions in humans[85,86] and animal models[87,88] have revealed learning and plasticity effects that are conditional on stimulation being delivered during NREM sleep, rather than during REM sleep or wakefulness. For example, Facchin and colleagues[88] used a mouse model of stroke to show that artificial slow waves, triggered optogenetically and delivered to the peri-infarct zone during stroke recovery, improve motor function and promote axonal sprouting. Critically, however, these effects occur only if stimulation is delivered during sleep rather than in the wake state. Several physiological mechanisms could contribute to these observed differences. For example, because punctate stimuli propagate differently through the network, distinct pathways could be potentiated or depotentiated depending on the state. Plasticity induction itself is probably modulated by different neurotransmitters and neuromodulators. It has also been hypothesized that the ability of brain stimulation to modulate rhythmic neural activity depends on the strength and peak frequencies of ongoing oscillations[89,90], which are prominently altered across conscious states, and that these oscillations are causally related to plasticity[91]. In a recent computational model, Li and colleagues[92] further explored this idea. They demonstrated that a biophysically plausible thalamic network can be configured to give rise to rhythmic activity when subjected to different afferent excitation levels and neuromodulatory influences, thus acting as a proxy for different sleep–wake states (FIG. 2c). Rhythmic input was applied to the model to mimic rhythmic brain stimulation at a range of frequencies. This resulted in entrainment (that is, the locking of intrinsic oscillations to the stimulation frequency) which was highly dependent on the state, being most prominent for gamma-like activity characteristic of the active waking state. While the model does not incorporate plasticity components, it allows exploration of a large number of stimulation parameters and generates testable predictions about state-dependent effects of brain stimulation.

Drowsiness — the transition between sleep and wake. The transition between wake and sleep is not instantaneous, and may occur several times a day with fluctuations in alertness without the individual entering deep sleep. In a recent study of drowsiness, Noreika and colleagues[93] showed a nonlinear increase in TMS-evoked potential amplitude and variability during transitions between wakefulness and light sleep, even while individuals were still responsive and able to perform a simple perceptual task. Likewise, increased TMS-evoked corticospinal activity was found in a sustained attention motor task in which participants showed attention decrements and global changes in brain activity[94]. Since different brain areas are known to display graded transition to sleep states[95], the impact of drowsiness on the effects of brain stimulation might be expected to differ according to the stimulation target. These findings are of particular relevance for the use of brain stimulation in the laboratory and the clinic, given that participant drowsiness is common among laboratory volunteers and in patients undergoing brain stimulation treatment[96]. The findings also highlight how changes in states of wakefulness are often similar to — although not identical to — fluctuations in attention to a task, object or thought. In the following section, we provide an overview of recent work showing that mechanisms of attention can also reliably alter the influence of brain stimulation on brain activity and behaviour.

Attentional information routing

Mechanisms of selective attention prioritize and filter both sensory inputs and internal thoughts. Dynamic changes in neuronal activity underlie an increased signal-to-noise ratio and regulate selective routing of information to guide optimal behaviour[97,98]. As a consequence, attentional states and the content of the attentional 'spotlight' fluctuate from moment to moment, depending on such diverse factors as task demands, salience and temporal predictability of incoming sensory information. Here we briefly consider how voluntary attention is manipulated in experimental settings and what physiological changes are associated with its deployment. We then highlight studies that have shown how voluntary attentional engagement at the time of brain stimulation regulates 'bottom-up' and 'top-down' network activity, and how it can modify cortical plasticity.

Manipulating voluntary attention. Voluntary attention is under the control of a frontoparietal network, including the frontal eye fields (FEF) and posterior parietal cortex[99], which are thought to provide 'top-down' input to sensory areas, thus modulating 'bottom-up' information processing throughout the network[100]. Experimental manipulations of voluntary attention typically hold stimuli constant while varying the requirement to attend to a specific sensory modality, location in space or stimulus feature, as illustrated in FIG. 3a. In the visual modality, attention is often deployed covertly (that is, without moving the eyes) to control for modulations of brain activity that arise in response to changes in the retinal image due to eye movements. When covert attention is mobilized, a number of changes occur in neural ensembles selective for the attended modality, spatial location or feature. Imaging methods such as EEG and fMRI have shown that, for attended events, local neural activity is increased[1,101,102] and cortical rhythms are biased towards the gamma range (more than 40 Hz)[103]. Similarly, electrophysiological recordings from single neurons have revealed increased spike rates and decreased neuronal covariability for attended stimuli[97,104]. In turn, cortical networks processing non-attended information tend to exhibit decreased haemodynamic activity[105], lower-frequency electrophysiological rhythms in the alpha range (~10 Hz)[106] and decreased neuronal responsiveness.

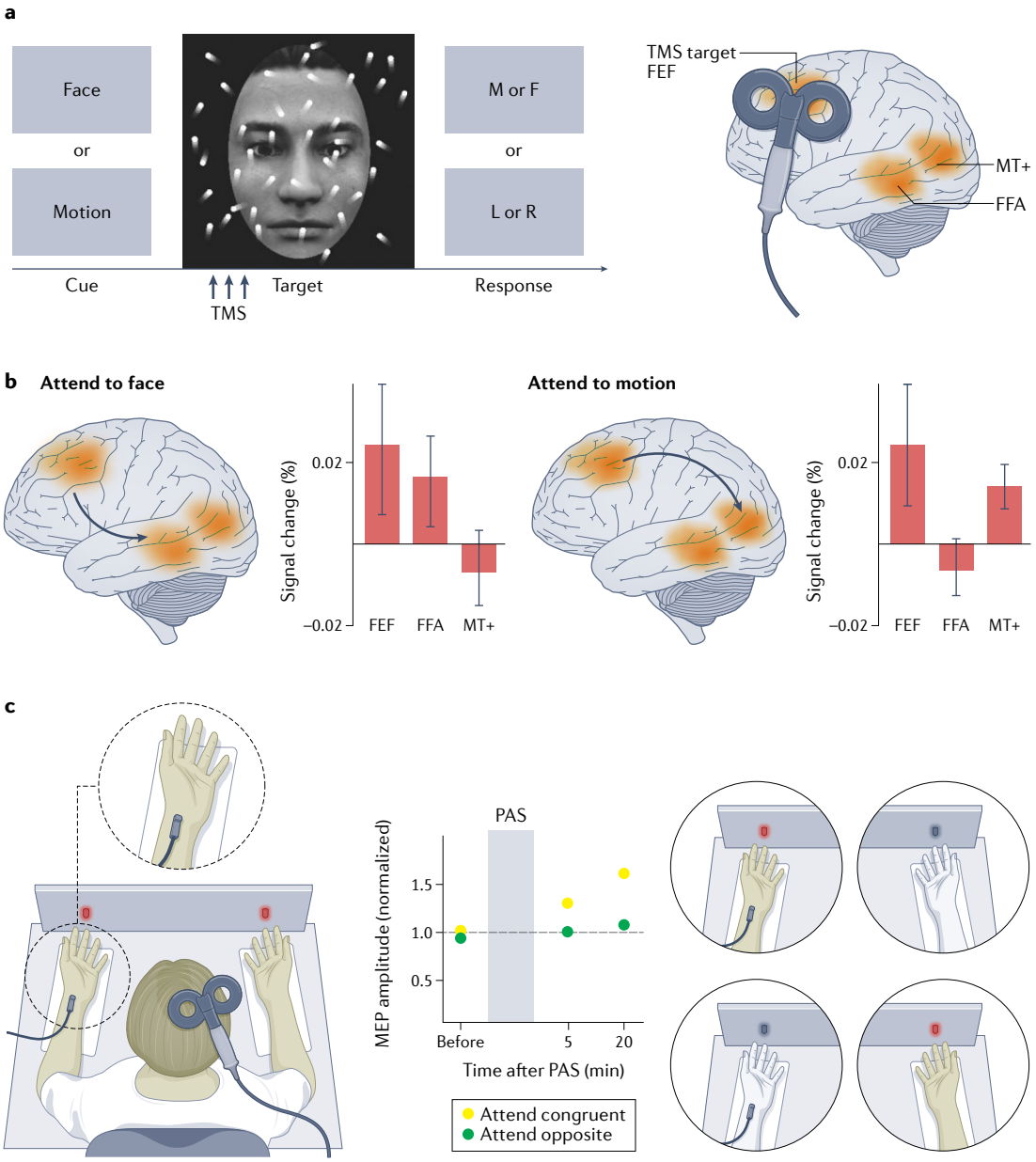


Fig. 3 | **Effects of attention on brain stimulation-triggered activity and neural plasticity. a** | In an attention task used by Heinen and colleagues[115], participants were cued to attend either to a face or to moving dots, and to perform a sex judgement (male (M) or female (F)) or a motion-direction judgement (left (L) or right (R)). Brain stimulation (three transcranial magnetic stimulation (TMS) pulses, black arrows) was delivered during the target display, which always contained both the face and the dots, thus keeping visual input constant across attention conditions. TMS was directed to the frontal eye field (FEF), and activity in category-specific areas (fusiform face area (FFA) for faces and human motion-sensitive complex MT+ for motion) was measured with functional MRI (orange shading). Note that the FFA is located medially within the temporal lobe. **b** | TMS stimulation increased activity in the targeted FEF. Critically, FEF TMS increased activity in the FFA when participants attended to faces, whereas the same stimulation increased activity in MT+ when participants attended instead to motion. The results suggest dynamic routing of TMS pulses from the FEF to category-specific cortical areas depending on participants' state of attentional allocation **c** | Kamke and colleagues[124] used repeated pairing of TMS pulses over the motor cortex with median nerve stimulation (left panel, inset), a technique known as paired associative stimulation (PAS), to induce transient plasticity in the motor system. Spatial attention was manipulated by requiring participants to monitor an LED light. The light was positioned either adjacent to the hand controlled by the hemisphere undergoing PAS (congruent condition) or adjacent to the other hand (opposite condition). Motor evoked potential (MEP) amplitude following PAS revealed that plasticity was expressed only when participants attended to the side of space congruent with PAS. By contrast, when they attended away from the hand involved in PAS, the normal plasticity effects were abolished. Image in part **a** courtesy of David Lloyd. Part **b** adapted with permission from REF.[115], Oxford Univ. Press. Part **c** adapted with permission from REF.[124], Society for Neuroscience.

Changes in 'bottom-up' stimulation-induced neural transmission. Visual attention improves perception of attended objects by fine-tuning their representations and optimizing communication between neuronal populations that respond to these objects across different levels of the visual processing hierarchy. Weak direct electrical stimulation of the lateral geniculate nucleus, which is responsible for transmission of visual information to the primary visual cortex, can be used to investigate synaptic efficacy between pairs of lateral geniculate nucleus and primary visual cortex neurons. Briggs and colleagues found that such stimulation drives spiking activity more effectively when the animal is attending to a visual stimulus inside the recorded neuron's receptive field than when it is attending to a stimulus outside it[107]. This was reflected by an increased number of stimulation pulses triggering postsynaptic responses, increased spiking synchrony between neurons receiving separate presynaptic inputs and decreased spiking synchrony between neurons that share common presynaptic inputs. These results show that attention increases synaptic efficacy and modulates stimulation-induced synchronous activity in the milliseconds following a single stimulation pulse. They provide a compelling example of how shifting spatial attention can lead to preferential transmission of stimulation-evoked activity in neurons whose receptive fields overlap with the locus of attention. Focusing on slightly longer timescales of tens of milliseconds, Ruff and Cohen demonstrated that microstimulation-evoked neuronal firing from one visual cortical area to another is increased at the locus of spatial attention[108]. Firing rates were increased in macaque middle temporal area (MT) immediately after brief (50 ms), repetitive electrical stimulation of primary visual cortex neurons. This increase was larger under conditions in which the animal was attending to stimuli falling within, as opposed to outside, the relevant primary visual cortex neuron's receptive field. While generalization of these findings to applications of non-invasive TMS in humans is not straightforward, these two studies reveal that the effects of stimulation of a neuronal population involved in feedforward processing of sensory information can be reliably altered by the current locus of spatial attention.

A broadly analogous finding in humans comes from a study that combined TMS of the occipital cortex and EEG[109]. An early response to the TMS pulse, presumably originating from the visual cortex, was enhanced when participants attended to the visual stimuli, as opposed to auditory stimuli, suggesting a local increase in the excitability of visual cortex under visual attention. Rhythmic activity following the pulse[110,111] was also affected: TMS-evoked alpha power in the parieto-occipital cortex was reduced when participants attended to visual stimuli, suggesting that the ability of TMS to induce oscillatory responses in a network varies with the network's ongoing activity and processing mode[109].

Selective 'top-down' routing of brain stimulation-triggered activity. In humans, a frontoparietal network is involved in voluntary attentional orienting and top-down modulation of sensory activity based on task demands[112]. Using fMRI, Blankenburg and colleagues[113] found that brief bursts of 10-Hz TMS over the right posterior parietal cortex (PPC) modulated activity in extrastriate visual cortices in a manner which depended on whether attention was directed to the ipsilateral or contralateral visual field. Whereas TMS delivered over the right PPC had no effect on extrastriate activity in a non-demanding control task, the same stimulation resulted in a relative increase in activity when attention was directed contralaterally, and in a relative decrease when attention was directed ipsilaterally. In other words, stimulation of the PPC amplified the patterns of upregulation and downregulation of activity that would normally arise when attention is voluntarily allocated to the left or right visual hemifield.

A similar effect has been found for feature-based visual attention, in which processing resources are allocated to a specific feature of an object, such as its colour or orientation, rather than to a specific location in space. Morishima and colleagues[114] used combined TMS and EEG to reveal task-dependent effective connectivity between the FEF and posterior visual areas. Participants viewed overlapping displays containing both a face and a patch of moving dots, and were cued to attend to one or the other stimulus category (FIG. 3a). Single pulses of TMS delivered to the FEF increased activity in the fusiform face area when participants attended to the faces, but increased activity in human motion-sensitive complex MT+ when they attended instead to the moving dots. This finding was independently replicated with use of TMS combined with fMRI[115] (FIG. 3b). The findings of these studies complement earlier findings by Sack and colleagues[116], who showed that the behavioural and network effects of stimulating the right PPC differ depending on the task at hand.

A key conclusion arising from these findings taken together is that when frontoparietal areas that control attention are stimulated, TMS-triggered activity propagates more readily through the network defined by the location, feature or modality being attended, depending on the degree of its engagement.

Impact of attention on brain stimulation-induced plasticity. When non-invasive brain stimulation is applied with the aim of creating a lasting change (for example, rTMS plasticity induction), attentional state during stimulation can dramatically affect the outcome. For example, a protocol known as 'paired associative stimulation' (PAS) can be used to increase or suppress corticospinal excitability for up to several hours[117,118], as measured by the amplitude of MEPs triggered by a TMS pulse over the primary motor cortex. PAS involves repeatedly stimulating a peripheral nerve in combination with the primary motor cortex so that afferent activity from the peripheral stimulation reaches the primary motor cortex shortly before or after the TMS pulse (FIG. 3c). The direction of excitability change is crucially dependent on the time interval between peripheral (nerve) and central (cortical) stimulation. Because of their strong time dependency and other properties, PAS-induced changes have been likened to long-term potentiation (LTP) and long-term depression (LTD), two key mechanisms underlying synaptic plasticity in the nervous system[119,120].

Decoding
A data analysis technique that uses a computer algorithm — a 'classifier' — to predict which class of stimulus or experimental condition was present in a given trial, based on multivariate features of brain activity for that trial.

Critically, if attention is engaged during a visual detection task, normal PAS plasticity occurs under low attentional load conditions, but is abolished under high attentional load conditions[121]. This is in line with early work showing that demanding cognitive tasks can disrupt both PAS and tES plasticity effects[122,123], and further demonstrates the specific state-dependent influence of visual attentional load. Using a similar approach in which spatial attention was manipulated, Kamke and colleagues[124] showed that if attention is drawn away from the hand undergoing plasticity induction (for example, to the opposite hand or centrally), LTP-like plasticity is reduced (see also REF.[122]). By contrast, if attention is drawn to the same region of space as the hand undergoing plasticity, LTP-like plasticity is increased[124] (FIG. 3c). In other words, visual spatial attention increases LTP-like plasticity and reduces LTD-like plasticity in human motor cortex. These findings have important implications for the application of plasticity-inducing brain stimulation for therapeutic purposes in patients with neurological disorders, in whom attentional allocation is often impaired[125].

In summary, it is clear that the effects of brain stimulation on neural networks are modulated by the allocation of attention to features or locations of sensory input in the external world. Attention can also be mobilized to give priority to internal representations[126], such as those held in working memory. In the next section, we examine how the neural states associated with working memory affect brain stimulation outcomes.

Dynamic contents of working memory

The capacity to store and manipulate information in working memory is central to many higher cognitive processes[127]. Human fMRI and animal physiology studies converge in implicating the prefrontal cortex, PPC and primary sensory areas in a working memory network[128,129]. Both the configuration and the activity level within this network can change across different stages of working memory processing[130], including encoding and consolidation, retention and retrieval[131]. Recent work on the effects of brain stimulation on working memory has shown that the type of information held in working memory, as well as the demands placed on the memory system, significantly alters how stimulation interacts with neural activity and behaviour.

Prioritization state in working memory. Classical investigations of working memory have focused on the delay period — or retention interval — of a recognition or comparison task[131,132]. Typically, a task-relevant stimulus is encoded for a finite period. Information about this stimulus must then be maintained in an accessible state in the absence of the stimulus (maintenance) until a probe appears, prompting a judgement and response from the participant (retrieval). Several items can thus be 'held' in working memory. Strikingly, TMS pulses delivered during the delay period of a working memory task are able to uncover network configurations that change dynamically depending on the specific content of working memory[133]. By successively cueing two items held in working memory (FIG. 4a), Rose and colleagues[133] shifted each item's status from attended in memory to unattended. They were able to decode the category of the attended memory item from ongoing brain activity but could not decode the unattended memory item, lending support to the idea that the attended memory item is stored as persistent activity[134], while the unattended item may be stored as activity-silent modifications of synaptic weights or intracellular activity[135,136]. Importantly, a moderate-intensity TMS pulse targeting category-selective brain regions caused a brief recovery of decodability for the unattended memory item, possibly through activation or reactivation of a latent memory pattern (FIG. 4b). No such boost in decoding accuracy occurred for items that had been cleared from working memory, nor did the TMS pulse affect the decodability of the attended memory item. In other words, the electrophysiological readout of a TMS pulse during the working memory delay period depends on the content of working memory, and may specifically reveal activity-silent patterns of information (FIG. 4c). Furthermore, items in a prioritized working memory state are more susceptible to disruption by short bursts of TMS to early visual areas than items that are in a non-prioritized state[137], suggesting that stimulation-induced interference is restricted to certain stimuli depending on their prioritization state in working memory.

Quality of representations over time. Critically, the representations of items to be remembered are not static over time but may vary in initial quality, evolve over time or even be reactivated between trials over the course of a task[138]. In other words, stored representations of items may vary under different states of the working memory process. In line with the involvement of specific brain structures at distinct information-processing stages, the particular time point at which brain stimulation is delivered during a working memory task is of critical importance. For instance, TMS pulses delivered to the occipital cortex at various delays during a retention interval exert distinct disruptive effects on performance[139–142], producing either spatial specificity or generalizable effects across the visual field, consistent with emerging evidence that stimulus representations can change over the retention interval[136] (FIG. 4d).

On a longer timescale, recent work in patients with epilepsy has shown that the effect of brain stimulation on memory varies on a trial-by-trial basis, together with the quality of encoding of the item to be memorized[143]. Short bursts of high-frequency electric pulses delivered to the medial temporal lobe during word encoding resulted in inconsistent effects on overall recall. However, stratification of trials using a multivariate pattern classifier trained in a different session to predict recall from early encoding-related activity revealed an interaction between stimulation outcome and encoding quality. Stimulation delivered in trials with low initial encoding enhanced recall and encoding quality, whereas stimulation delivered in trials with high initial encoding disrupted later recall and encoding.

The precise mechanisms through which different types of brain stimulation interact with concurrent and successive stimulus representations merit further study.

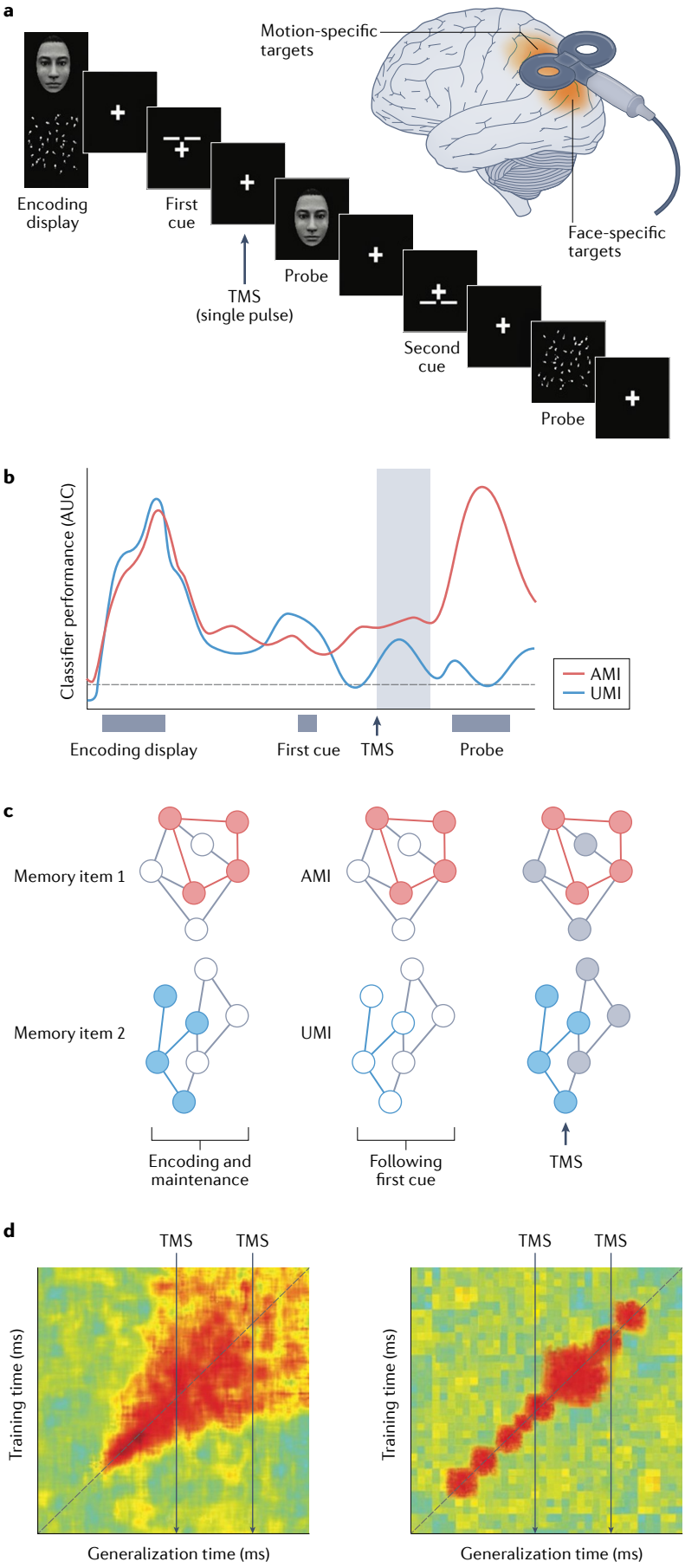


Fig. 4 | **Brain stimulation interacts with latent working memory representations. a** | Rose and colleagues[133] manipulated working memory content by asking participants to encode two memory items — here, a face and moving dots. A first cue indicated which item would be the object of an upcoming recognition memory probe. Both items were equally likely to be used in a second cued judgement, thereby ensuring that no item information was discarded in the first half of the trial, but that one was given priority (the attended memory item (AMI)) over the other (the unattended memory item (UMI)). Following the first cue but before the first probe, a transcranial magnetic stimulation (TMS) pulse (black arrow) was delivered to a face-selective or motion-selective area of the cortex. **b** | Using electroencephalography (EEG) data, a classifier was able to identify the two items during and after encoding. Following the first cue, the decodability of the UMI decreased to chance level. Critically, the TMS pulse briefly recovered UMI decodability (grey-shaded window). **c** | The findings suggest that a TMS pulse can briefly reactivate a latent representation of a UMI that is stored in a format not accessible to EEG-based decoding — hypothetically in potentiated synaptic connections (lines between blue nodes). Note that the TMS pulse affects all elements but is hypothesized to interact differently with active (red), potentiated (blue) and inactive (grey) elements. **d** | Schematic illustration showing that TMS pulses (black arrows) delivered at different times during a cognitive task may interact with different underlying representations. Training a classifier at one time point and testing it at other time points during a putative cognitive task reveals the extent to which a representation generalizes over time[169]. Depending on the context, representations may generalize differently over time, indicating more or less stable codes (left and right panels, respectively). Warmer shading denotes higher classifier performance. The effect of TMS pulses on classifier performance is not represented here. AUC, area under the curve. Parts **a**, **b** and **c** adapted with permission from REF.[133], AAAS. Image in part **a** courtesy of David Lloyd. Part **d** is adapted from REF.[170], CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/).

At the very least, such findings imply that the effects of brain stimulation may vary as a function of trial history and stimulus history, and as a function of the strength and nature of the underlying neural representations.

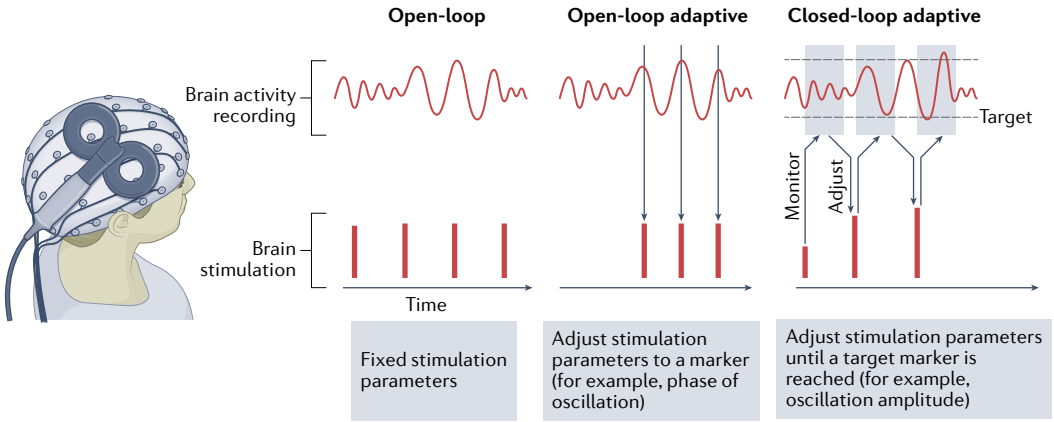
Network effects uncovered by the presence of distracting stimuli. Another way in which brain stimulation has uncovered latent network configurations that change with working memory requirements has been revealed by work on the effects of interference from distractors during the delay period of a working memory task. Feredoes and colleagues[144] had human participants remember items from one of two categories (houses or faces), which generated sustained activity increases in category-specific brain regions[145] (the parahippocampal place area for houses and the fusiform face area for faces). They also presented participants with a distractor of the opposite category during the delay period, with the goal of interfering with performance, a process that the dorsolateral prefrontal cortex (DLPFC) should normally mitigate. TMS pulses (suprathreshold, three pulses, 11 Hz) delivered to the right DLPFC during the

Box 2 | **Towards closed-loop brain stimulation**

In recent years, significant advances have been made in delivering brain stimulation adaptively[8,178–180]. The general idea of open-loop, adaptive brain stimulation is to tailor when and how brain stimulation is delivered on the basis of a specific marker (see the figure). That marker might be defined by behaviour (for example, 'stimulate every time the participant generates a motor response'), physiology (for example, pupil diameter or heart rate) or neural activity (for example, oscillatory power, phase or detection of neural patterns obtained through prior training of a classifier). Closed-loop brain stimulation takes this idea one step further and aims to not only monitor but also control the marker value. In such paradigms, brain stimulation is delivered until a target state is achieved, with possible iterative parameter adjustment (see the figure). Such an approach creates particular challenges in exploring stimulation parameters and measuring markers in real time in the presence of stimulation artifacts.

What do these technical advances have to offer? In the laboratory, adaptive brain stimulation allows more efficient and targeted experimental designs. For instance, consider the question of whether the phase of 'mu' oscillations (~8–13 Hz) and beta oscillations (~13–30 Hz) in sensorimotor cortex modulates propagation of transcranial magnetic stimulation or direct electrical stimulation pulses in local and long-range circuits. Classical, non-adaptive brain stimulation involves delivery of many pulses, sporadically covering all phase values of the oscillation. By contrast, adaptive stimulation can be used to target a few key phase values and requires fewer pulses overall to gather information for each phase value. This line of work has started to illuminate how the phase and power of ongoing oscillations affect the manner in which brain stimulation propagates in the corticomotor network[181–183], disrupts or enhances local oscillatory processes[184], and triggers transient plasticity of connectivity between connected areas[185].

In the clinic, adaptive and closed-loop brain stimulation — both invasive and non-invasive — show promise for optimizing treatment of drug-resistant epilepsy[186,187] and tremor[188–191]. These advances provide a general proof of concept for the utility and feasibility of these approaches in clinical contexts. In theory, adaptive brain stimulation could be incorporated in brain–machine interfaces[192] such as those used to control bionic limbs or to supplement impaired senses. Beyond the sensorimotor domain, exciting applications are being developed in the cognitive and affective realms[193], in particular for the treatment of mood disorders[194]. For instance, a recent study used a novel, closed-loop deep-brain stimulation protocol in a patient with treatment-resistant depression. The study authors used gamma-range activity recorded in the amygdala as a neural biomarker tailored to the individual patient[195].



delay period caused an increase in fMRI signal in the relevant category-specific brain area for the memory item, but only when a distractor was present[144]. Under conditions of interference, therefore, the DLPFC may strengthen category-specific information about the memory item, rather than suppressing interfering information, as causally uncovered by the TMS pulse. This finding is reminiscent of an effect described earlier[114,115], in which feature-selective attention altered effective connectivity between the FEF and posterior visual areas following TMS delivered over the FEF. The network effects of TMS over the DLPFC during working memory are therefore critically dependent on task context and difficulty (that is, the presence of distractors).

Working memory load. Non-invasive brain stimulation effects are typically increased under high versus low working memory loads[139,146–150]. For example, combining working memory training — in the form of an *N*-back task — with anodal tDCS over the DLPFC has been shown to increase performance on a subsequent auditory working memory task relative to training alone[148]. The synergy between concurrent tDCS and training was expressed under high working memory load training (a 3-back condition) relative to low working memory load training (a 1-back condition). Interestingly, the high-load condition may have resulted in more distractor interference, and thus enhanced interactions between the DLPFC and areas responsible for item maintenance. Could these results be explained by a task-dependent network effect of brain stimulation, similar to the effects reported by Feredoes and colleagues[144]? Extrapolating from the results obtained with TMS is difficult, but it might be speculated that anodal tDCS modulates membrane potential, and ongoing activity of some neurons, leading to consolidation of synapses most active in the network revealed by TMS. However, such an explanation would not easily account for generalization of working memory effects to a different task and stimuli, unless plasticity in other networks

showing load-dependent effects in working memory[151] is postulated. Alternative explanations include consolidation of synapses in the local stimulated brain area, as they are modulated by the task, or in the modulation of specific oscillatory processes[152,153]. Further experimental evidence is needed to disambiguate these possible explanations.

Other brain stimulation techniques that are hypothesized to entrain oscillatory activity, such as rhythmic TMS and tACS, have yielded examples of task dependency. For example, theta-rhythmic TMS of the parietal cortex has been shown to entrain theta oscillations and to improve behavioural performance, specifically for a difficult auditory working memory task, as opposed to simple retention and comparison[149]. Recent work has revealed that age-related decline in performance on a change-detection task involving memory processes can be rescued by concurrent frontotemporal tACS, delivered at an individually defined theta frequency[154]. In this work, the stimulation normalized disrupted frontotemporal theta–gamma phase–amplitude coupling while participants were holding information in working memory, as opposed to when they were performing a vigilance task on the same stimuli.

Conclusions and outstanding questions

There is no such thing as an idle brain. As a consequence, brain stimulation interventions designed to directly manipulate brain activity need to take into account its fluctuating states, as illustrated here across the domains of consciousness, attention and working memory. With the caveat that generalization from one brain stimulation technique to others is not trivial, we nevertheless summarize these findings below and flag some outstanding questions.

States of consciousness can significantly alter the way in which stimulation-induced neural activity propagates across the brain, particularly over long-range connections. Findings in sedated animals therefore need to be extrapolated with caution. Incursions into drowsiness, which are likely to affect many applications of brain stimulation, create subtler changes, showing increased variability of responses. Likewise, plasticity induction by brain stimulation is dramatically constrained by conscious state — in particular, some protocols that aim to entrain or trigger slow oscillations appear to be effective when delivered during 'deep' sleep only. This illustrates the general idea that entrainment of oscillations by brain stimulation may occur preferentially when these specific oscillations are dominant in the network.

Shifts of attention between different sensory modalities, locations and features generally lead to enhanced transmission of stimulation-evoked activity and flexible routing through the attentional network. Areas involved in the feedforward transmission of sensory information display an increase in stimulation-evoked synaptic efficacy, an increase in microstimulation-induced firing rates and a reduction in TMS-evoked alpha oscillations at the cortical locus of attention. By contrast, stimulation of 'control' areas in the frontoparietal cortex exerts network effects on location-specific or category-specific areas in a way that depends on the locus of attention. Moreover, visual spatial attention appears to bias plasticity induced by rTMS in the motor system towards facilitation and away from depression.

Finally, variations in the state of representations held in working memory, such as the strength, duration and current attentional focus in working memory, influence brain stimulation effects on physiology and behaviour. In particular, TMS increases the decodability of unattended but not attended memory items from ongoing EEG activity, highlighting that TMS can interact differently with spatially overlapping subsets of neural elements. When frontoparietal control areas are stimulated, network and frequency-specific brain stimulation effects are more readily revealed under task conditions of distractor interference and increased load.

As we have highlighted herein, although there has been significant progress in understanding the influence of state dependency on the effects of brain stimulation, many questions remain to be answered. First, how can observations from different scales and techniques be combined to better understand the influence of state on brain stimulation? In particular, reliable and generalizable approaches for quantifying excitability of networks outside the motor system are needed. Studies taking on the challenging task of combining multiple imaging methods, such as concurrent TMS–EEG–fMRI[155], will undoubtedly contribute to filling this mechanistic gap. Computational models, which offer a bridge between different levels of observation, may also be helpful[156]. The best marker, or set of markers, that characterizes a desired state might then be harnessed to adaptively trigger stimulation (BOX 2). Second, how do the contributions of several concurrent states combine to affect brain stimulation outcomes? There is evidence that states linked, for example, to expectation[157–160], reward[161–163]

Box 3 | **Cognitive state dependency of brain stimulation in the clinic**

Brain stimulation protocols have shown promise in treating a range of neurological and neuropsychiatric conditions[48,49,196,197], including major depressive disorder[198–200], addiction[22], Parkinson disease[201] and obsessive compulsive disorder[202–204]. In an effort to understand the large interindividual and intra-individual variability that is characteristic of these interventions, the current 'state' of patients at the time of brain stimulation has been considered along many dimensions, including the severity of disease and ongoing disease presentation[205]. A recent case report has shown that a patient receiving deep brain stimulation for severe treatment-resistant depression benefited from stimulation of different target sites (orbitofrontal cortex and perigenual cingulate) depending on the patient's initial mood at the time of stimulation[206]. These findings raise the prospect of delivering multisite stimulation, adaptively patterned (BOX 2) to fit ongoing patient mood and arousal states.

While most clinical brain stimulation is delivered with the patient awake and at rest, efforts to actively manipulate the cognitive state to increase the effectiveness of brain stimulation have increased in recent years (see REFS[207,208] for reviews), with initiatives such as delivering repetitive transcranial magnetic stimulation or transcranial direct current stimulation concurrently with cognitive behavioural therapy or cognitive control training in major depressive disorder[209,210]. Importantly, given the effort involved in patients performing a task during stimulation, the superiority of these interventions relative to stimulation at rest must be clearly established[209,211–213], specifically in patients. Indeed, direct application of basic research findings would not be appropriate, at the very least because patient pathophysiology may impact the feasibility of recruiting a specific state (for example, owing to attention deficits, sleep disorders or memory impairments), on the effects of brain stimulation (for example, potential for impaired plasticity induction) and on the interaction between state and stimulation. Well-powered, controlled studies incorporating imaging and brain stimulation in patients are clearly needed.

and decision-making[164–166] can all interact with brain stimulation, sometimes in opposite directions. Do some states exert larger influences over brain stimulation-triggered neural effects than others? Third, how is stimulation-induced plasticity expressed in a network that is engaged during stimulation? Does stimulation-induced plasticity affect latent versus active representations differently? How might this affect the transfer of learning to other cognitive processes normally supported by the same network?

Many of the studies reviewed here demonstrate state-dependent routing of neural activity induced by brain stimulation. The consequences of repeated stimulation under these conditions are mostly unexplored. This is particularly important for our understanding of brain stimulation-induced plasticity and for applications in the clinic (BOX 3). In particular, more studies combining tDCS with imaging during cognitive tasks would be beneficial, as such approaches are more applicable to clinical applications yet remain poorly understood. With a renewed focus on methodological rigour[31,167] and the introduction of new techniques such as focused transcranial ultrasound stimulation[168] of deep brain structures, the future promises fresh insights into state-dependent effects of neural stimulation on brain activity and behaviour in health and disease.

Published online: 16 May 2022

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Acknowledgements
This work was supported by a grant from the Australian National Health and Medical Research Council awarded to J.B.M. and P.E.D. (GNT1129715). J.B.M. was supported by a National Health and Medical Research Council Investigator Award (GNT2010141), and by the Australian Research Council Centre of Excellence for Integrative Brain Function (Australian Research Council Centre of Excellence grant CE140100007). The authors thank D. Lloyd for assistance with the figures, K. Garner for helpful discussion, and A. Harris, W. Harrison, D. Rangelov, R. Rideaux and R. Tweedale for their comments on earlier drafts of the manuscript.

Author contributions
C.B., A.S.N. and J.B.M. researched data for the article, provided substantial contributions to discussion of its content, and wrote, reviewed and edited the manuscript before submission. P.E.D. provided a substantial contribution to discussion of the article's content and reviewed and edited the manuscript before submission.

Competing interests
The authors declare no competing interests.

Peer review information
Nature Reviews Neuroscience thanks J. Duque, who co-reviewed with G. Derosiere, C. Ruff, A. Sack and the other anonymous reviewer(s) for their contribution to the peer review of this work.

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