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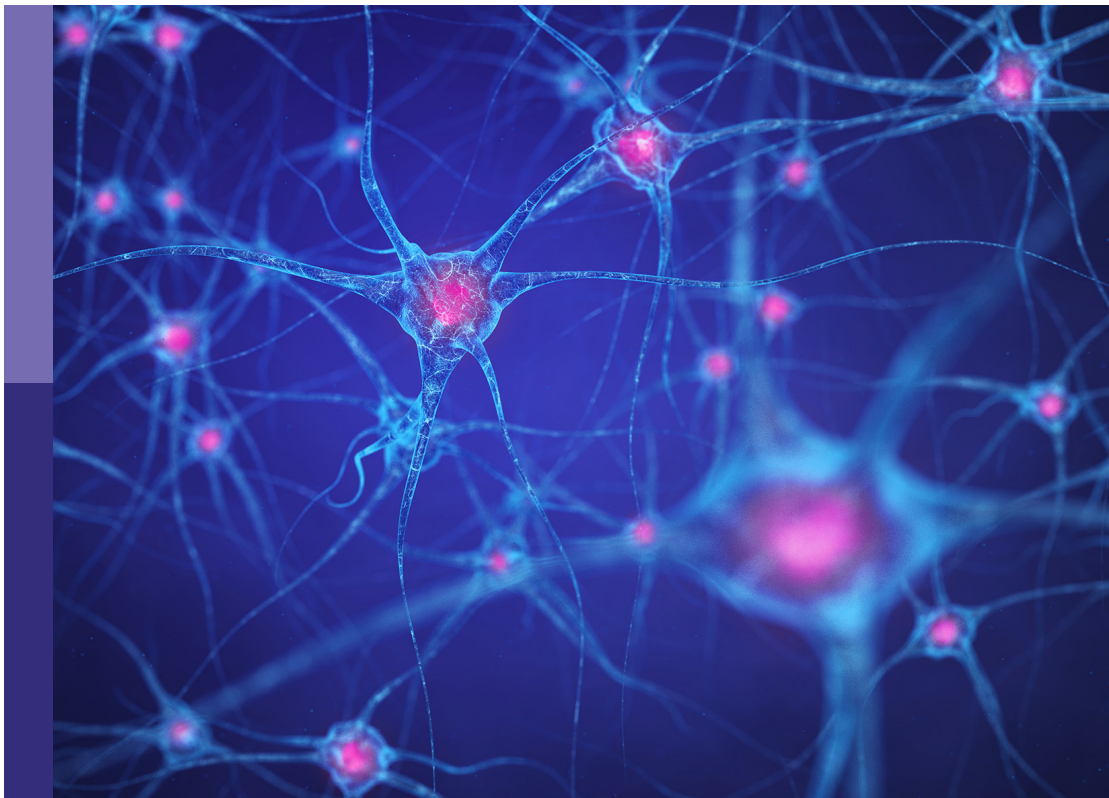

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Horizons in Systems Neuroscience 2022

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Editorial: Horizons in Systems Neuroscience 2022

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Editorial on the Research Topic
Horizons in Systems Neuroscience 2022

With its intricate network of billions of neurons, the human brain functions like a conductor, orchestrating thoughts, emotions, and actions. Systems Neuroscience aims to understand this complex symphony. Driven by technological advancement and a surge in interdisciplinary collaborations, this field has undergone a remarkable transformation.

The Research Topic "*Horizons in Systems Neuroscience 2022*" showcases fascinating new avenues of exploration. The nine articles cover diverse topics, including neural oscillations, perception, anxiety, memory, neuroplasticity, hypothesis, and theory. These works collectively provide insights into the brain's complexity and pave the way for future discoveries. All contributing authors were nominated in recognition of their prominence and influence in their respective fields.

Perception and actions are fundamental processes that characterize our lives and our possibility to modify the world around us. Bosco et al. reviewed the literature on how "*The influence of action on perception spans different effectors.*" The manuscript focuses on the influence of action on perception, specifically on the action planning and the phase following the execution of the action. The authors conclude that action planning and action execution constantly influence perception, which may be used to improve artificial intelligence (AI) systems and increase users' trust in AI.

At the systems level, recent research into neural oscillations spans different brain areas, species, and disciplines, granting us a common ground for the disparate fields of neuroscience. In a minireview, Miles et al. reviewed articles related to "*Hippocampal beta rhythms as a bridge between sensory learning and memory-guided decision-making.*" The authors highlight the role of beta oscillations in mediating coupling between the hippocampus and other regions involved in coordinating memory-guided behavior. This review puts forward hypothesis extending the role of beta oscillations beyond sensory systems toward a general role of hippocampal beta in enabling inter-regional coupling for sensory-driven, cue-reward associations and for enabling memory-guided behavior.

Long-term memory is achieved through a consolidation process where structural and molecular changes integrate information into a stable memory. In a review, Osorio-Gomez et al. discuss "*Transforming experiences: Neurobiology of memory updating/editing*." It explains how long-term memory is formed and updated through a consolidation process involving structural and molecular changes. The process is dynamic, adapting to environmental changes and integrating new experiences. The article highlights the potential clinical implications of memory updating in conditions like drug addiction, phobias, and post-traumatic stress disorder.

Heck et al. further summarize the "*Cerebellar control of thalamocortical circuits for cognitive function: A review of pathways and a proposed mechanism*" in a minireview. The article explores the cerebrocerebellar interactions and cerebellothalamic pathways in cognitive and motor functions. It discusses the role of the thalamus in coordinating neuronal oscillations, indicating increased functional connectivity. The authors suggest that cerebellothalamic pathways may be crucial in coordinating neuronal communication.

In a systematic review, Mowery and Garranghty discuss "*Adult neuroplasticity employs developmental mechanisms.*" It summarizes studies showing adult neural plasticity, including primate somatosensory cortex. The article also discusses experiments revealing the physiological, morphological, and neurochemical mechanisms permitting this plasticity. It concludes that adult cells return to critical period-like plastic states under prolonged sensory deprivation.

Historically, spinal cord processes were considered mere mechanical relays for signals. Recent research challenges this view, this review by Grau et al. reveals that spinal cord mechanisms can organize behavior, alter pain processing, and infer stimulus relations. These processes resemble brain-dependent learning pathways. Spinal cord injury can induce plasticity while GABA transmission has a crucial role regulating such plasticity. Understanding spinal cord functions informs brain models and offers new treatments for spinal cord injury.

Anxiety disorders are the most common class of mental illness. A wealth of data has implicated the medial prefrontal cortex in the regulation of anxiety, and norepinephrine is a crucial neuromodulator of arousal and vigilance believed to be responsible for many of the symptoms of anxiety disorders. Bouras et al. reviewed "*Prefrontal modulation of anxiety through a lens of noradrenergic signaling*." This article details the various potential projections and mechanisms through which the medial prefrontal cortex can exert executive control over subcortical regions involved in anxiety following locus coeruleus activation with the proposed model and fascinating future directions.

In a clinically relevant review, Bonin et al. summarize the "*Assessment and management of pain/nociception in patients with disorders of consciousness or locked-in syndrome*." The authors discuss the challenges in assessing and managing pain in such patients. It highlights the need for clear guidelines and explores various topics, including the neurophysiology of pain, its impact, and treatment strategies. The review also suggests potential research directions for improving patient management.

Finally, as stated in the thought-provoking search for a theory summed up by Roland, the debate about "*How far neuroscientists are from understanding brains*" remains. This article highlights the current gaps in neuroscience, particularly in understanding how neurons interact at all scales and how brains function. It points out conceptual obstacles, such as the lack of models explaining neuron interactions, ambiguity in distinguishing different types of brain activities, and the insufficiency of dynamical systems theory to account for central nervous system activities. The author suggests that spatial dynamics could be a solution. The author also emphasizes the need for single-trial designs and statistics, as pooling and averaging data can destroy their underlying dynamics. The hypothesis/theory presented in the article is significant but perhaps also provocative, including the critical challenges identified and potential solutions proposed by the author. Nevertheless, it paves the way for the need for a theory explaining how the brains work.

These articles highlight the challenges in integrating findings across scales, deciphering the brain's code, and understanding its embodiment in the world. Despite these challenges, the diverse perspectives showcased in his Research Topic demonstrate the potential for groundbreaking discoveries in Systems Neuroscience. We eagerly await pioneering research that will sharpen the future of Systems Neuroscience.

Overall, the research and perspectives presented in this Research Topic underscore the complexity and interconnectedness of the brain's systems. By pushing the boundaries of knowledge, Systems Neuroscience has the potential to revolutionize our understanding of the brain and open new avenues for treating neurological and mental disorders.

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Adult neuroplasticity employs developmental mechanisms

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Although neural plasticity is now widely studied, there was a time when the idea of adult plasticity was antithetical to the mainstream. The essential stumbling block arose from the seminal experiments of Hubel and Wiesel who presented convincing evidence that there existed a critical period for plasticity during development after which the brain lost its ability to change in accordance to shifts in sensory input. Despite the zeitgeist that mature brain is relatively immutable to change, there were a number of examples of adult neural plasticity emerging in the scientific literature. Interestingly, some of the earliest of these studies involved visual plasticity in the adult cat. Even earlier, there were reports of what appeared to be functional reorganization in adult rat somatosensory thalamus after dorsal column lesions, a finding that was confirmed and extended with additional experimentation. To demonstrate that these findings reflected more than a response to central injury, and to gain greater control of the extent of the sensory loss, peripheral nerve injuries were used that eliminated ascending sensory information while leaving central pathways intact. Merzenich, Kaas, and colleagues used peripheral nerve transections to reveal unambiguous reorganization in primate somatosensory cortex. Moreover, these same researchers showed that this plasticity proceeded in no less than two stages, one immediate, and one more protracted. These findings were confirmed and extended to more expansive cortical deprivations, and further extended to the thalamus and brainstem. There then began a series of experiments to reveal the physiological, morphological and neurochemical mechanisms that permitted this plasticity. Ultimately, Mowery and colleagues conducted a series of experiments that carefully tracked the levels of expression of several subunits of glutamate (AMPA and NMDA) and GABA (GABAA and GABAB) receptor complexes in primate somatosensory cortex at several time points after peripheral nerve injury. These receptor subunit mapping experiments revealed that membrane expression levels came to reflect those seen in early phases of critical period development. This suggested that under conditions of prolonged sensory deprivation the adult cells were returning to critical period like plastic states, i.e., developmental recapitulation. Here we outline the heuristics that drive this phenomenon.

KEYWORDS

adult neuroplasticity, GABA receptors, glutamate receptors, developmental recapitulation, sensory deprivation

Introduction

Although neural plasticity is now one of the most widely researched phenomena in the field, there was a time when the idea of adult plasticity was antithetical to the mainstream. The essential stumbling block was that the robust structural and functional effects of early disruptions of normal visual experience were not apparent in adult models. For example, Wiesel and Hubel (1963a) reported marked atrophy of cells in the deprived layers of the cat lateral geniculate nucleus (LGN) when monocular visual deprivation began early in life. Adult-onset monocular deprivation, on the other hand, had no effect on LGN cell size. Similarly, early visual deprivation resulted in a profound effect in striate cortex such that nearly all of the recorded cells responded only to inputs conveyed by the non-deprived eye but no such effect was found when the deprivation began in adulthood (Wiesel and Hubel, 1963b). Subsequently, Hubel and Wiesel (1970) extended these findings and identified "the period of susceptibility." These studies provided convincing evidence that there existed a critical period for plasticity during visual system development after which the brain lost its ability to change in accordance to shifts in sensory input.

Despite the prevailing wisdom that mature brain is relatively immutable to change, there were a number of examples of adult neural plasticity emerging in the scientific literature. Interestingly, some of the earliest of these studies involved visual plasticity in the adult cat. A brief paper by Fiorentini and Maffei (1974) reported reduced binocularity in simple cells in adult cat visual cortex after the surgical immobilization of one eye, even with concurrent binocular deprivation (Maffei and Fiorentini, 1976). Other researchers (Brown and Salinger, 1979) reported the loss of X-cells in the layers of the adult cat LGN innervated by the immobilized eye following monocular paralysis, showing that adult neural plasticity could also be demonstrated in subcortical sites. A number of other examples of experience-dependent changes in adult visual system followed (e.g., Creutzfeldt and Heggelund, 1975; Hoffmann and Cynader, 1977; Salinger et al., 1977a,b, 1980a,b; Berlucchi et al., 1978a,b,c, 1979; Hoffmann and Holländer, 1978; Garraghty et al., 1982).

Even earlier, Wall and Egger (1971) reported functional reorganization in adult rat somatosensory thalamus after dorsal column lesions. Other experiments followed that showed plasticity in the dorsal spinal cord (e.g., Bausbaum and Wall, 1976; Wall, 1977), brainstem (e.g., Dostrovsky et al., 1976), and thalamus (e.g., Wall and Egger, 1971; Pollin and Albe-Fessard, 1979) after dorsal rhizotomies or dorsal column lesions. In these studies, cells in deafferented regions displayed abnormal receptive field properties that included responses to stimulation of intact peripheral pathways. Furthermore, it became apparent that this phenomenon was more than a transient response to deafferentation, as investigation of the temporal nature of these effects suggested that these changes could be both very acute (immediate) as well as chronic (e.g., Dostrovsky et al., 1976; Millar et al., 1976). Surprisingly (in retrospect), resistance to the possibility of adult neural plasticity remained strong.

Plasticity in adult primate somatosensory cortex

In 1983, Merzenich et al. (1983a,b), reported on a series of seminal investigations that provided conclusive evidence that the topographic map of the body in adult primate somatosensory cortex could undergo substantial changes when parts of the map were deprived of their activating inputs *via* peripheral nerve transection. These experiments had two major advantages over the findings briefly discussed above. First, the transection of a peripheral nerve (the median nerve in these experiments) deprives a precise portion of the topographic map, eliminating any possible ambiguity as to the extent of the deafferentation. Second, these researchers used New World primates, such as the squirrel monkey *Saimiri Saimirinae* or owl monkey *Aotus Aotidae* as their subjects. These smaller primates, which descended from old world monkeys and apes about 40 million years ago, have brains that are relatively lissencephalic, and primary somatosensory cortex is exposed on the outer surface of the brain, rather than being buried in the central sulcus as it is in Old World primates and humans. Thus, the recording sites in the deprived portion of the topographic map could be unambiguously sited on photographs of the cortical surface as the primary somatosensory area (see Figure 1; Merzenich et al., 1983b). This latter fact made it possible to monitor the progression of the topographic reorganization over time after the nerve transection within individual subjects. These sequential mappings over time demonstrated that the reorganization proceeded in no less than two phases (see Churchill et al., 1998). Immediately following nerve transection, "new" inputs were recorded in restricted regions of the deprived patch of cortex. Over the following days to weeks, the second phase of reorganization proceeded, as the remaining areas of the deprived cortex became responsive to skin surfaces on the hand with intact innervation.

These ground-breaking discoveries engendered a number of new lines of research. Included among these were experiments that examined use-dependent alterations in cortical topography (e.g., Jenkins et al., 1990; Recanzone et al., 1992), in experiments that behaviorally controlled the tactile experience of the subjects. Allard et al. (1991) used digit syndactyly to show that when receptors adjacent digits were consistently coactivated because the digits were surgically fused, the normally discrete digit representation in primary somatosensory cortex became fused as well. Garraghty and Muja (1995) showed similar fusions in

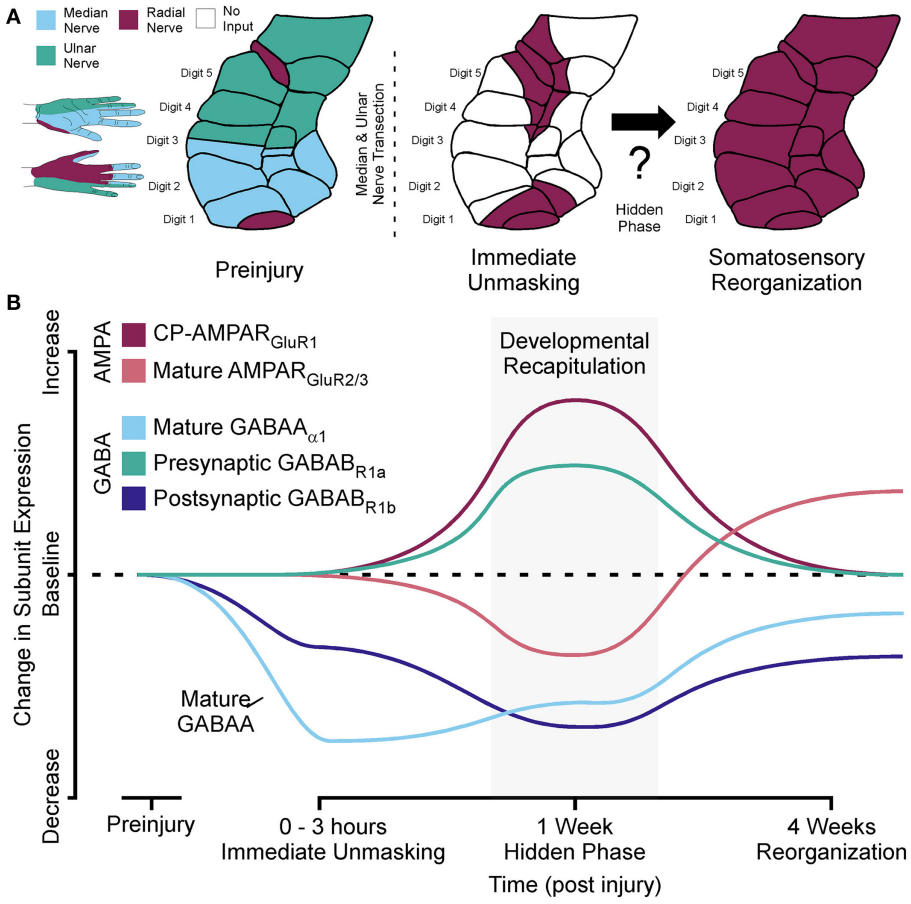

FIGURE 1
Developmental recapitulation: a hidden phase of somatosensory reorganization. **(A)** Left: Cartoon showing the innervation by the median, ulnar, and radial nerve inputs and corresponding receptive fields in area 3b cortex of the non-human primate hand region prior to injury. Right: Cartoon showing how the radial nerve inputs are immediately unmasked prior to complete reorganization of non-human primate area 3b hand representations after median and ulnar nerve transection. **(B)** Line diagram demonstrating how the shift in AMPA and GABA receptor subunit expressions reveal a previously hidden phase of adult somatosensory reorganization associated with the recapitulation of developmental receptor states.

a monkey with a paralytic condition in one hand such that cortical neuronal receptive fields matched the aberrant pattern of skin surface coactivations that the paralysis produced. By labeling individual thalamocortical axonal arbors, the possible anatomical substrates supporting the plasticity were explored (e.g., Garraghty et al., 1989; Garraghty and Sur, 1990). These experiments showed that individual axonal arbors were larger than the grain of the topographic map, offering a means by which receptive fields could move across the cortex, as happens with nerve injury-induced reorganization. Potential neurochemical mechanisms were examined. Garraghty et al. (1991) used immunostaining for GABA to show reductions in the region of cortex that had undergone reorganization after nerve injury. Avendaño et al. (1995) showed that cholinergic mechanism were involved in the brain's response to sensory loss. Additional studies evaluated other patterns or extents of sensory loss (e.g., Wall et al., 1983; Merzenich et al., 1984; Garraghty and Kaas, 1991a; Garraghty et al., 1994). Observations of nerve injury-induced plasticity were also extended to subcortical levels (e.g., Garraghty and Kaas, 1991b; Faggin et al., 1997; Churchill et al., 2001).

The earlier work of Wall and colleagues (e.g., Merrill and Wall, 1972; Wall, 1977) characterized the immediate phase of plasticity as the "unmasking" of latent inputs. These were defined as peripheral nerve receptive fields that were normally suppressed by the dominant nerve inputs to these cortical areas (e.g., radial nerve receptive fields in median nerve cortical territory). When the dominant input was removed, these subordinate receptive fields were expressed or "unmasked." Several lines of research subsequently offered confirmation for

this idea. First, there were several reports of increases in the receptive field sizes of cortical neurons when inhibition within the cortex was blocked with bicuculline (e.g., Hicks and Dykes, 1983; Dykes et al., 1984; Alloway et al., 1989), indicating that "latent" inputs were available to cortical neurons. Second, using suprathreshold whole nerve stimulation, Schroeder et al. (1995) showed that latent inputs could be revealed in somatosensory cortex. In these experiments, latent radial, but not ulnar, nerve inputs were recorded in "median nerve cortex," a finding that was consistent with the fact that the expansion of radial nerve-innervated skin surfaces accounted for most of the reorganization found in monkey cortex after median nerve transection (Merzenich et al., 1983a; Schroeder et al., 1997b; Myers et al., 2000). Finally, receptor autoradiographic (Wellman et al., 2002; Garraghty et al., 2006) and immunohistochemical experiments (Mowery et al., 2011) showed changes in GABA receptors that are consistent with a reduction in intracortical inhibition. Thus, the immediate topographic changes in the cortex after peripheral nerve injury appear to depend on the revelation of latent inputs that are normally under tonic inhibitory suppression.

The search for the mechanism(s) responsible for the protracted phase of reorganization was more challenging. At the simplest level, this stage of reorganization had to be due to either the sprouting of new connections, the strengthening of existing connections, or both. Anatomical studies examining the sizes of thalamocortical axonal arbors showed that the existing infrastructure was sufficient to permit the plasticity (Garraghty et al., 1989; Garraghty and Sur, 1990), suggesting that previously ineffective synapses were being strengthened. Motivated by the extensive literature involving glutamatergic NMDA receptor-dependent plasticity, experiments were conducted to investigate the possible contributions of these receptors to the topographic plasticity following peripheral nerve injury in adult monkeys. Not surprisingly, the immediate phase of reorganization proceeded whether NMDA receptors were blocked or not (Myers et al., 2000). The second stage of reorganization, on the other hand, was prevented if NMDA receptors were blocked (Garraghty and Muja, 1996). Thus, NMDA receptors were shown to be necessary for the "expression" of the second phase of cortical reorganization but not for its "maintenance." Moreover, receptor autoradiography showed increases in AMPA glutamatergic receptors that correlated with the second stage of reorganization (Garraghty et al., 2006). Classic long-term potentiation (LTP) in the hippocampus had been shown previously to be NMDA receptor-dependent for its induction but not for its maintenance (e.g., Collingridge and Bliss, 1987). Furthermore, the maintenance of the LTP has been shown to involve the postsynaptic accumulation of AMPA receptors (e.g., Tocco et al., 1992; Maren et al., 1993; for a recent review, see Díaz-Alonzo and Nicoll, 2021). These obvious parallels between hippocampal LTP and nerve injury-induced topographic reorganization in primate somatosensory cortex have been previously addressed (Garraghty et al., 1998, 2006).

Evidence for the recapitulation of developmental plasticity in adult somatosensory cortex after peripheral nerve injury

Despite their similarities, fundamental differences remained between hippocampal LTP and somatosensory plasticity in their routes of induction, longevity, and temporal progression. Most importantly was the transient nature of hippocampal LTP vs. the presumed permanence of the nerve injury-induced changes in the somatosensory cortex. These differences led to the consideration of other possibilities. Dykes and Lamour (1988) reported the intriguing finding that the majority of neurons in primary somatosensory cortex (in cats) had no receptive fields. That is, they could not be activated by peripheral stimulation. Subsequently, Warren and Dykes (1992) showed that a subset of these unresponsive neurons became responsive when glutamate was applied to the cortex iontophoretically, but nearly half of the recorded neurons remained unresponsive to peripheral stimulation. These findings raised the possibility that the large subset of neurons with no demonstrable peripheral receptive field became responsive during the second stage of reorganization in monkey cortex. Some support for this possibility was reported by Schroeder et al. (1997a) who showed that the blockade of GABA in the cortex (here, visual cortex) resulted in a marked increase in cortical excitability that could be reversed with the blockade of NMDA receptors. Intracortical measures of GABAA and GABAB receptors are found to be low as the second stage of reorganization proceeds (Garraghty et al., 2006). Moreover, this plasticity is prevented by NMDA receptor blockade (Garraghty and Muja, 1996). Thus, it seemed possible that increased excitability in the cortex mediated by NMDA receptors was a critical contributor in this plasticity.

When network activity drops drastically, as happens with a stroke, amputation, or nerve injury, synaptic excitatory and inhibitory receptor trafficking is dramatically altered in an experience dependent way (Arancibia-Cárcamo et al., 2009; Lussier et al., 2011). Under normal conditions, excitatory synapse maintenance is carried out through postsynaptic receptor trafficking of AMPA receptors containing largely Glur2/3 subunits (Tanaka et al., 2000). *In vitro*, when presynaptic glutamate release falls drastically (e.g., with tetrodotoxin application), cells increase excitability by trafficking calcium permeable forms of AMPA receptor (CP-AMPARs) to the synapse (Wierenga et al., 2005), CP-AMPARs are special types of receptors that gate calcium and drive NMDA-like processes that can induce LTP (e.g., Asrar et al., 2009). These GluR2 lacking calcium permeable AMPA receptors have been shown to play a

major role in promoting circuit lability and metaplasticity (Clem and Huganir, 2010; Herry et al., 2010; Shepherd, 2012), and, thus, can enable potentiation at deprived synapses. This increase in lability occurs through the ability of the CP-AMPARs ability to gate calcium, thus giving them potentiating potential when NMDAR function is limited. This type of synaptic plasticity falls into the category of meta-plasticity, where neural activity can influence synaptic function at adjacent synapses over longer timelines. In fact, CP-AMPARs appear to play a significant role in activating silent synapses (Isaac et al., 1995; Liao et al., 1995). Silent synapses exist in developing systems prior to the onset of feed-forward activation in sensory systems. Here, primary inputs achieve dominance of the network while latent inputs remain muted. With adult-onset sensory deprivations, the latent inputs can be unmasked and the silent synapses activated through the CP-AMPARs.

As discussed above, an immediate unmasking of latent inputs occurs after a network wide reduction in dominant afferent drive with nerve injury (Merzenich et al., 1983b; Schroeder et al., 1997b; Myers et al., 2000). This unmasking is enabled by the removal of GABAA and GABAB receptors from synaptic sites of deprived networks (Wellman et al., 2002; Garraghty et al., 2006). In the weeks following this unmasking, these latent inputs come to reliably activate the deprived cortical region (Merzenich et al., 1983a,b; Garraghty and Kaas, 1991a; Schroeder et al., 1997a), and this process is NMDA receptor-dependent (Garraghty and Muja, 1996). NMDA receptor potentiation typically requires strong levels of feed forward activity to drive synaptic strengthening; however, activity levels are greatly diminished in a deprived network. This implied the existence of a previously hidden form of metaplasticity that could facilitate the onset of the NMDA dependent phase of sensory reorganization, which is active by 2 weeks post injury (see Cusick et al., 1990). Selective targeting of AMPA and GABA receptor subunits with immunocytochemical techniques at 1 week post injury in the deprived cortex showed receptor subunit configurations for AMPA (Mowery and Garraghty, 2009) and GABAA/GABAB receptors (Mowery et al., 2011) that were different from those associated with the immediate unmasking phase and the subsequent NMDA receptor-dependent phase of adult somatosensory plasticity. This pattern of receptor expression was more consistent with a recapitulation of "developmental" plasticity (Figure 1).

In developing networks, this pattern is associated with a reduced level of mature GluR2/3 subunit containing AMPAR in the active synapses that instead contain an elevated level of GluR1 subunits (Kumar et al., 2002; Eybalin et al., 2004; Ho et al., 2007; Whitney et al., 2008). In these immature networks, weak sensory afferent inputs (eyes, ears, and skin) can be potentiated through GluR1 containing AMPA receptor-mediated calcium gating that serves to un-silence the synapse and tag it for GluR2 containing AMPA receptor delivery and mature forms of NMDAR Hebbian strengthening. In the adult primate somatosensory cortex, similar changes to the expression of GluR1 and GluR2/3 subunits occurred shortly after peripheral nerve injury (Mowery and Garraghty, 2009) suggesting that GluR1 containing calcium permeable AMPARs might govern synaptic excitatory plasticity in cases where dominant excitatory inputs are severely reduced (injury) or lost (amputation). After sensory loss in the adult, a re-emergence of this mechanism could facilitate the synaptic strengthening of latent subordinate synaptic connections located in more distal regions of the dendritic trees of cortical neurons (see Churchill et al., 2004).

In an emerging sensory system, excitation and inhibition are skewed toward excitatory processes to allow the onset of peripheral input to engage synaptic strengthening mechanisms. In very immature neural networks, GABAergic synapses form first and are depolarizing until the chloride battery comes online (see Ben-Ari, 2002). The onset of glutamatergic feedforward activity begins the process. As the chloride transporter KCC2 matures, weak inhibitory hyperpolarization gradually emerges as the chloride reversal potential moves toward adult levels. This activity dependent step is vital for the progressive rebalancing of excitatory and inhibitory synapses toward their mature states (Cancedda et al., 2007). During development lowered inhibition serves an important purpose, as the lack of mature hyperpolarizing postsynaptic GABAA receptors increases the probability of postsynaptic depolarization and promotes CP-AMPA mediated potentiation. At the same time, the lack of functional postsynaptic GABAB receptors, which inhibit NMDA receptor activation, promotes NMDA induced strengthening of the synapses (see Otmakhova and Lisman, 2004). Presynaptic GABAB receptors; however, are functionally active during development. These autoreceptors regulate postsynaptic GABAergic signaling in the face of immature postsynaptic GABAergic synapses (McLean et al., 1996) that lack a functionally relevant population of GABAA receptors (Paysan et al., 1994). In network states where inhibitory tone has been reduced, presynaptic GABAB autoreceptors likely regulate GABAergic transmission.

In cases of sensory deprivation in the adult, a recapitulation of this postsynaptic inhibitory configuration as described above would again support the activation of silent latent synapses from the remaining intact peripheral nerves. The reduction in postsynaptic GluR2/3, GABAA, GABAB subunits, as well as the increase in GluR1 and presynaptic GABAB subunits found in adult primate somatosensory cortex 1 week after nerve injury (Mowery and Garraghty, 2009; Mowery et al., 2011) mirrors the conditions seen in developing networks (Figure 2). That is, the excitatory/inhibitory (E/I) tone is imbalanced toward excitation with low levels of active GABAA (Golshani et al., 1997; Paysan and Fritschy, 1998) and postsynaptic GABAB receptors (Fukuda et al., 1993; Fritschy et al., 1999) that are regulated by presynaptic GABAB receptors (McLean et al., 1996). The

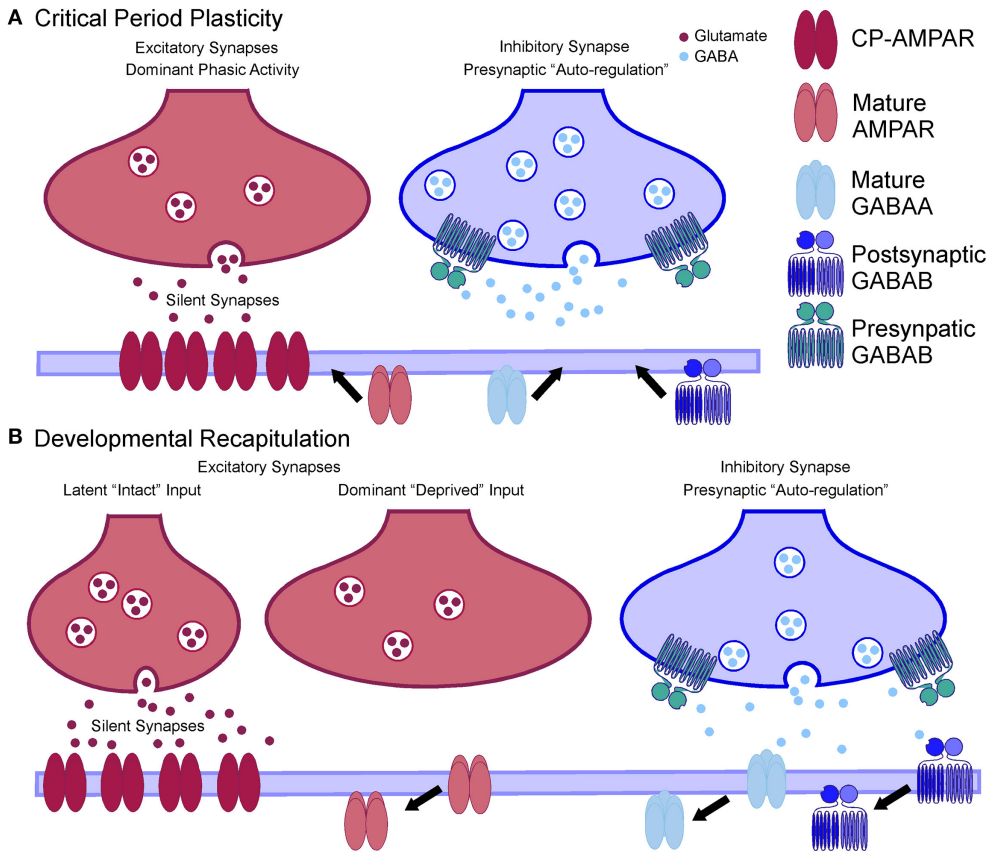

FIGURE 2
Parallels between critical period plasticity at developing synapses and developmental recapitulation at adult synapses. **(A)** Left: Cartoon showing calcium permeable AMPAR at silent excitatory synapses being activated and recruiting mature GluR2/3 containing AMPAR to the active dominant synapse. Right: Cartoon showing presynaptic GABAB autoregulation of inhibitory synapses prior to delivery of the mature postsynaptic GABAA and GABAB receptors, which are a hallmark of the closure of critical period plasticity. **(B)** Left: Cartoon showing the activation of calcium-permeable AMPAR at latent silent synapses after sensory deprivation of the normally dominant inputs. GluR2/3 containing AMPAR are removed from the deprived synapses until CP-AMPAR mediated processes can establish new "dominant" inputs. Right: Postsynaptic GABAB receptor autoregulation controls GABAergic inhibitory tone at synapses that have had the mature GABAA and GABAB receptors removed to promote activation of silent synapses.

heightened excitatory state is only rebalanced to the mature E/I tone after active synapses are re-established by the still active latent inputs, which is a similar set of conditions these networks are exposed to when feedforward peripheral activity first emerges during development.

Evidence for the recapitulation of developmental plasticity in other sensory and central systems after deprivation and injury

The onset of "adult-like" cortical inhibition is highly correlated with the closure of the critical period of plasticity in the visual cortex (e.g., Huang et al., 1999; Hensch, 2005) and auditory cortex (Mowery et al., 2015, 2019). After this period, both visual (Hubel and Wiesel, 1963; Berardi et al., 2000) and auditory systems become resistant to general changes in sensory input (Takesian et al., 2012; Mowery et al., 2016). However, drastic changes to sensory input comparable to somatosensory nerve injuries (e.g., retinal and cochlear denervation) induce retinotopic reorganization of the adult visual cortex (Kaas et al., 1990) and tonotopic reorganization in the adult auditory cortex (Schwaber et al., 1993; Eggermont, 2017). Furthermore, the reorganization phase occurs after an "unmasking" phase where latent intact inputs are immediately expressed in visual (e.g., Chino et al., 1992) and auditory cortex (e.g., Irvine and Rajan, 1997; Mossop et al., 2000). Thus, it seems plausible that the previously hidden phase of plasticity revealed in the somatosensory cortex exists for the visual and auditory systems as well.

A careful review of the literature in which data exist for intermediary time-points between unmasking and reorganization does provide some initial evidence that a brief window of developmental recapitulation opens. However, carefully designed research will be needed to confirm this (e.g., see Nahmani and Turrigiano, 2014 for review). A reduction of GABAergic inhibition is present at all three stages of reorganization so studies supporting this effect are not surprising. Thus, many studies have provided evidence of reduced GABAergic inhibition related to lowered expression or down-regulation of GABA subunits in the deprived ocular dominance column of the visual cortex (Hendry et al., 1994) or areas of the auditory neuraxis after cochlear ablation (e.g., inferior colliculus, Bledsoe Jr et al., 1995; Mossop et al., 2000) or denervation (e.g., auditory cortex, Balaram et al., 2019). To date, no studies have investigated the effect of adult onset visual or auditory sensory loss for either pre- or post-synaptic GABAB expression or function. On the other hand, a hallmark of the developmental plasticity is a reduction of the GluR2 containing AMPA receptors, which are replaced by calcium permeable homomeric GluR1 receptors. Both monocular deprivation and cochlear denervation lead to an acute reduction of GluR2 receptor in the deprived visual dominance column (Wong-Riley and Jacobs, 2002) and the inferior colliculus or auditory cortex (Balaram et al., 2019). Furthermore, an increase in phosphorylation of the GluR1 containing AMPAR (serine 845 site) accompanied the appearance of CP-AMPARs at synapses following visual deprivation (Goel et al., 2011). Direct studies of this phenomenon in the visual or auditory cortex have not been carried out as of yet, but there is evidence to support preliminary investigation. It is worth noting that similar evidence for the emergence of developmental plasticity has been reported after other forms of central nervous system injuries (Emery et al., 2003), such as ischemia (e.g., Gorter et al., 1997), spinal cord injury (e.g., Harel and Strittmatter, 2006), and epilepsy (e.g., Rivera et al., 2005). Together, these pieces of evidence from many brain regions provide the rationale to search for a universal neural mechanism governing this brief window of plasticity.

The role of developmental recapitulation in the onset of maladaptive plasticity

Sensory deprivation during the critical period of development leads to persistent changes in sensory receptive fields (for review see Pedrosa et al., 2022). This can include massive reorganizations within a sensory modality or even across modalities such as when children are born deaf or blind (Sadato et al., 2002; Sathian, 2005). As we have outlined above, similar reorganizations happen in the adult networks when changes to dominant sensory inputs occur, but it is important to outline any possible differences between developmental plasticity in neonates and developmental recapitulation in adult neural networks. Topographic mapping in non-human primate neonates using microelectrode recordings (Krubitzer and Kaas, 1988) or fMRI (Arcaro et al., 2019) have shown that the cortical topographic map in infants are basically indistinguishable from those in older monkeys. Given this fact, it is perhaps not surprising that nerve transections performed on infant primates resulted in patterns of topographic reorganization very comparable to the map changes with adult-onset nerve injury (Wall et al., 1992a,b).

Unfortunately, no time course or acute mapping studies were carried out after the infant-onset nerve transections, so it cannot be known that the mechanisms involved in the map reorganizations from following early sensory loss are the same as those discussed above for adult-onset nerve transections. However, the comparability of the topographic maps in infant and adult primates (Krubitzer and Kaas, 1988; Arcaro et al., 2019) does suggest that similar neural mechanisms guide the neural response to deprivation and injury in neonates and adults. Therefore, the major difference between the two states of critical period plasticity and developmental recapitulation doesn't involve the plasticity mechanism, but the neural scaffolding that is available to harness this plasticity. In adults, nerve injuries are often accompanied by the emergence of chronic side effects that greatly lower quality of life. For example, after somatosensory injury, chronic pain and phantom sensations often emerge (Flor et al., 2006). In the auditory system, the onset of tinnitus (phantom auditory tones) accompanies recovery from auditory nerve/hair cell injury (Baguley, 2002). For the visual system, retinopathy can lead to reorganization that eventually causes visual field defects (Safran and Landis, 1999).

These reorganizations are thought to be the consequence of maladaptive plasticity, and the etiological culprit could be related to the re-emergence of critical period-like states that allow aberrant functional connections to form between synapses deprived of their dominant inputs and adjacent intact functional synapses. This could offer an important clue toward the development of classes of drugs targeting the calcium permeable AMPARs or GABARs at these sensitive points to prevent this maladaptive plasticity from taking hold. Being able to evoke developmental recapitulation in the adult nervous system outside of reorganizing injuries would also be an interesting line of research toward the development of effective interventions for chronic nerve injuries that are largely untreatable. In the auditory system, exposure to auditory noise, has been suggested to "re-open" the auditory critical period (Zhou et al., 2011). Bavelier et al. (2010) used a pharmacological approach to re-induce the critical-period and treat amblyopia. Perhaps a similar approach using tactile stimulation or neuromodulators could be explored toward the treatment of nerve injury induced somatosensory disorders.

Conclusion

Our first foray into the issue of adult somatosensory plasticity examined the sizes of thalamocortical axonal arbors, as this was an essential piece of information needed to guide subsequent experiments. If thalamocortical axonal arbors precisely terminated in topographically appropriate patches of cortex, the sprouting of new connections would seemingly be required to move receptive fields across the cortex. As it turned out, we found that the axonal arbors were larger than the zones of cortex where their receptive fields were manifested. This "degenerate" anatomy (Edelman, 1987) clearly suggested that subthreshold inputs existing in the cortex gained strength during the reorganizational process. Thus, research in the field came to center on the mechanism(s) by which this strengthening occurred. Experiments targeting GABAergic mechanisms revealed the contribution of this neurochemical system to the immediate unmasking that followed the sensory loss. The relaxation of feedforward inhibition also permitted glutamatergic mechanisms to contribute to the latter phases of reorganization. With the finding that glutamatergic NMDA receptors are necessary for the latter stages of reorganization, we began view the peripheral nerve transection paradigm as a platform for studying adult neural plasticity *per se*, and not merely a feature of the somatosensory system. Ultimately, in our view, this nerve injury model in adult primates has revealed mechanisms of neural change that apply broadly across the brain, and the recapitulation of developmental plasticity is an important feature of experience-dependent adult plasticity.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Allard, T., Clark, S. A., Jenkins, W. M., and Merzenich, M. M. (1991). Reorganization of somatosensory area 3b representations in adult owl monkeys after digit syndactyly. *J. Neurophysiol.* 66, 1048–1058. doi: 10.1152/jn.1991.66.3.1048

Alloway, K. D., Rosenthal, P., and Burton, H. (1989). Quantitative measurements of receptive field changes during antagonism of GABAergic transmission in primary somatosensory cortex. *Exp. Brain Res.*78, 514–532. doi: 10.1007/BF00230239

Arancibia-Cárcamo, I. L., Yuen, E. Y, Muir, J., Lumb, M. J., Michels, G., Saliba, R. S., Smart, T. G., et al. (2009). Ubiquitin-dependent lysosomal targeting of GABA(A) receptors regulates neuronal inhibition. *Proc. Natl. Acad. Sci. USA* 106, 17552–17557. doi: 10.1073/pnas.0905502106

Arcaro, M. J., Schade, P. F., and Livingstone, M.S. (2019). Body map proto-organization in newborn macaques. *Proc. Natl. Acad. Sci. U S A.* 116, 24861–24871. doi: 10.1073/pnas.1912636116

Asrar, S., Zhou, Z., Ren, W., and Jia, Z. (2009). Ca(2+) permeable AMPA receptor induced long-term potentiation requires PI3/MAP kinases but not Ca/CaM-dependent kinase II. *PLoS ONE* 4, e4339. doi: 10.1371/journal.pone.0004339

Avendaño, C., Umbriaco, D., Dykes, R. W., and Descarries, L. (1995). Decrease and long-term recovery of choline acetyltransferase immunoreactivity in adult cat somatosensory cortex after peripheral nerve transections. *J. Comp. Neurol.* 354, 321–332. doi: 10.1002/cne.903540302

Baguley, D. M. (2002). Mechanisms of tinnitus. *Br. Med. Bull.* 63, 195–212. doi: 10.1093/bmb/63.1.195

Balaram, P., Hackett, T. A., and Polley, D. B. (2019). Synergistic transcriptional changes in AMPA and GABAA receptor genes support compensatory plasticity following unilateral hearing loss. *Neuroscience* 407, 108–119. doi: 10.1016/j.neuroscience.2018.08.023

Bausbaum, A. I., and Wall, P. D. (1976). Chronic changes in the response of cells in adult cat dorsal horn following partial deafferentation. The appearance of responding cells in a previously non-responsive region. *Brain Res.* 116, 181–204. doi: 10.1016/0006-8993(76)90899-4

Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., and Hensch, T. K. (2010). Removing brakes on adult brain plasticity: from molecular to behavioral interventions. *J. Neurosci.* 30, 14964–14971. doi: 10.1523/JNEUROSCI.4812-10.2010

Ben-Ari, Y. (2002). Excitatory actions of gaba during development: the nature of the nurture. *Nat. Rev. Neurosci.* 3, 728–739. doi: 10.1038/nrn920

Berardi, N., Pizzorusso, T., and MaVei, L. (2000). Critical periods during sensory development. *Curr. Opin. Neurobiol.* 10, 138–145. doi: 10.1016/S0959-4388(99)00047-1

Berlucchi, G., Buchtel, E., Marzi, C. A., Mascetti, G. G., and Simoni, A. (1978a). Effects of experience on interocular transfer of pattern discriminations in split-chiasm and split-brain cats. *J. Comp. Physiol. Psych.* 92, 532–543. doi: 10.1037/h0077482

Berlucchi, G., Buchtel, H. A., and Lepore, F. (1978b). Successful interocular transfer of visual pattern discriminations in split-chiasm cats with section of the intertectal and posterior commissures. *Physiol. Behav.* 20, 331–338. doi: 10.1016/0031-9384(78)90228-7

Berlucchi, G., Sprague, J. M., Antonini, A., and Simoni, A. (1979). Learning and interhemispheric transfer of visual pattern discriminations following unilateral suprasylvian lesions in split-chiasm cats. *Exp. Brain Res.* 34, 551–574. doi: 10.1007/BF00239149

Berlucchi, G., Sprague, J. M., Lepore, F., and Mascetti, G. G. (1978c). Effects of lesions of areas 17, 18 and 19 on interocular transfer of pattern discriminations in split-chiasm cats. *Exp. Brain Res.* 31, 275–297. doi: 10.1007/BF00237604

Bledsoe Jr, S. C., Nagase, S., Miller, J. M., and Altschuler, R. A. (1995). Deafness-induced plasticity in the mature central auditory system. *Neuroreport* 7, 225–229. doi: 10.1097/00001756-199512000-00054

Brown, D. L., and Salinger, W. L. (1979). Loss of X cells in the lateral geniculate nucleus with monocular paralysis: neural plasticity in the adult cat. *Science* 189, 1011–1012. doi: 10.1126/science.1220007

Cancedda, L., Fiumelli, H., Chen, K., and Poo, M. (2007). Excitatory GABA action is essential for morphological maturation of cortical neurons in vivo. *J. Neurosci.* 27, 5224–5235. doi: 10.1523/JNEUROSCI.5169-06.2007

Chino, Y. M., Kaas, J. H., Smith 3rd, E. L., Langston, A. L., and Cheng, H. (1992). Rapid reorganization of cortical maps in adult cats following restricted deafferentation in retina. *Vision Res.* 32, 789–796. doi: 10.1016/0042-6989(92)90021-A

Churchill, J. D., Arnold, L. L., and Garraghty, P. E. (2001). Somatotopic reorganization in the brainstem and thalamus following peripheral nerve injury in adult primates. *Brain Res.* 910, 142–152. doi: 10.1016/S0006-8993(01)02703-2

Churchill, J. D., Muja, N., Myers, W. A., Besheer, J., and Garraghty, P. E. (1998). Somatotopic consolidation: a third phase of reorganization after peripheral nerve injury in adult squirrel monkeys. *Exp. Brain Res. Trends Neurosci.* 118, 189–196. doi: 10.1007/s002210050271

Churchill, J. D., Tharp, J. A., Wellman, C. L., Sengelaub, D. R., and Garraghty, P. E. (2004). Morphological correlates of injury-induced reorganization in primate somatosensory cortex. *BMC Neurosci.* 5, 43. doi: 10.1186/1471-2202-5-43

Clem, R. L., and Huganir, R. L. (2010). Calcium-permeable AMPA receptor dynamics mediate fear memory erasure. *Science.* 330, 1108–1112. doi: 10.1126/science.1195298

Collingridge, G. L., and Bliss, T. V. P. (1987). NMDA receptors—their role in long-term potentiation. *Trends Neurosci.*10, 288–293. doi: 10.1016/0166-2236(87)90175-5

Creutzfeldt, O. D., and Heggelund, P. (1975). Neural plasticity in visual cortex of adult cats after exposure to visual patterns. *Science* 188, 1025–1027. doi: 10.1126/science.1145187

Cusick, C. G., Wall, J. T., Whiting Jr, J. H., and Wiley, R. G. (1990). Temporal progression of cortical reorganization following nerve injury. *Brain Res.* 537, 355–358. doi: 10.1016/0006-8993(90)90385-O

Díaz-Alonzo, J., and Nicoll, R. A. (2021). AMPA receptor trafficking and LTP: carboxy-termini, amino-termini and TARPS. *Neuropharmcology* 197, 108710. doi: 10.1016/j.neuropharm.2021.108710

Dostrovsky, J. O., Millar, J., and Wall, P. D. (1976). The immediate shift of afferent drive of dorsal column nucleus cells following deafferentation: a comparison of acute and chronic deafferentation in gracile nucleus and spinal cord. *Exp. Neurol.* 52, 480–495. doi: 10.1016/0014-4886(76)90219-3

Dykes, R., and Lamour, Y. (1988). Neurons without demonstrable receptive fields outnumber neurons having receptive fields in samples from the somatosensory cortex of anesthetized or paralyzed cats and rats. *Brain Res.*440, 133–143. doi: 10.1016/0006-8993(88)91165-1

Dykes, R. W., Landry, P., Metherate, R., and Hicks, T. P. (1984). Functional role of GABA in cat primary somatosensory cortex: shaping receptive fields of cortical neurons. *J. Neurophysiol.* 52, 1066–1093. doi: 10.1152/jn.1984.52.6.1066

Edelman, G. M. (1987). *Neural Darwinism: The Theory of Neuronal Group Selection.* New York, NY: Basic Books Inc.

Eggermont, J. J. (2017). Acquired hearing loss and brain plasticity. *Hear. Res.* 343, 176–190. doi: 10.1016/j.heares.2016.05.008

Emery, D. L., Royo, N. C., Fischer, I., Saatman, K. E., and McIntosh, T. K. (2003). Plasticity following injury to the adult central nervous system: is recapitulation of a developmental state worth promoting? *J. Neurotrauma.* 20, 1271–1292. doi: 10.1089/089771503322686085

Eybalin, M., Caicedo, A., Renard, N., Ruel, J., and Puel, J. L. (2004). Transient Ca2+-permeable AMPA receptors in postnatal rat primary auditory neurons. *Eur. J. Neurosci.* 20, 2981–2989.

Faggin, B. M., Nguyen, K. T., and Nicolelis, M. A. L. (1997). Immediate and simultaneous sensory reorganization at cortical and subcortical levels of the somatosensory system. *Proc. Natl. Acad. Sci. USA* 94, 9428–9433. doi: 10.1073/pnas.94.17.9428

Fiorentini, A., and Maffei, L. (1974). Change of binocular properties of the simple cells of the cortex in adult cats following immobilization of one eye. *Vision Res.* 14, 217–218. doi: 10.1016/0042-6989(74)90104-7

Flor, H., Nikolajsen, L., and Staehelin Jensen, T. (2006). Phantom limb pain: a case of maladaptive CNS plasticity? *Nat. Rev. Neurosci.* 7, 873–881. doi: 10.1038/nrn1991

Fritschy, J. M., Meskenaite, V., Weinmann, O., Honer, M., Benke, D., and Mohler, H. (1999). GABAB-receptor splice variants GB1a and GB1b in rat brain: developmental regulation, cellular distribution and extrasynaptic localization. *Eur. J. Neurosci.* 11, 761–768. doi: 10.1046/j.1460-9568.1999.00481.x

Fukuda, A., Mody, I., and Prince, D. A. (1993). Differential ontogenesis of presynaptic and postsynaptic GABAB inhibition in rat somatosensory cortex. *J. Neurophysiol.* 70, 448–452. doi: 10.1152/jn.1993.70.1.448

Garraghty, P. E., Arnold, L. L., Wellman, C. L., and Mowery, T. M. (2006). Receptor autoradiographic correlates of deafferentation-induced reorganization in adult primate somatosensory cortex. *J. Comp. Neurol.* 497, 636–645. doi: 10.1002/cne.21018

Garraghty, P. E., Churchill, J. D., and Banks, M. K. (1998). Adult neural plasticity: similarities between two paradigms. *Curr. Dir. Psych. Sci.* 7, 87–91. doi: 10.1111/1467-8721.ep10774661

Garraghty, P. E., Hanes, D. P., Florence, S. L., and Kaas, J. H. (1994). Pattern of peripheral deafferentation predicts reorganizational limits in adult primate somatosensory cortex. *Somatosens. Motor Res.* 11, 109–117. doi: 10.3109/08990229409028864

Garraghty, P. E., and Kaas, J. H. (1991a). Largescale functional reorganization in adult monkey cortex after peripheral nerve injury. *Proc. Natl. Acad. Sci. USA* 88, 69766980. doi: 10.1073/pnas.88.16.6976

Garraghty, P. E., and Kaas, J. H. (1991b). Functional reorganization in adult monkey thalamus after peripheral nerve injury. *NeuroReports* 2, 747–750. doi: 10.1097/00001756-199112000-00004

Garraghty, P. E., LaChica, E. A., and Kaas, J. H. (1991). Injuryinduced reorganization of somatosensory cortex is accompanied by reductions in GABA staining. *Somatosens. Motor Res.* 8, 347–354. doi: 10.3109/08990229109144757

Garraghty, P. E., and Muja, N. (1995). Possible usedependent changes in adult primate somatosensory cortex. *Brain Res.*686, 119–121. doi: 10.1016/0006-8993(95)00506-L

Garraghty, P. E., and Muja, N. (1996). NMDA receptors and plasticity in adult primate somatosensory cortex. *J. Comp. Neurol.* 367, 319–326. doi: 10.1002/(SICI)1096-9861(19960401)367:2<319::AID-CNE12>3.0.CO;2-L

Garraghty, P. E., Pons, T. P., Sur, M., and Kaas, J. H. (1989). The arbors of axons terminating in middle cortical layers of somatosensory area 3b in owl monkeys. *Somatosens. Motor Res.* 6, 401411. doi: 10.3109/08990228909144683

Garraghty, P. E., Salinger, W. L., MacAvoy, M. G., Schroeder, C. E., and Guido, W. (1982). The shift in X/Y ratio after chronic monocular paralysis: a binocularly mediated, barbituratesensitive effect in the adult lateral geniculate nucleus. *Exp. Brain Res.* 47, 301308. doi: 10.1007/BF00239390

Garraghty, P. E., and Sur, M. (1990). The morphology of single intracellularly stained axons terminating in area 3b of macaque monkeys. *J. Comp. Neurol.* 294, 583593. doi: 10.1002/cne.902940406

Goel, A., Xu, L., Snyder, K. P., Song, L., Goenaga-Vazquez, Y., Megill, A., et al. (2011). Phosphorylation of AMPA receptors is required for sensory deprivation-induced homeostatic synaptic plasticity. *PLoS ONE.* 6, e18264. doi: 10.1371/journal.pone.0018264

Golshani, P., Truong, H., and Jones, E. G. (1997). Developmental expression of GABA(A) receptor subunit and GAD genes in mouse somatosensory barrel cortex. *J. Comp. Neurol.* 383, 199–219. doi: 10.1002/(SICI)1096-9861(19970630)383:2<199::AID-CNE7>3.0.CO;2-W

Gorter, J. A., Petrozzino, J. J., Aronica, E. M., Rosenbaum, D. M., Opitz, T., Bennett, M. V., et al. (1997). Global ischemia induces downregulation of Glur2 mRNA and increases AMPA receptor-mediated Ca^{2+} influx in hippocampal CA1 neurons of gerbil. *J. Neurosci.* 17, 6179–6188. doi: 10.1523/JNEUROSCI.17-16-06179.1997

Harel, N. Y., and Strittmatter, S. M. (2006). Can regenerating axons recapitulate developmental guidance during recovery from spinal cord injury? *Nat. Rev. Neurosci.* 7, 603–616. doi: 10.1038/nrn1957

Hendry, S. H, Huntsman, M. M., Viñuela, A., Möhler, H., de Blas, A. L., and Jones, E. G. (1994). GABAA receptor subunit immunoreactivity in primate visual cortex: distribution in macaques and humans and regulation by visual input in adulthood. *J. Neurosci.* 14, 2383–2401. doi: 10.1523/JNEUROSCI.14-04-02383.1994

Hensch, T. K. (2005). Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* 6, 877–888. doi: 10.1038/nrn1787

Herry, C., Ferraguti, F., Singewald, N., Letzkus, J. J., Ehrlich, I., and Lüthi, A. (2010). Neuronal circuits of fear extinction. *Eur. J. Neurosci.* 31, 599–612. doi: 10.1111/j.1460-9568.2010.07101.x

Hicks, T. P., and Dykes, R. W. (1983). Receptive field size for certain neurons in primary somatosensory cortex is determined by GABA-mediated intracortical inhibition. *Brain Res.* 274, 160–164. doi: 10.1016/0006-8993(83)90533-4

Ho, M. T., Pelkey, K. A., Topolnik, L., Petralia, R. S., Takamiya, K., Xia, J., et al. (2007). Developmental expression of Ca2+-permeable AMPA receptors underlies depolarizationinduced long-term depression at mossy fiber CA3 pyramid synapses. *J. Neurosci.* 27, 11651–11662. doi: 10.1523/JNEUROSCI.2671-07.2007

Hoffmann, K.-P., and Holländer, H. (1978). Physiological and morphological changes in cells of the lateral geniculate nucleus in monocularly-deprived and reverse-sutured cats. *J. Comp. Neurol.* 177, 145–158. doi: 10.1002/cne.901770110

Hoffmann, K. P., and Cynader, M. (1977). Functional aspects of plasticity in the visual system of adult cats after early monocular deprivation. *Philos. Trans. B* 278, 411–424. doi: 10.1098/rstb.1977.0051

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M. F., et al. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* 98, 739–755. doi: 10.1016/S0092-8674(00)81509-3

Hubel, D. H., and Wiesel, T. N. (1963). Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *J. Neurophysiol.* 26, 994–1002. doi: 10.1152/jn.1963.26.6.994

Hubel, D. H., and Wiesel,. T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* 206, 419–436. doi: 10.1113/jphysiol.1970.sp009022

Irvine, D. R., and Rajan, R. (1997). Injury-induced reorganization of frequency maps in adult auditory cortex: the role of unmasking of normally-inhibited inputs. *Acta Otolaryngol. Suppl.* 532, 39–45. doi: 10.3109/00016489709126143

Isaac, J. T., Nicoll, R. A., and Malenka, R. C. (1995). Evidence for silent synapses: implications for the expression of LTP. *Neuron.* 15, 427–434. doi: 10.1016/0896-6273(95)90046-2

Jenkins, W. M., Merzenich, M. M., Ochs, M. T., Allard, T., and Guic-Robles, E. (1990). Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *J. Neurophysiol.* 63, 82–104. doi: 10.1152/jn.1990.63.1.82

Kaas, J. H., Krubitzer, L. A., Chino, Y. M., Langston, A. L., Polley, E. H., and Blair, N. (1990). Reorganization of retinotopic cortical maps in adult mammals after lesions of the retina. *Science* 248, 229–231. doi: 10.1126/science.2326637

Krubitzer, L. A., and Kaas, J. H. (1988). Responsiveness and somatotopic organization of anterior parietal field 3b and adjoining cortex in newborn and infant monkeys. *Somatosens Mot. Res.* 6, 179–205. doi: 10.3109/08990228809144673

Kumar, S. S., Bacci, A., Kharazia, V., and Huguenard, J. R. (2002). A developmental switch of AMPA receptor subunits in neocortical pyramidal neurons. *J. Neurosci.* 22, 3005–3015. doi: 10.1523/JNEUROSCI.22-08-03005.2002

Liao, D., Hessler, N. A., and Malinow, R. (1995). Activation of postsynaptically silent synapses during pairing-induced LTP in CA1 region of hippocampal slice *Nature* 375, 400–404. doi: 10.1038/375400a0

Lussier, M. P., Nasu-Nishimura, Y., and Roche, K. W. (2011). Activity-dependent ubiquitination of the AMPA receptor subunit GluA2. *J. Neurosci.* 31, 3077–3081. doi: 10.1523/JNEUROSCI.5944-10.2011

Maffei, L., and Fiorentini, A. (1976). Asymmetry of motility of the eyes and changes in binocular properties of cortical cells in adult cats. *Brain Res.* 105, 73–78. doi: 10.1016/0006-8993(76)90923-9

Maren, S., Tocco, G., Baudry, M., and Thompson, R. F. (1993). Postsynaptic factors in the expression pf long-term potentiation (LTP): increased glutamate receptor binding following LTP induction in vivo. *Proc. Natl. Acad. Sci. USA* 90, 9654–9658. doi: 10.1073/pnas.90.20.9654

McLean, H. A., Caillard, O., Khazipov, R., Ben-Ari, Y., and Gaiarsa, J. L. (1996). Spontaneous release of GABA activates GABAB receptors and controls network activity in the neonatal rat hippocampus. *J. Neurophysiol.* 76, 1036–1046. doi: 10.1152/jn.1996.76.2.1036

Merrill, E. G., and Wall, P. D. (1972). Factors forming the edge of a receptive field. The presence of relatively ineffective afferents. *J. Physiol.* 226, 825–846. doi: 10.1113/jphysiol.1972.sp010012

Merzenich, M. M., Kaas, J. H., Nelson, R. J., Sur, M., and Felleman, D. (1983a). Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience* 8, 33–55. doi: 10.1016/0306-4522(83)90024-6

Merzenich, M. M., Kaas, J. H., Wall, J. T., Sur, M., Nelson, R. J., and Felleman, D. J. (1983b). Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience* 10, 639–665. doi: 10.1016/0306-4522(83)90208-7

Merzenich, M. M., Nelson, R. J., Stryker, M. P., Cynader, M. S., Schoppmann, A., and Zook, J. M. (1984). Somatosensory cortical map changes following digit amputation in adult monkeys. *J. Comp. Neurol.* 224, 591–605. doi: 10.1002/cne.902240408

Millar, J., Bausbaum, A. I., and Wall, P. D. (1976). Restructuring of the somatotopic map and appearance of abnormal neuronal activity in the gracile nucleus after partial deafferentation. *Exp. Neurol.* 50, 658–672. doi: 10.1016/0014-4886(76)90035-2

Mossop, J. E., Wilson, M. J., Caspary, D. M., and Moore, D. R. (2000). Down-regulation of inhibition following unilateral deafening. *Hear. Res.* 147, 183–187. doi: 10.1016/S0378-5955(00)00054-X

Mowery, T. M., Caras, M. L., Hassan, S. I., Wang, D. J., Dimidschstein, J., Fishell, G., et al. (2019). Preserving inhibition during developmental hearing loss rescues auditory learning and perception. *J. Neurosci.* 39, 8347–8361. doi: 10.1523/JNEUROSCI.0749-19.2019

Mowery, T. M., and Garraghty, P. E. (2009). Nerve-injury induced changes to GluR1 and GluR2/3 sub-unit expression in the area 3b of adult squirrel monkeys: developmental recapitulation. *Front. Syst. Neurosci.* 3, 1–7. doi: 10.3389/neuro.06.001.2009

Mowery, T. M., Kotak, V. C., and Sanes, D. H. (2016). The onset of visual experience gates auditory cortex critical periods. *Nat. Commun.* 7, 10416. doi: 10.1038/ncomms10416

Mowery, T. M., Sarin, R. M., Elliott, K. S., and Garraghty, P. E. (2011). Nerve injury-induced changes in GABAA and GABAB sub-unit expression in area 3b and cuneate nucleus of adult squirrel monkeys: further evidence of developmental recapitulation. *Brain Res.* 1415, 63–75. doi: 10.1016/j.brainres.2011.07.066

Mowery, T. M., Sarin, R. M., Kostylev, P. V., and Garraghty, P. E. (2015). Differences in AMPA and GABAA/B receptor subunit expression between the chronically reorganized cortex and brainstem of adult squirrel monkeys. *Brain Res.* 1611, 44–55. doi: 10.1016/j.brainres.2015.03.010

Myers, W. A., Churchill, J. D., Muja, N., and Garraghty, P. E. (2000). The role of NMDA receptors in adult primate cortical somatosensory plasticity. *J. Comp. Neurol.* 418, 373–382. doi: 10.1002/(SICI)1096-9861(20000320)418:4<373::AID-CNE1>3.0.CO;2-F

Nahmani, M., and Turrigiano, G. G. (2014). Adult cortical plasticity following injury: Recapitulation of critical period mechanisms? *Neuroscience.* 283, 4–16. doi: 10.1016/j.neuroscience.2014.04.029

Otmakhova, N. A., and Lisman, J. E. (2004). Contribution of Ih and GABAB to synaptically induced afterhyperpolarizations in CA1: a brake on the NMDA response. *J. Neurophysiol.* 92, 2027–2039. doi: 10.1152/jn.00427.2004

Paysan, J., Bolz, J., Mohler, H., and Fritschy, J. M. (1994). GABAA receptor alpha 1 subunit, an early marker for area specification in developing rat cerebral cortex. *J. Comp. Neurol.* 350, 133–149. doi: 10.1002/cne.903500110

Paysan, J., and Fritschy, J. M. (1998). GABAA-receptor subtypes in developing brain. Actors or spectators? *Perspect. Dev. Neurobiol.* 5, 179–192.

Pedrosa, L. R., Coimbra, G. S., Corrêa, M. G., Dias, I. A., and Bahia, C. P. (2022). Time window of the critical period for neuroplasticity in S1, V1, and A1 sensory areas of small rodents: a systematic review. *Front. Neuroanat.* 16, 763245. doi: 10.3389/fnana.2022.763245

Pollin, B., and Albe-Fessard, D. (1979). Organization of somatic thalamus in monkeys with and without section of dorsal spinal tracts. *Brain Res.*173, 431–449. doi: 10.1016/0006-8993(79)90240-3

Recanzone, G. H., Merzenich, M. M., and Jenkins, W. M. (1992). Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. *J. Neurophysiol.* 67, 1057–1070. doi: 10.1152/jn.1992.67.5.1057

Rivera, C., Voipio, J., and Kaila, K. (2005). Two developmental switches in GABAergic signalling: the K+-Cl- cotransporter KCC2 and carbonic anhydrase CAVII. *J. Physiol.* 562, 27–36. doi: 10.1113/jphysiol.2004.077495

Sadato, N., Okada, T., Honda, M., and Yonekura, Y. (2002). Critical period for cross-modal plasticity in blind humans: a functional MRI study. *Neuroimage* 16, 389–400. doi: 10.1006/nimg.2002.1111

Safran, A. B., and Landis, T. (1999). From cortical plasticity to unawareness of visual field defects. *J. Neuroophthalmol.* 19, 84–88. doi: 10.1097/00041327-199906000-00002

Salinger, W. L., Garraghty, P. E., MacAvoy, M. G., and Hooker, L. F. (1980b). Sensitivity of the mature lateral geniculate nucleus to components of monocular paralysis. *Brain Res.* 187, 307320. doi: 10.1016/0006-8993(80)90205-X

Salinger, W. L., Garraghty, P. E., and Schwartz, M. A. (1980a). Response of the mature lateral geniculate nucleus to monocular paralysis: contributions of nonretinal and retinal components. *Brain Res.* 192, 255260. doi: 10.1016/0006-8993(80)91025-2

Salinger, W. L., Schwartz, M. A., and Wilkerson, P. R. (1977a). Selective cell loss in the lateral geniculate nucleus of adult cats following binocular lid suture. *Brain Res.* 130, 81–88. doi: 10.1016/0006-8993(77)90843-5

Salinger, W. L., Schwartz, M. A., and Wilkerson, P. R. (1977b). Selective loss of lateral geniculate cells in the adult cat after chronic monocular paralysis. *Brain Res.* 125, 257–263. doi: 10.1016/0006-8993(77)90619-9

Sathian, K. (2005). Visual cortical activity during tactile perception in the sighted and the visually deprived. *Dev. Psychobiol.* 46, 279–286. doi: 10.1002/dev.20056

Schroeder, C. E., Javitt, D. C., Steinschneider, M., Mehta, A. D., Givre, S. J., Vaughan Jr, H. G., et al. (1997a). N-methyl-D-aspartate enhancement of phasic responses in primate neocortex. *Exp. Brain Res.* 114, 271–278. doi: 10.1007/PL00005635

Schroeder, C. E., Seto, S., Arezzo, J. C., and Garraghty, P. E. (1995). Electrophysiologic evidence for overlapping dominant and latent inputs to somatosensory cortex in squirrel monkeys. *J. Neurophysiol.* 74, 722732. doi: 10.1152/jn.1995.74.2.722

Schroeder, C. E., Seto, S., and Garraghty, P. E. (1997b). Emergence of radial nerve dominance in "median nerve cortex" after median nerve transection in an adult squirrel monkey. *J. Neurophysiol.* 77, 522526. doi: 10.1152/jn.1997.77.1.522

Schwaber, M. K., Garraghty, P. E., Morel, A., and Kaas, J. H. (1993). Neuroplasticity of the adult primate auditory cortex following cochlear hearing loss. *Am. J. Otol.* 14, 252258.

Shepherd, J. D. (2012). Memory, plasticity and sleep - A role for calcium permeable AMPA receptors? *Front. Mol. Neurosci.* 5, 49. doi: 10.3389/fnmol.2012.00049

Takesian, A. E., Kotak, V. C., and Sanes, D.H. (2012). Age-dependent effect of hearing loss on cortical inhibitory synapse function. *J. Neurophysiol.* 107, 937–947. doi: 10.1152/jn.00515.2011

Tanaka, H., Grooms, S. Y., Bennett, M. V., and Zukin, R. S. (2000). The AMPAR subunit GluR2: still front and center-stage. *Brain Res.* 886, 190–207. doi: 10.1016/S0006-8993(00)02951-6

Tocco, G., Maren, S., Shors, T. J., Baudry, M., and Thompson, R. F. (1992). Long-term potentiation is associated with increased [3H]AMPA binding in rat hippocampus. *Brain Res.* 573, 228–234. doi: 10.1016/0006-8993(92)90767-4

Wall, J. T., Felleman, D. J., and Kaas, J. H. (1983). Recovery of normal topography in the somatosensory cortex of monkeys after nerve crush and regeneration. *Science* 221, 771–773. doi: 10.1126/science.6879175

Wall, J. T., Huerta, M. F., and Kaas, J. H. (1992a). Changes in the cortical map of the hand following postnatal median nerve injury in monkeys: modification of somatotopic aggregates. *J. Neurosci.* 12, 3445–3455. doi: 10.1523/JNEUROSCI.12-09-03445.1992

Wall, J. T., Huerta, M. F., and Kaas, J. H. (1992b). Changes in the cortical map of the hand following postnatal ulnar and radial nerve injury in monkeys: organization and modification of nerve dominance aggregates. *J Neurosci.* 12:3456–3465.

Wall, P. D. (1977). The presence of ineffective synapses and the circumstances which unmask them. *Philos. Trans. B* 278, 361–372. doi: 10.1098/rstb.1977.0048

Wall, P. D., and Egger, M. D. (1971). Formation of new connections in adult rat brain after partial deafferentation. *Nature* 232, 542–545. doi: 10.1038/232542a0

Warren, R. A., and Dykes, R. W. (1992). Population analysis of single neurons in cat somatosensory cortex. *Somatosens. Motor Res.* 9, 297–312. doi: 10.3109/08990229209144779

Wellman, C. L., Arnold, L. L., Garman, E. E., and Garraghty, P. E. (2002). Acute reductions in GABAA receptor binding in layer IV of adult primate somatosensory cortex after peripheral nerve injury. *Brain Res.* 954, 68–72. doi: 10.1016/S0006-8993(02)03343-7

Whitney, N. P., Peng, H., Erdmann, N. B., Tian, C., Monaghan, D. T., and Zheng, J. C. (2008). Calcium-permeable AMPA receptors containing Q/R-unedited GluR2 direct human neural progenitor cell differentiation to neurons. *FASEB J.* 22, 2888–2900. doi: 10.1096/fj.07-104661

Wierenga, C. J., Ibata K., and Turrigiano, G. G. (2005). Postsynaptic expression of homeostatic plasticity at neocortical synapses. *J. Neurosci.* 25, 2895–2905. doi: 10.1523/JNEUROSCI.5217-04.2005

Wiesel, T. N., and Hubel, D. H. (1963a). Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. *J. Neurophysiol.* 26, 978–993. doi: 10.1152/jn.1963.26.6.978

Wiesel, T. N., and Hubel, D. H. (1963b). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* 26, 1003–1017. doi: 10.1152/jn.1963.26.6.1003

Wong-Riley, M. T., and Jacobs, P. (2002). AMPA glutamate receptor subunit 2 in normal and visually deprived macaque visual cortex. *Vis. Neurosci.* 19, 563–573. doi: 10.1017/S0952523802195022

Zhou, X., Panizzutti, R., de Villers-Sidani, E., Madeira, C., and Merzenich, M. M. (2011). Natural restoration of critical period plasticity in the juvenile and adult primary auditory cortex. *Neuroscience* 31, 5625–5634. doi: 10.1523/JNEUROSCI.6470-10.2011

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Transforming experiences: Neurobiology of memory updating/editing

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Long-term memory is achieved through a consolidation process where structural and molecular changes integrate information into a stable memory. However, environmental conditions constantly change, and organisms must adapt their behavior by updating their memories, providing dynamic flexibility for adaptive responses. Consequently, novel stimulation/experiences can be integrated during memory retrieval; where consolidated memories are updated by a dynamic process after the appearance of a prediction error or by the exposure to new information, generating edited memories. This review will discuss the neurobiological systems involved in memory updating including recognition memory and emotional memories. In this regard, we will review the salient and emotional experiences that promote the gradual shifting from displeasure to pleasure (or vice versa), leading to hedonic or aversive responses, throughout memory updating. Finally, we will discuss evidence regarding memory updating and its potential clinical implication in drug addiction, phobias, and post-traumatic stress disorder.

KEYWORDS

recognition memory, associative learning, valence shifting, novelty and familiarity, reconsolidation

1. Introduction

Organisms, including humans, thrive in complex heterogeneous environments by modifying their behavior, increasing chances of survival and reproduction. Thus, memory is an indispensable mechanism that integrates knowledge and directs future behavior. The integrated information is preserved across different stages in which memory is encoded, integrated, and retrieved (Squire, 2009). Organisms generally recollect information about shelters, food sources, mate recognition and location, and dangerous situations. However, environmental conditions are not fixed, and milieus constantly change; therefore, organisms must adapt their behavior by modifying the previously integrated information. Hence, memory is also a dynamic process that provides flexibility for adaptive response during sustained environmental change. This flexibility enhances survival by updating and editing the integrated information and redirecting behavior according to fluctuating events.

Memory integrates various experiences for different intervals; therefore, memory could be classified depending on the duration and participation of discrete brain structures and circuits, resulting in different memory systems. Memory is classified according to its duration as short-term (STM) and long-term memory (LTM) (Atkinson and Shiffrin, 1968; Norris, 2017). STM concerns the maintenance of information during short periods and involves the covalent modification of existing proteins, temporally changing the strength of pre-existing synaptic connections, while LTM involves persistent morphological and physiological changes yielded by *de novo* protein synthesis facilitating the retention of information for long-lasting periods, even a lifetime (Goelet et al., 1986; McGaugh, 2000; Dudai, 2004; Kandel, 2012). Memory is also classified by the integrated information type and divided into two categories: declarative and non-declarative (Squire, 2004). Non-declarative memory, also named implicit memory, integrates information acquired through repetition, such as habits or motor skills and conditioning (Squire, 2004; Ferbinteanu, 2019). Declarative memory is recalled consciously and subdivided into semantic and episodic memory; semantic memory concerns information associated with facts, whereas episodic memory is related to experienced events (Squire, 2009; Nadel and Hardt, 2011). Episodic memory organizes information associated with "where," "what," and "when" an event occurred (Tulving, 2002), facilitating the judgment of whether a recent experience has been previously experienced or encountered and the identification of specific information modalities, including faces, places, sounds, objects, or contextual changes. Recently, emotional components broadened the definition of these classifications, since all these kinds of memories can be integrated under different emotional states, thus enhancing their strength and duration.

Memory goes through different stages: encoding, consolidation, retrieval and reconsolidation (Sara, 2000; Abel and Lattal, 2001; Dudai, 2004; Rodriguez-Ortiz and Bermúdez-Rattoni, 2017). Encoding is an attention-dependent process where information is acquired (McGaugh, 2000). Then, information is processed—through protein synthesis—in a time-dependent stabilization mechanism that requires synaptic connectivity modifications within local and systems circuits for LTM integration (McGaugh, 2013, 2000; Bisaz et al., 2014). Memory retrieval refers to the process by which interoceptive and exteroceptive cues select and reactivate integrated information within memory systems resulting in a behavioral outcome (Ben-Yakov et al., 2015; Frankland et al., 2019). After retrieval, LTM can undergo destabilization and restabilization processes conjointly referred to as reconsolidation. Like consolidation, reconsolidation is a time-dependent event that could be affected by amnesic treatments (Nader et al., 2000). Nevertheless, the behavioral response is a dispensable condition during memory retrieval to trigger reconsolidation, since the pharmacological inhibition of memory expression does not affect memory reconsolidation (Rodriguez-Ortiz et al., 2012; Balderas et al., 2013; Santoyo-Zedillo et al., 2014). In this review, we will present evidence suggesting that reconsolidation is initiated every time information is updated, arguing that information updating, and not retrieval, is the crucial factor that triggers the reconsolidation process (Lee et al., 2017; Rodriguez-Ortiz and Bermúdez-Rattoni, 2017). Moreover, reactivated memories can be destabilized after the occurrence of a prediction error when new information is presented concerning previous knowledge. Afterward, LTM goes through a consolidation-like process known as reconsolidation/updating (Nader et al., 2000; Sara, 2000), where memory is enhanced, restabilized, impaired, or modified; it is during this stage that memory updating occurs (see **Figure 1**; Sara, 2000; Lee et al., 2017; Rodriguez-Ortiz and Bermúdez-Rattoni, 2017). In this work, we will focus on recognition memory editing (Squire and Zola, 1996; Tulving, 2002; Bermúdez-Rattoni, 2004; Balderas et al., 2015; Morici et al., 2015) and valence modification (positive or negative characteristics of the experienced stimulus) (Popik et al., 2020), generating memory updating.

2. Updating memory

2.1. Recognition and contextual memory

Integrated information within memories is not fixed and is constantly updated because of environmental changes. Declarative and non-declarative memories are susceptible to memory updating and editing; the integrated information predicts the following events. Then, a discrepancy between expectation and reality induces memory destabilization. Declarative memories, like recognition memories, integrate two distinctive processes: familiarity and recollection (Brown and Aggleton, 2001; Merkow et al., 2015). Familiarity conceives whether an event has already been experienced (Mandler, 1980), and the recollection process integrates the event's specific characteristics (qualitative–valence) (Evans and Wilding, 2012). Recollection is usually associated with the conscious retrieval of the contextual details in which a stimulus occurred (Yonelinas et al., 2010) and requires the integral functionality of several brain structures, including the hippocampal formation and prefrontal, perirhinal, entorhinal, insular, and postrhinal cortices (Brown and Aggleton, 2001; Yonelinas, 2002; Evans and Wilding, 2012; Bermudez-Rattoni, 2014; Merkow et al., 2015). Our understanding of the neurobiological mechanisms related to declarative memory, particularly recognition memory, has been mainly obtained through the evaluation of spontaneous object exploration paradigms. Novel object recognition (NOR) is based on an animal's innate tendency to explore novel stimuli, where animals discriminate between a previously encoded object and a novel one (familiarity) (Ennaceur, 2010). Another widely employed paradigm is object location memory (OLM). In this task, organisms identify a familiar object in a novel contextual distribution (recollection) (Ennaceur and Delacour, 1988). Both paradigms involve various behavioral sessions; initially, animals are handled and habituated to an empty open field or exploration arena. Then, animals freely explore one or two identical novel objects during the sample phase; throughout the test session, animals are reintroduced to the exploration arena. Recognition memory is assessed either by presenting a different novel object or changing the contextual configuration, NOR and OLM, respectively (Ennaceur and Delacour, 1988; Moreno-Castilla et al., 2018). Novelty demands attention, motivation, and memory processes (Bastin et al., 2019). Thus, NOR alludes that a stimulus has never been encountered (Kafkas and Montaldi, 2018), while an unexpected position/location of the familiar elements is named contextual novelty, as in OLM (Ranganath and Rainer, 2003; Kafkas and Montaldi, 2018; Bastin et al., 2019). NOR (Kelly et al., 2003; Akirav and Maroun, 2006; Rossato et al., 2007;

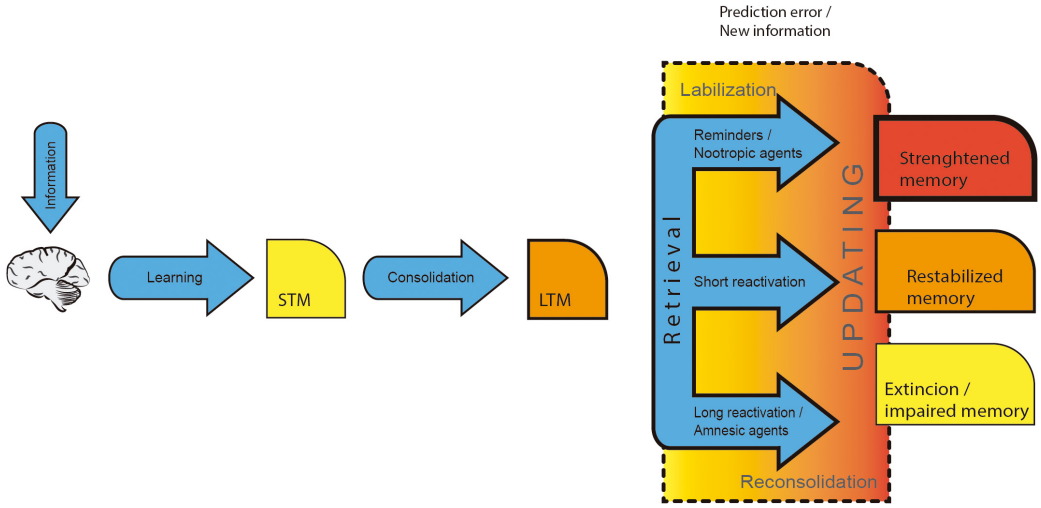

FIGURE 1
Long-term memory stages. Exteroceptive and interoceptive information is encoded during learning and subsequently stabilized into long-term memory through memory consolidation. Integrated memories are recalled throughout retrieval when they are reactivated and expressed. Furthermore, memory updating occurs only when new information is integrated into the previously formed memory traces.

Balderas et al., 2013, 2015; Santoyo-Zedillo et al., 2014) and OLM (Villain et al., 2016; Kwapis et al., 2020; Wright et al., 2020) are susceptible to updating when new information (new object or novel configuration) is presented during reactivation/retrieval and is evaluated in a test session.

2.2. NOR and OLM updating

Object-related recognition memory is susceptible to modification and editing. Evidence suggests that NOR memory is only updated when a prediction error occurs. In a NOR updating experiment, animals equally explored two identical objects during the sample phase and then, during the reactivation phase, animals were exposed to different situations. A group of rats explored the same objects as in the sample phase (no prediction error). In contrast, another group explored a new pair of novel objects (totally novel information), and a third group explored a copy of the familiar object with a novel one (prediction error). For OLM updating, a different contextual conformation induces a prediction error. Administration of anisomycin, a protein synthesis inhibitor, within the perirhinal cortex (Balderas et al., 2013) or the hippocampus (Rossato et al., 2007; Choi et al., 2010; Huff et al., 2022) promotes retrograde amnesia, impairing object and contextual memory updating only in the prediction error group. To illustrate this, in an OLM updating protocol, rodents preferred to explore the switched objects due to a novel contextual configuration during the reactivation session. However, if rodents had successfully updated the changed information, they showed a similar preference for all objects, in the test session, when re-exposed to the same contextual configuration, because of contextual familiarity. Nevertheless, administration of anisomycin into the hippocampus impedes memory updating because rodents identify the familiar contextual arrangement as a novel one (Kwapis et al., 2020; Huff et al., 2022). Recognition memory enrolls different structures to update integrated memories depending on the prediction error session. When a prediction error occurs in the expected objects, the perirhinal cortex is mainly involved; however, when the prediction error occurs in the expected context, the perirhinal cortex and the dorsal hippocampus are implicated (Balderas et al., 2008; Winters et al., 2011).

Therefore, memories are reactivated and destabilized after a prediction error during memory retrieval to integrate updated information. Another characteristic of memory retrieval is the behavioral expression. However, memory expression is not essential for memory editing and updating. The pharmacological inhibition of the perirhinal cortex by the administration of muscimol—a GABA receptor agonist—before the reactivation/retrieval session hinders recognition memory expression, leaving memory destabilization and updating intact (Balderas et al., 2013). Muscimol administration impaired memory expression during the reactivation/retrieval session, since rats had no preference for the novel object, indicating that they could not differentiate between novel and familiar objects. However, in the test session, rats showed preference for a novel object, revealing that the original object-related memory was unimpaired despite the inhibition of memory expression. Moreover, administration of a protein synthesis inhibitor after the reactivation/retrieval session promotes object-related retrograde amnesia, since rats could not differentiate between the familiar and the novel object during the test session. The combined administration of muscimol (before reactivation/retrieval session) and a protein synthesis inhibitor (after reactivation/retrieval session) within the perirhinal cortex inhibits memory expression during the reactivation/retrieval session and induces object-related amnesia (Balderas et al., 2015, 2013; see **Figure 2**). Likewise, administration of CNQX (before the reactivation/retrieval session), an AMPA receptor antagonist, into the perirhinal cortex interferes with memory expression, observed as a failure to recognize the novel object during the reactivation phase, but maintaining original object-related memory; while the inhibition of N-methyl D-aspartate (NMDA) receptors (after reactivation/retrieval session) with APV or MK-801 leaves NOR expression intact but generates retrograde amnesia (Winters et al., 2009; Santoyo-Zedillo et al., 2014). Conversely, pharmacological

blockade of muscarinic receptors or inhibition of protein degradation within the hippocampus prevents destabilization of recognition memory during retrieval, arresting the amnesic effect induced by the administration of a protein synthesis inhibitor stimulus (Choi et al., 2010; Huff et al., 2022). Altogether, these results indicate that NOR destabilization and updating are independent processes from memory expression during retrieval (**Figure 2**). Although recognition memory updating is usually evaluated by administering amnesic agents, memory updating could also be assessed by its enhancement during the reactivation session. For example, a systemic nicotine administration during the NOR reactivation session promotes better performance during LTM (Tian et al., 2015), indicating that memory strengthening is also a kind of memory updating (**Figure 1**). Thus, discrepancies between the expected and experienced promote recognition memory destabilization and subsequent integration of the updated information, enabling the editing and modification of existing memories.

Prediction error is commonly associated with dopamine when a discrepancy between the expected and received rewards occurs (Schultz, 2016). However, dopaminergic activity is also involved in other cognitive processes beyond rewards. Dopamine is a modulatory neurotransmitter associated with the regulation of perceptual salience. This memory process modulates the integration of inconspicuous stimuli into a relevant memory facilitating the transition from novelty to familiarity without enhancing the initial sensory perception in recognition memory (Gil-Lievana et al., 2022; Osorio-Gómez et al., 2022). In this regard, the integral functionality of the dopaminergic inputs from the ventral tegmental area and the locus coeruleus is required for novelty detection, comparing the presented information to previously integrated memories (Lisman and Grace, 2005; Lisman et al., 2011). Thus, it has been postulated that dopamine is a general mechanism for predictive processing; this activity signals the prediction error and the difference between the expected value of consequences and the received value (Diederen and Fletcher, 2021). Dopaminergic activity within the hippocampus and insular and perirhinal cortices promotes the consolidation and persistence of familiarity in recognition memory. Howbeit, the evidence related to catecholaminergic activity during NOR updating is limited. D1/D5 receptors pharmacological blockade through administration of SCH 23390 within the hippocampus prevents amnesia caused by the administration of a protein synthesis inhibitor during the reactivation session; these results suggest that D1/D5 receptors are involved in the destabilization process induced by the novel stimulus presented during the reactivation phase (Rossato et al., 2015; Gonzalez et al., 2021). Recently, we demonstrated that optogenetic inhibition of catecholaminergic projections arriving at the dorsal CA1 hippocampus, coming from the locus coeruleus but not from the ventral tegmental area, impedes object location memory updating. Significantly, the pharmacological blockade of hippocampal β-adrenergic receptors with propranolol hinders memory expression without altering memory updating, whereas D1/D5 receptors blockade, by SCH 23390 administration, impairs memory expression and updating (Gálvez-Márquez et al., 2022). These results suggest that dopaminergic activity arising from the locus coeruleus modulates both memory expression and updating when new contextual information is presented. More data are still necessary to comprehend the involvement of dopamine and noradrenaline in the transition of novelty to familiarity in recognition memory. Nevertheless, the gradual transition from novelty to familiarity usually requires several exposures to the novel stimulus, facilitating new information learning (Henson and Gagnepain, 2010) and neural plasticity changes (Lisman et al., 2011). This process suggests that every presentation induces progressive memory updating through reconsolidation processes until complete familiarization is accomplished (Rodriguez-Ortiz et al., 2005).

2.3. Taste recognition memory

Novelty detection is crucial since it has been suggested that the novelty-familiarity transition modulates overall recognition memory performance (Parker et al., 1998). Recognition memory is evaluated through different strategies; however, it has also been estimated through evolution-related paradigms, like taste recognition memory, referred to as the ability to identify a particular taste and its relation to post-ingestive consequences (Bermúdez-Rattoni, 2004). Organisms differentiate between novel and familiar food, reducing the ingestion of potentially harmful foods. This behavior is known as taste neophobia; if the tastant stimulus is not associated with positive/negative post-ingestive consequences, the taste becomes familiar, promoting attenuation of neophobia, observed as a gradual augmentation of the stimulus ingestion (Domjan, 1976). Accordingly, novelty detection induces a maximum behavioral response that is gradually diminished after the following presentations, suggesting that taste recognition memory is progressively updated until complete familiarization is accomplished (Rodriguez-Ortiz et al., 2005). Thus, neophobia and its attenuation assess the recognition of memory events necessary to transition from novel to familiar tastes (Osorio-Gómez et al., 2018). Moreover, neophobia and its attenuation are vulnerable to perirhinal and hippocampal lesions (Morillas et al., 2017), like the deficits observed in NOR. This evidence suggests that attenuation of neophobia employs brain structures involved in declarative memories (Moron et al., 2002; Manrique et al., 2009; Grau-Perales et al., 2019).

Another widely used taste recognition paradigm is conditioned taste aversion (CTA). Unlike neophobia and its attenuation, where there are no evident post-ingestive consequences, in CTA, the novel taste is associated with gastric malaise, preventing the animals from consuming the taste in future events (Garcia et al., 1955; Bermúdez-Rattoni, 2004). Hence, aversive taste recognition memory is essential to reject illness-associated tastes. This memory also requires updating and has been evaluated by promoting CTA strengthening through several training sessions (Rodriguez-Ortiz et al., 2012) or changing the expected consequence as in extinction (Garcia-Delatorre et al., 2010) or latent inhibition (Rodriguez-Ortiz et al., 2005). Taste recognition memory comprises two aspects: familiarity and relation to post-ingestive consequences. Therefore, taste recognition memory integrates the information related to the specific characteristics of taste, such as identity, intensity or valence (Breslin, 2013; Wang et al., 2018). Cooperatively, familiarity integrates the information to remember if a taste has been previously experienced. In this regard, results show that novel and familiar stimuli induce the graded activation of several brain regions (Kafkas and Montaldi, 2014). Novel taste exposure promotes catecholaminergic activity within several brain structures

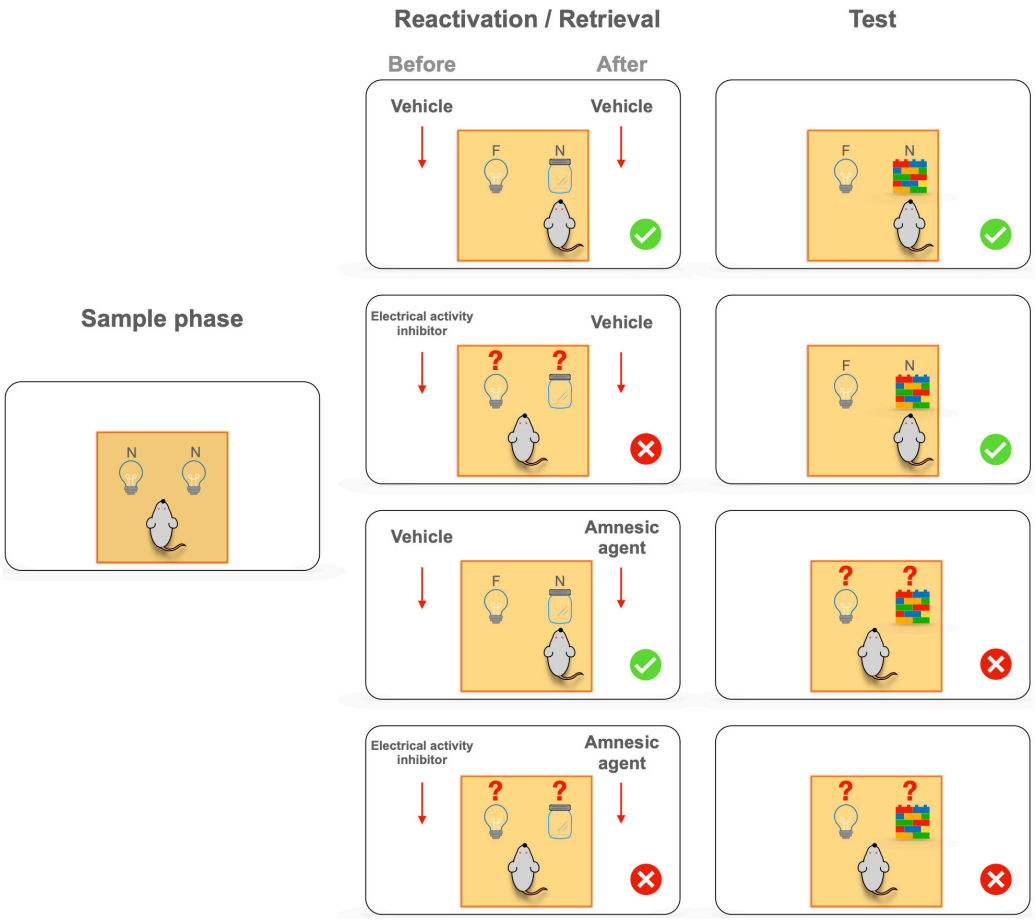

FIGURE 2
Memory expression is not essential for memory editing and updating. The administration of an expression blocker (a GABA receptor agonist or an AMPA receptor antagonist) before the reactivation/retrieval session impairs recognition memory, since rats could not differentiate between the novel (N) and familiar objects (F). However, rats showed preference for a novel object in the test session, revealing that the original object-related memory remained intact despite inhibition of memory expression. Moreover, the administration of an amnesic agent (a protein synthesis inhibitor) after the reactivation/retrieval session promotes object-related retrograde amnesia, since rats could not differentiate between the familiar and novel objects during the test session. The combined administration of an expression blocker (before reactivation/retrieval session) and an amnesic agent (after reactivation/retrieval session) blunts memory expression during the reactivation/retrieval session and induces object-related amnesia (Based on Balderas et al., 2015).

(Royet et al., 1983; Dunn and Everitt, 1987; Steketee et al., 1989; Bassareo et al., 2002), including the amygdala (Guzmán-Ramos et al., 2012) and insular cortex (Guzmán-Ramos et al., 2010; Moreno-Castilla et al., 2016; Osorio-Gómez et al., 2021). When the taste becomes familiar, catecholaminergic response is reduced within the nucleus accumbens (De Luca, 2014), amygdala (Osorio-Gómez et al., 2017, 2016), and insular cortex (Osorio-Gómez et al., 2017). Similarly, exposure to a new taste elevates extracellular cholinergic levels within the insular cortex (Miranda et al., 2000; Rodríguez-García and Miranda, 2016); after the taste stimulus becomes familiar, these cholinergic levels decrease and are inversely related to the consumption of the familiar taste stimulus (Miranda et al., 2000).

Consequently, novelty detection induces a maximum response that is gradually diminished after the following presentations, suggesting that attenuation of neophobia can be assessed from a reconsolidation and updating perspective; every time animals are exposed to the taste stimulus, recognition memory is reactivated until complete familiarization is achieved, promoting memory destabilization and facilitating the integration of new information (familiarity) for memory updating (Rodriguez-Ortiz et al., 2005). The administration of a protein synthesis inhibitor into the insular cortex during the initial retrieval sessions of neophobia attenuation hinders memory reconsolidation and updating, generating the familiar taste that is recognized as novel again. However, when the stimulus is familiar, memory is no longer vulnerable to the amnesic effect (Rodriguez-Ortiz et al., 2005). Similarly, administering a muscarinic receptor antagonist within the insular cortex before a second taste familiarization session retards the attenuation of neophobia, and the taste is recognized as novel again (Gutiérrez et al., 2003), impeding memory updating.

Regarding catecholaminergic activity, optogenetic activation of the ventral tegmental area increases the neophobic response. However, optogenetic stimulation of dopaminergic terminals arriving at the insular cortex spares neophobia (Gil-Lievana et al., 2022). Moreover, pharmacological manipulation of the dopaminergic receptors within the nucleus accumbens (shell) or the amygdala impairs taste recognition memory updating. Blockade of D1/D5 receptors in both structures exacerbates the neophobic response even when the stimulus is becoming familiar

(second exposure to the stimulus), but attenuation of neophobia is hindered only after the blockade of amygdalar D1/D5 receptors. Nevertheless, activation of D1/D5 receptors within the amygdala diminishes the neophobic response and impedes the attenuation of neophobia updating (Grau-Perales et al., 2020). Therefore, dopaminergic activity requires modulation of the neophobic response and its updating during attenuation of neophobia.

Like object recognition, taste recognition memory updating only occurs when new information is aggregated. Gradual presentation of new information occurs during the novel-familiar transition, but also, novel information is incorporated when the stimulus' learned characteristics (valence) are changed. In this regard, taste recognition memory is again vulnerable to updating when a familiar stimulus is now associated with post-ingestive consequences, such as gastric malaise, generating a clear taste aversion even after complete attenuation of neophobia has occurred, indicating memory updating (Rodriguez-Ortiz et al., 2005). Inhibition of protein synthesis spares memory updating when the stimulus is familiar since no new information is added. Nevertheless, new information is integrated when the familiar taste is now followed by gastric malaise, making memory vulnerable again to the amnesic effect of protein synthesis inhibition, preventing the incorporation of updated information, i.e., taste aversion (Rodriguez-Ortiz et al., 2005). Taste aversion memory is updated through strengthening. Administration of a protein synthesis inhibitor into the insular cortex or central amygdala impairs aversive memory strengthening during repeated training sessions (García-DeLaTorre et al., 2009). However, when the taste becomes strongly familiar and aversive, due to several conditioning trials, memory is no longer vulnerable to destabilization and memory updating (García-DeLaTorre et al., 2009).

Taste aversion memory updating is an independent process from memory expression. The blockade of D1 dopaminergic receptors within the amygdala spares memory expression but impedes taste aversion updating (Osorio-Gómez et al., 2016). Furthermore, the pharmacological blockade of AMPA receptors within the amygdala (Garcia-Delatorre et al., 2014) impairs conditioned aversive response but spares memory updating, whereas inhibition of protein synthesis (Rodriguez-Ortiz et al., 2012) or the blockade of NMDA (Garcia-Delatorre et al., 2014) within the insular cortex hinders memory updating without interfering with memory expression. In this regard, there is a functional interaction between the amygdala and the insular cortex for taste aversion establishment (Escobar and Bermúdez-Rattoni, 2000; Guzmán-Ramos et al., 2010; Osorio-Gómez et al., 2019) and memory expression and updating (Osorio-Gómez et al., 2017). Through pharmacological manipulations, behavioral analysis, and microdialysis in freely moving rats, we observed that the administration of an AMPA receptor antagonist into the amygdala impairs aversive taste memory expression and prevents norepinephrine and dopamine release within the insular cortex. In contrast, the blockade of NMDA receptors within the amygdala spares aversive taste expression but hinders changes in glutamatergic levels within the insular cortex (Osorio-Gómez et al., 2017). These results suggest that the amygdala modulates memory expression by regulating catecholaminergic activity in the cortex. This was confirmed since blockade of D1 and β-adrenergic receptors within the insular cortex impairs aversive taste memory expression (Osorio-Gómez et al., 2017). However, glutamatergic activity *via* NMDA receptor activation in the amygdala and insular cortex is necessary for memory strengthening through updating (García-DeLaTorre et al., 2009; Garcia-Delatorre et al., 2010; Osorio-Gómez et al., 2016).

Memory updating happens after the appearance of a prediction error, inducing memory destabilization to integrate the new information into the previously formed memory. This process happens during extinction when animals expect that taste will be followed by illness. However, when taste is not followed by gastric malaise, this event promotes memory extinction updating taste information. Inhibition of protein synthesis within the hippocampus or the insular cortex hinders memory extinction since animals still recognize the tastant as aversive, even though the taste is no longer associated with gastric malaise, suggesting that the new information is not integrated into the memory trace (Garcia-Delatorre et al., 2010). Regardless, memory updating induces memory destabilization *via* activation of the ubiquitin-proteasome system; the pharmacological inactivation of this system impairs memory updating, avoiding destabilization and the subsequent integration of new information (Rodriguez-Ortiz et al., 2011). Altogether, if new information is presented during retrieval sessions, memories are destabilized, promoting the integration of the updated information. Taste recognition memory can be updated by familiarizing the taste stimulus when no post-ingestive consequences occur, throughout strengthening memory sessions or when there is a modification in the stimulus' learned characteristics (valence).

3. Emotional valence in memory updating

3.1. Integration of interoceptive and exteroceptive information

Several pieces of evidence indicate that the insular cortex translates and integrates external cues into interoceptive states that regulate a broad range of physiological and cognitive processes (Craig, 2009). Consequently, the insular cortex could be postulated as an integrative hub due to the vast reciprocal connections that exist between it and an extensive network of cortical and subcortical structures (Saper, 1982; Craig, 2009; Nguyen et al., 2016; Benarroch, 2019). Thus, as the insular area is responsible for the interoceptive processing of multisensory information, this region could play a vital role in the extensive processing of internal states involved in memory updating (Gu et al., 2013). This hypothesis could be sustained with the established role of the insular cortex in pain processing (Starr et al., 2009; Lu et al., 2016) and negative affective states like anxiety (Paulus and Stein, 2006). According to recent research, the insular cortex participates in mediating several processes related to craving and drug-seeking (Contreras et al., 2007; Naqvi and Bechara, 2009; Moschak et al., 2018) through the upregulation of opioidergic signaling, leading to an altered subcortical function and downstream activity (Pina et al., 2020). Thus, the insular cortex seems to be involved in the integration of multimodal information, including interoceptive and contextual information.

In this regard, contextual information is essential for several learning and memory processes. In a more direct contextual paradigm, the conditioned place preference model, where rodents are trained to associate a rewarding stimulus with contextual cues, memory could be destabilized when mice are re-exposed to the training context without the rewarding stimulus (Milekic et al., 2006; Gil-Lievana et al., 2020). This destabilization makes memory vulnerable to disruption through blockade of NMDA receptors in the insular cortex, inducing amnesia and facilitating the association of new contextual cues with a rewarding stimulus (Gil-Lievana et al., 2020). Interestingly, memory could be re-stabilized when no amnesic agents are given; thus, the original contextual memory is maintained and competes with the new contextual association, even after extinction trials (see **Figure 3**). Besides, contextual information is gradually incorporated by updating mechanisms that are dependent of protein synthesis. Administration of a protein synthesis inhibitor into the hippocampus impairs memory updating in partially trained animals, whereas the same manipulation in well-trained animals spares spatial memory (Rodriguez-Ortiz et al., 2008). This memory impairment is only observed after new memory encoding at the time of memory destabilization, including memory strengthening, updating or extinction (Morris et al., 2006; Rodriguez-Ortiz et al., 2008).

3.2. Salient experiences

During learning, and memory retrieval, specific neural circuits transduce salient experiences (e.g., rewarding and aversive as emotional valence) into instructive neural signals integrated into the memory circuitries (Schultz, 2015). Therefore, salient and emotional experiences processing during learning and memory is a multi-step phenomenon initiated by forming an association between a given stimulus and a related positive or negative consequence every time the stimuli and context are similar. After learning, experience is followed by the development or increase of attention, motivation and/or anticipation, generating a prediction of the event and defined by some as a "state of readiness for a consequence" (Kring and Barch, 2014; Rizvi et al., 2016). Moreover, there is feedback based on consequences and learning during memory retrieval, where a proper sequence of events is required for balanced integration between the expected value of a given stimulus and the predicted consequence (e.g., updating). The consummatory phase of reward or aversive avoidance processing occurs when the goal is achieved, leading to a hedonic (Kring and Barch, 2014; Rizvi et al., 2016) or aversive response (Ozawa and Johansen, 2018).

As expected, several systems that regulate positive or negative valence during emotional/affective processing also interact during associative learning, retrieval and updating. Research of the negative valence role in aversive processing during learning and memory provides insight into the complexity of numerous neurotransmitter pathways that simultaneously impact during aversive vs. hedonic memory. Pharmacological findings demonstrate that noradrenergic activity within the amygdala during aversive and emotional arousal training experiences enhances memory consolidation (Ellis and Kesner, 1983; Liang et al., 1990, 1986; Hatfield and McGaugh, 1999). It is known that aversive experiences produce a surge of noradrenaline in the amygdala (Quirarte et al., 1998; Guzmán-Ramos et al., 2012; Osorio-Gómez et al., 2016). This noradrenergic surge promotes aversive associative learning and memory by activating β-adrenergic receptors (Uematsu et al., 2017). The noradrenergic response arises from the locus coeruleus, which projects to the hippocampus, amygdala and insular cortex, eliciting noradrenaline release (Guzmán-Ramos et al., 2012, 2010; Robertson et al., 2013; McCall et al., 2017; Osorio-Gómez et al., 2021, 2016). Particularly, the noradrenergic modulation of amygdalar activity promotes aversive association since it receives nociceptive information (Bernard et al., 1993, 1992; Bester et al., 1997), improving pain-induced associative learning (Watabe et al., 2013; Han et al., 2015; Sato et al., 2015) and anxiety-related responses (Galvez et al., 1996; Quirarte et al., 1998). Consequently, stress is argued to impact several stages of consolidation and memory updating during complex experiences where an emotional valence induces changes in the allostatic state (e.g., interoceptive and nociceptive modulation) that forms the growing motivational changes in the learned and updated behavior. In healthy humans, the β-adrenergic receptor antagonist propranolol blocks memory reconsolidation in a fear conditioning test (Kindt et al., 2009) and lasts at least 1 month resisting fear reinstatement (Lonergan et al., 2013). Viewing emotional memory updating as a process that includes an allostatic mechanism provides critical insights into how dysregulated neurocircuitry involved in basic motivational systems can transition into pathophysiology. Recent findings (Xue et al., 2017) demonstrate that the administration of propranolol disrupts memory reconsolidation in rats and humans in a nicotine disorder study (Lin et al., 2021). Similarly, propranolol impaired long-term alcohol context-related memory reconsolidation in a rat model (Wouda et al., 2010). Furthermore, some evidence suggests the efficacy of β-blockers in reducing post-traumatic stress disorder (PTSD) symptoms. Thus, blocking memory reconsolidation with propranolol reduced drug addiction and several anxiety/stress disorders (Brunet et al., 2018; Roullet et al., 2021). β-blockers could prevent the associations between environmental stimuli and the effects of self-administered drugs with their respective aversive emotional states. β-blockers decrease the aversive states that include interoceptive nociceptive signals associated with states of anxiety and stress due to the lack of the consumption of substances of abuse (Koob and Schulkin, 2019). Altogether, the evidence indicates the influence of noradrenaline on memory consolidation and memory updating in pathological and salient aversive experiences (Pigeon et al., 2022).

Regarding glutamatergic activity, nociceptive stimuli promote glutamate release, increasing responsiveness, enhancing the aversive response, and inducing the association between nociception and the experienced context (LeDoux, 2000; Bornhövd et al., 2002; Cardinal et al., 2002; Baliki et al., 2006). Furthermore, a recent study reports an increase in calcineurin, an essential plasticity protein, within the basolateral amygdala during fear memory updating (extinction); this protein is modulated *via* NMDA glutamate receptors (Merlo et al., 2014). Consequently, changes in the aversive/negative valence may be related to an increase in glutamatergic activity, through AMPA receptors (Cheng et al., 2011) and NMDA receptor activation, inducing plasticity reeling upon the synthesis of new proteins (Nader et al., 2000) favoring memory updating. Along with it, corticosteroids activate projections from the locus coeruleus to the amygdala, promoting the release of norepinephrine (McCall et al., 2017). Thus, glutamate and

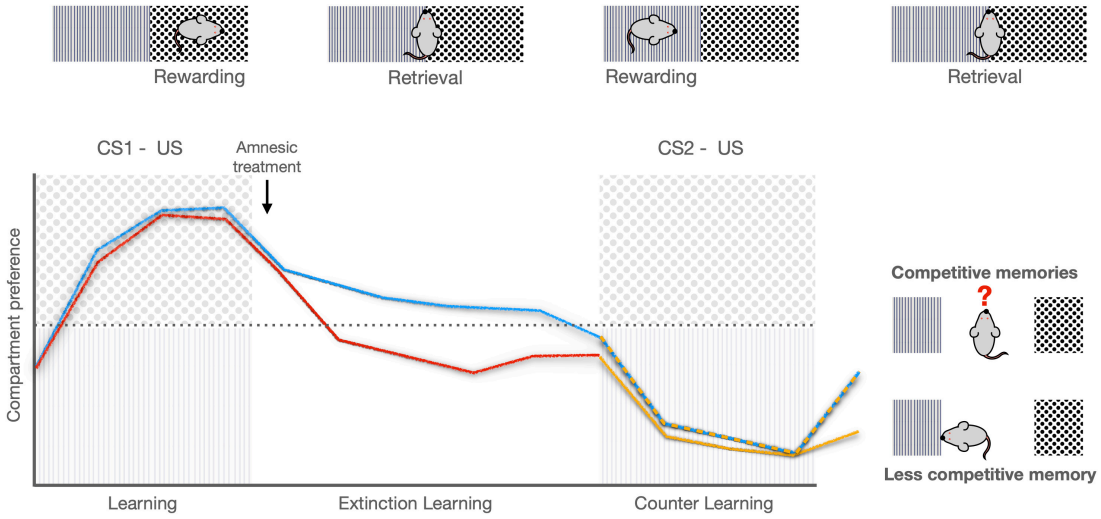

FIGURE 3
Contextual memory updating. Animals were trained to prefer a compartment (CS1) with a rewarding stimulus (ventral tegmental area photo-stimulation; unconditioned stimulus, US). During the extinction training sessions, control animals are exposed to the conditioned stimulus (CS) without US, initiating extinction learning. The group of treated animals (red) received an amnesic treatment in the insular cortex (NMDA receptor antagonist) and place preference conditioning was extinguished. Then, both groups of animals were counter-trained in the other compartment (CS2) with the same rewarding stimulus. In the retrieval session, the control group maintains the original contextual memory that competes with the new contextual association (blue and orange-dashed line), indicating memory updating. However, the amnesic treatment disrupted the original memory, facilitating the association of new contextual cues with a rewarding stimulus (orange solid line) (Based on Gil-Lievana et al., 2020).

norepinephrine modulation of the amygdala enhances aversive memory acquisition and consolidates aversion-related tasks (Roozendaal and McGaugh, 1996; Roozendaal, 2002), and perhaps modulates memory updating. Particularly, noradrenergic and glutamatergic transmission could play an essential role in these pathologies, giving a crucial function to the amygdala-cortical pathways. These findings (see below) suggest that pharmacological intervention in cue-exposure therapies for addictive behaviors and anxiety disorders may be potentiated in understanding the mechanisms involved during new learning, memory retrieval, and memory updating.

Furthermore, emerging evidence gives insights into how acute modulation of opioids can influence memory consolidation and memory updating. Recent reports highlight the importance of the opioid system in regulating not just aversive experiences but also motivation and the sense of hedonic impact (e.g., "*liking*," the pleasurable/hedonic impact or various expressions of subjective pleasure induced by rewarded appetitive experience) (Peciña and Smith, 2010; Baldo, 2016). In this regard, several neural circuits that are thought to orchestrate feeding behavior overlap with the reward circuitry (Rossi and Stuber, 2018). Some reports agree that opioid peptide neurotransmission causes a shift in the valuation of the "hedonic gradient," ranging from displeasure to pleasure, which is not limited to the liking of stimuli (Eippert et al., 2008; Haaker et al., 2017). Moreover, micro-stimulation with opioid peptides increases motivation for different cue-triggered seeking responses and innate reward stimuli in rodents (Wassum et al., 2009; Mahler and Berridge, 2012); this data could be linked with growing evidence in animal models and human studies on the involvement of reconsolidation processes in related memories upon their reactivation during relapse to an addictive substance or after traumatic experiences or pathologies.

4. Clinical implications of memory updating

Drug addiction and substance abuse disorders are related to the leading causes of mortality and morbidity worldwide (Ritchie and Roser, 2019; Shield et al., 2020; Roser et al., 2021). Some current treatments involve behavioral and pharmacological strategies that acknowledge the psychobiological processes underlying addictions. These can be considered maladaptive reward memories, and the modification or updating of such memories, especially the cue/context reinforcer association, has been addressed through the manipulation of memory reconsolidation (Torregrossa and Taylor, 2013; Liu et al., 2019). Cumulative evidence indicates that propranolol, a β-adrenergic blocker, could be a valuable pharmacological agent to achieve long-lasting results affecting drug-related memories by altering the stability of the memory trace. For instance, in animal models, post-retrieval propranolol administration reduces alcohol-seeking behavior and impairs alcohol-associated memory (Wouda et al., 2010; Schramm et al., 2016). A similar effect was observed with cocaine (Bernardi et al., 2006) and morphine-associated memories (Robinson and Franklin, 2010). In human studies, the administration of propranolol after cocaine cue exposure (memory reconsolidation) decreases craving and physiological responses during a test session. However, this does not indicate memory erasure (Saladin et al., 2013). A small pilot study had similar results over craving severity in patients diagnosed with substance dependence when drug-related memory retrieval took place under propranolol effects (Lonergan et al., 2016). A recent study found a decrease in craving after propranolol reconsolidation disruption in smokers (Lin et al., 2021).

Another process explored to achieve drug-related memory modification is the modulation of the extinction process *via*

the glutamatergic system. NMDA receptor agonists (D-serine and D-cycloserine) facilitate the extinction of drug-induced conditioned place preference and reduce reinstatement (Botreau et al., 2006; Myers and Carlezon, 2012; Hammond et al., 2013). In humans, D-cycloserine has been assessed prior to extinction sessions, with poor results in alcohol-dependent subjects and cocaine addicts (Hofmann et al., 2012; Price et al., 2013; Santa Ana et al., 2015) and promising results in smokers (Santa Ana et al., 2009; Kamboj et al., 2012; Otto et al., 2019). Clinical studies have used cue exposure therapy based on the extinction of the conditioned responses elicited by environmental stimuli. The effectiveness of this therapy is limited in a lab-controlled environment (Franken et al., 1999; Marissen et al., 2007; Germeroth et al., 2017), which stresses that the relevance of extinction is mainly context dependent, challenging new therapies to prevent relapse under natural environments.

Emotional memories can be altered through the modulation of integrated information during reconsolidation, opening a possibility for treatment of other types of maladaptive memory traces that trigger undesirable symptoms affecting life quality like the ones associated with PTSD. Propranolol has been assessed as a safe pharmacological strategy to decrease these symptoms (Pigeon et al., 2022). A study reported positive effects after memory reconsolidation under propranolol administration (Brunet et al., 2018). The subjects showed decreased PTSD symptoms under propranolol influence, but other studies failed to produce memory trace destabilization that would allow complete or long-lasting remission (Wood et al., 2015; Roullet et al., 2021). Psychological interventions that aim to disrupt memories during reconsolidation by decreasing the intrusive symptoms have shown some positive effects (Astill Wright et al., 2021); for instance, traumatic memory reconsolidation, a cognitive-behavioral treatment focused on PTSD symptoms, expressed as immediate phobic-like responses triggered by stimuli over a series of treatment sessions where the memory is reactivated and destabilized with a narrative to modify that memory (for details on the treatment see Gray et al., 2019).

Phobias are considered anxiety disorders (American Psychiatric Association [APA], 2013) and are formed by aberrant emotional memories that have a profound and persistent impact on behavior. Different therapeutic approaches have explored the manipulation of memory destabilization-dependent processes (Vaverková et al., 2020). Several reconsolidation-based interventions in animal models of anxiety disorders have successfully used propranolol (Villain et al., 2016). A recent meta-analysis indicated that propranolol administration reduced cue-elicited emotional responses in healthy humans. In contrast, in clinical samples of aversive memories reactivated under propranolol, symptom severity was significantly reduced (Pigeon et al., 2022). This study contrasts with others reporting a lack of post-reactivation propranolol effect on fear of public speaking treatment (Elsey et al., 2020) and arachnophobia (Elsey and Kindt, 2021). Due to the heterogeneity of protocols and environmental conditions of memory reactivation, it has been complicated to reach a clear consensus on the efficacy of propranolol as a treatment tool for any anxiety disorder. A key question is whether the extensive evidence compiled on animal models can be translated as part of a successful treatment of maladaptive memories underlying some psychiatric disorders, given the significant number of confounding factors and limitations.

5. Conclusion

Memory editing and updating involve the dynamic and flexible information integration required to thrive under constant environmental alterations. This memory updating modifies the previously integrated information redirecting behavioral response for proper adaptive behavior. Memories are established by consolidation mechanisms that promote morphological and physiological neural changes that subserve memory persistence. Notably, after learning, information integration is accompanied by developing the prediction and expectation of the event and its consequences. Discrepancies between the expected and the experienced promote memory reactivation and destabilization during retrieval, encouraging the integration of new information that adjusts the previously integrated information. Memory updating is necessary for a novel to familiar transition, gradually shifting from displeasure to pleasure, or when a stimulus is no longer followed by a consequence like in extinction trials. Several neurotransmitter systems have been involved in the expression, destabilization, and updating of memories; however, the catecholaminergic system is mainly implicated in memory expression and destabilization, while the glutamatergic system allows the integration of the updated information. After memory destabilization, there is a temporal window where memories are vulnerable to interference. Thus, there is a particular interest in gaining more knowledge about the neurobiological mechanisms involved in destabilization and memory updating. Studying the neurobiological underpinning of memory updating will have potential implications for treating maladaptive memories such as addiction, phobias, and PTSD.

Author contributions

DO-G, MM, KG-R, and FB-R conceptualized, wrote, reviewed, and edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Abel, T., and Lattal, K. M. (2001). Molecular mechanisms of memory acquisition, consolidation and retrieval. *Curr. Opin. Neurobiol.* 11, 180–187. doi: 10.1016/S0959-4388(00)00194-X

Akirav, I., and Maroun, M. (2006). Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. *Cereb Cortex.* 16, 1759–1765. doi: 10.1093/cercor/bhj114

American Psychiatric Association [APA] (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*, 5th Edn. Arlington, VA: American Psychiatric Association.

Astill Wright, L., Horstmann, L., Holmes, E. A., and Bisson, J. I. (2021). Consolidation/reconsolidation therapies for the prevention and treatment of PTSD and re-experiencing: A systematic review and meta-analysis. *Transl. Psychiatry* 11:453. doi: 10.1038/s41398-021-01570-w

Atkinson, R. C., and Shiffrin, R. M. (1968). "Human memory: A proposed system and its control," in *Psychology of learning and motivation*, eds K. W. Spence and J. T. Spence (Cambridge, MA: Academic Press), 89–195. doi: 10.1016/S0079-7421(08)60422-3

Balderas, I., Rodriguez-Ortiz, C. J., and Bermudez-Rattoni, F. (2013). Retrieval and reconsolidation of object recognition memory are independent processes in the perirhinal cortex. *Neuroscience* 253, 398–405. doi: 10.1016/j.neuroscience.2013.09.001

Balderas, I., Rodriguez-Ortiz, C. J., and Bermudez-Rattoni, F. (2015). Consolidation and reconsolidation of object recognition memory. *Behav. Brain Res.* 285, 213–222. doi: 10.1016/j.bbr.2014.08.049

Balderas, I., Rodriguez-Ortiz, C. J., Salgado-Tonda, P., Chavez-Hurtado, J., McGaugh, J. L., and Bermudez-Rattoni, F. (2008). The consolidation of object and context recognition memory involve different regions of the temporal lobe. *Learn. Mem.* 15, 618–624. doi: 10.1101/lm.1028008

Baldo, B. A. (2016). Prefrontal cortical opioids and dysregulated motivation: A network hypothesis. *Trends Neurosci.* 39, 366–377. doi: 10.1016/j.tins.2016.03.004

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., et al. (2006). Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. *J. Neurosci.* 26, 12165–12173. doi: 10.1523/JNEUROSCI.3576-06.2006

Bassareo, V., De Luca, M. A., and Di Chiara, G. (2002). Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. *J. Neurosci.* 22, 4709–4719. doi: 10.1523/JNEUROSCI.22-11-04709.2002

Bastin, C., Delhaye, E., Moulin, C., and Barbeau, E. J. (2019). Novelty processing and memory impairment in Alzheimer's disease: A review. *Neurosci. Biobehav. Rev.* 100, 237–249. doi: 10.1016/j.neubiorev.2019.02.021

Benarroch, E. E. (2019). Insular cortex: Functional complexity and clinical correlations. *Neurology* 93, 932–938. doi: 10.1212/WNL.0000000000008525

Ben-Yakov, A., Dudai, Y., and Mayford, M. R. (2015). Memory retrieval in mice and men. *Cold Spring Harb. Perspect. Biol.* 7:a021790. doi: 10.1101/cshperspect.a021790

Bermúdez-Rattoni, F. (2004). Molecular mechanisms of taste-recognition memory. *Nat. Rev. Neurosci.* 5, 209–217. doi: 10.1038/nrn1344

Bermudez-Rattoni, F. (2014). The forgotten insular cortex: Its role on recognition memory formation. *Neurobiol. Learn. Mem.* 109, 207–216. doi: 10.1016/j.nlm.2014.01.001

Bernard, J. F., Alden, M., and Besson, J. M. (1993). The organization of the efferent projections from the pontine parabrachial area to the amygdaloid complex: A *Phaseolus vulgaris* leucoagglutinin (PHA-L) study in the rat. *J. Comp. Neurol.* 329, 201–229. doi: 10.1002/cne.903290205

Bernard, J. F., Huang, G. F., and Besson, J. M. (1992). Nucleus centralis of the amygdala and the globus pallidus ventralis: Electrophysiological evidence for an involvement in pain processes. *J. Neurophysiol.* 68, 551–569. doi: 10.1152/jn.1992.68.2.551

Bernardi, R. E., Lattal, K. M., and Berger, S. P. (2006). Postretrieval propranolol disrupts a cocaine conditioned place preference. *Neuroreport* 17, 1443–1447. doi: 10.1097/01.wnr.0000233098.20655.26

Bester, H., Matsumoto, N., Besson, J. M., and Bernard, J. F. (1997). Further evidence for the involvement of the spinoparabrachial pathway in nociceptive processes: A c-Fos study in the rat. *J. Comp. Neurol.* 383, 439–458.

Bisaz, R., Travaglia, A., and Alberini, C. M. (2014). The neurobiological bases of memory formation: From physiological conditions to psychopathology. *Psychopathology* 47, 347–356. doi: 10.1159/000363702

Bornhövd, K., Quante, M., Glauche, V., Bromm, B., Weiller, C., and Büchel, C. (2002). Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: A single-trial fMRI study. *Brain J. Neurol.* 125, 1326–1336. doi: 10.1093/brain/awf137

Botreau, F., Paolone, G., and Stewart, J. (2006). d-Cycloserine facilitates extinction of a cocaine-induced conditioned place preference. *Behav. Brain Res.* 172, 173–178. doi: 10.1016/j.bbr.2006.05.012

Breslin, P. A. S. (2013). An evolutionary perspective on food and human taste. *Curr. Biol.* 23, R409–R418. doi: 10.1016/j.cub.2013.04.010

Brown, M. W., and Aggleton, J. P. (2001). Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2, 51–61. doi: 10.1038/35049064

Brunet, A., Saumier, D., Liu, A., Streiner, D. L., Tremblay, J., and Pitman, R. K. (2018). Reduction of PTSD symptoms with pre-reactivation propranolol therapy: A randomized controlled trial. *Am. J. Psychiatry* 175, 427–433. doi: 10.1176/appi.ajp.2017.17050481

Cardinal, R. N., Parkinson, J. A., Hall, J., and Everitt, B. J. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci. Biobehav. Rev.* 26, 321–352. doi: 10.1016/s0149-7634(02)00007-6

Cheng, S.-J., Chen, C., Yang, H.-W., Chang, Y.-T., Bai, S.-W., Chen, C., et al. (2011). Role of extracellular signal-regulated kinase in synaptic transmission and plasticity of a nociceptive input on capsular central amygdaloid neurons in normal and acid-induced muscle pain mice. *J. Neurosci.* 31, 2258–2270. doi: 10.1523/JNEUROSCI.5564-10.2011

Choi, J.-H., Kim, J.-E., and Kaang, B.-K. (2010). Protein synthesis and degradation are required for the incorporation of modified information into the pre-existing object-location memory. *Mol. Brain* 3:1. doi: 10.1186/1756-6606-3-1

Contreras, M., Ceric, F., and Torrealba, F. (2007). Inactivation of the interoceptive insula disrupts drug craving and malaise induced by lithium. *Science* 318, 655–658. doi: 10.1126/science.1145590

Craig, A. D. B. (2009). How do you feel–now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10, 59–70. doi: 10.1038/nrn2555

De Luca, M. A. (2014). Habituation of the responsiveness of mesolimbic and mesocortical dopamine transmission to taste stimuli. *Front. Integr. Neurosci.* 8:21. doi: 10.3389/fnint.2014.00021

Diederen, K. M. J., and Fletcher, P. C. (2021). Dopamine, prediction error and beyond. *Neuroscientist* 27, 30–46. doi: 10.1177/1073858420907591

Domjan, M. (1976). Determinants of the enhancement of flavored-water intake by prior exposure. *J. Exp. Psychol. Anim. Behav. Process.* 2, 17–27. doi: 10.1037//0097-7403.2.1.17

Dudai, Y. (2004). The neurobiology of consolidations, or, how stable is the engram? *Annu. Rev. Psychol.* 55, 51–86. doi: 10.1146/annurev.psych.55.090902.142050

Dunn, L. T., and Everitt, B. J. (1987). The effects of lesions to noradrenergic projections from the locus coeruleus and lateral tegmental cell groups on conditioned taste aversion in the rat. *Behav. Neurosci.* 101, 409–422. doi: 10.1037//0735-7044.101.3.409

Eippert, F., Bingel, U., Schoell, E., Yacubian, J., and Büchel, C. (2008). Blockade of endogenous opioid neurotransmission enhances acquisition of conditioned fear in humans. *J. Neurosci.* 28, 5465–5472. doi: 10.1523/JNEUROSCI.5336-07.2008

Ellis, M. E., and Kesner, R. P. (1983). The noradrenergic system of the amygdala and aversive information processing. *Behav. Neurosci.* 97, 399–415. doi: 10.1037//0735-7044.97.3.399

Elsey, J. W. B., Filmer, A. I., Galvin, H. R., Kurath, J. D., Vossoughi, L., Thomander, L. S., et al. (2020). Reconsolidation-based treatment for fear of public speaking: A systematic pilot study using propranolol. *Transl. Psychiatry* 10:179. doi: 10.1038/s41398-020-0857-z

Ennaceur, A. (2010). One-trial object recognition in rats and mice: Methodological and theoretical issues. *Behav. Brain. Res.* 215, 244–254. doi: 10.1016/j.bbr.2009.12.036

Ennaceur, A., and Delacour, J. (1988). A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. *Behav. Brain Res.* 31, 47–59. doi: 10.1016/0166-4328(88)90157-x

Elsey, J. W. B., and Kindt, M. (2021). Placebo and non-specific effects in reconsolidation-based treatment for arachnophobia. *Front. Psychiatry* 12:775770. doi: 10.3389/fpsyt.2021.775770

Escobar, M. L., and Bermúdez-Rattoni, F. (2000). Long-term potentiation in the insular cortex enhances conditioned taste aversion retention. *Brain Res.* 852, 208–212. doi: 10.1016/s0006-8993(99)02134-4

Evans, L. H., and Wilding, E. L. (2012). Recollection and familiarity make independent contributions to memory judgments. *J. Neurosci.* 32, 7253–7257. doi: 10.1523/JNEUROSCI.6396-11.2012

Ferbinteanu, J. (2019). Memory systems 2018 - towards a new paradigm. *Neurobiol. Learn. Mem.* 157, 61–78. doi: 10.1016/j.nlm.2018.11.005

Franken, I. H., de Haan, H. A., van der Meer, C. W., Haffmans, P. M., and Hendriks, V. M. (1999). Cue reactivity and effects of cue exposure in abstinent posttreatment drug users. *J. Subst. Abuse Treat.* 16, 81–85. doi: 10.1016/s0740-5472(98)00004-x

Frankland, P. W., Josselyn, S. A., and Köhler, S. (2019). The neurobiological foundation of memory retrieval. *Nat. Neurosci.* 22, 1576–1585. doi: 10.1038/s41593-019-0493-1

Galvez, R., Mesches, M. H., and McGaugh, J. L. (1996). Norepinephrine release in the amygdala in response to footshock stimulation. *Neurobiol. Learn. Mem.* 66, 253–257. doi: 10.1006/nlme.1996.0067

Gálvez-Márquez, D. K., Salgado-Ménez, M., Moreno-Castilla, P., Rodriguez-Duran, L. F., Escobar, M. L., Tecuapetla, F., et al. (2022). Spatial contextual recognition memory updating is modulated by dopamine release in the dorsal hippocampus from the locus coeruleus. *Proc. Natl. Acad. Sci. U.S.A.* 119:e2208254119. doi: 10.1073/pnas.2208254119

Garcia, J., Kimeldorf, D. J., and Koelling, R. A. (1955). Conditioned aversion to saccharin resulting from exposure to gamma radiation. *Science* 122, 157–158. doi: 10.1126/science.122.3160.157

Garcia-Delatorre, P., Pérez-Sánchez, C., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2014). Role of glutamate receptors of central and basolateral amygdala nuclei on retrieval and reconsolidation of taste aversive memory. *Neurobiol. Learn. Mem.* 111, 35–40. doi: 10.1016/j.nlm.2014.03.003

García-DeLaTorre, P., Rodriguez-Ortiz, C. J., Arreguin-Martinez, J. L., Cruz-Castañeda, P., and Bermúdez-Rattoni, F. (2009). Simultaneous but not independent anisomycin infusions in insular cortex and amygdala hinder stabilization of taste memory when updated. *Learn. Mem.* 16, 514–519. doi: 10.1101/lm.1356509

Garcia-Delatorre, P., Rodríguez-Ortiz, C. J., Balderas, I., and Bermúdez-Rattoni, F. (2010). Differential participation of temporal structures in the consolidation and reconsolidation of taste aversion extinction. *Eur. J. Neurosci.* 32, 1018–1023. doi: 10.1111/j.1460-9568.2010.07365.x

Germeroth, L. J., Carpenter, M. J., Baker, N. L., Froeliger, B., LaRowe, S. D., and Saladin, M. E. (2017). Effect of a brief memory updating intervention on smoking behavior: A randomized clinical trial. *JAMA Psychiatry* 74, 214–223. doi: 10.1001/jamapsychiatry.2016.3148

Gil-Lievana, E., Balderas, I., Moreno-Castilla, P., Luis-Islas, J., McDevitt, R. A., Tecuapetla, F., et al. (2020). Glutamatergic basolateral amygdala to anterior insular cortex circuitry maintains rewarding contextual memory. *Commun. Biol.* 3:139. doi: 10.1038/s42003-020-0862-z

Gil-Lievana, E., Ramírez-Mejía, G., Urrego-Morales, O., Luis-Islas, J., Gutierrez, R., and Bermúdez-Rattoni, F. (2022). Photostimulation of ventral tegmental area-insular cortex dopaminergic inputs enhances the salience to consolidate aversive taste recognition memory via D1-like receptors. *Front. Cell. Neurosci.* 16:823220. doi: 10.3389/fncel.2022.823220

Goelet, P., Castellucci, V. F., Schacher, S., and Kandel, E. R. (1986). The long and the short of long–term memory—a molecular framework. *Nature* 322, 419–422. doi: 10.1038/322419a0

Gonzalez, M. C., Rossato, J. I., Radiske, A., Bevilaqua, L. R. M., and Cammarota, M. (2021). Dopamine controls whether new declarative information updates reactivated memories through reconsolidation. *Proc. Natl. Acad. Sci. U.S.A.* 118:e2025275118. doi: 10.1073/pnas.2025275118

Grau-Perales, A. B., Expósito, A. N., Gómez-Chacón, B., Morón, I., and Gallo, M. (2020). Accumbens and amygdala in taste recognition memory: The role of d1 dopamine receptors. *Neurobiol. Learn. Mem.* 174:107277. doi: 10.1016/j.nlm.2020.107277

Grau-Perales, A. B., Levy, E. R. J., Fenton, A. A., and Gallo, M. (2019). Dorsal hippocampal damage disrupts the auditory context-dependent attenuation of taste neophobia in mice. *Neurobiol. Learn. Mem.* 157, 121–127. doi: 10.1016/j.nlm.2018.12.009

Gray, R., Budden-Potts, D., and Bourke, F. (2019). Reconsolidation of traumatic memories for PTSD: A randomized controlled trial of 74 male veterans. *Psychother. Res.* 29, 621–639. doi: 10.1080/10503307.2017.1408973

Gu, X., Hof, P. R., Friston, K. J., and Fan, J. (2013). Anterior insular cortex and emotional awareness. *J. Comp. Neurol.* 521, 3371–3388. doi: 10.1002/cne.23368

Gutiérrez, R., Téllez, L. A., and Bermúdez-Rattoni, F. (2003). Blockade of cortical muscarinic but not NMDA receptors prevents a novel taste from becoming familiar. *Eur. J. Neurosci.* 17, 1556–1562. doi: 10.1046/j.1460-9568.2003.02608.x

Guzmán-Ramos, K., Osorio-Gómez, D., Moreno-Castilla, P., and Bermúdez-Rattoni, F. (2010). Off-line concomitant release of dopamine and glutamate involvement in taste memory consolidation. *J. Neurochem.* 114, 226–236. doi: 10.1111/j.1471-4159.2010.06758.x

Guzmán-Ramos, K., Osorio-Gómez, D., Moreno-Castilla, P., and Bermúdez-Rattoni, F. (2012). Post-acquisition release of glutamate and norepinephrine in the amygdala is involved in taste-aversion memory consolidation. *Learn. Mem.* 19, 231–238. doi: 10.1101/lm.024703.111

Haaker, J., Yi, J., Petrovic, P., and Olsson, A. (2017). Endogenous opioids regulate social threat learning in humans. *Nat. Commun.* 8:15495. doi: 10.1038/ncomms15495

Hammond, S., Seymour, C. M., Burger, A., and Wagner, J. J. (2013). D-Serine facilitates the effectiveness of extinction to reduce drug-primed reinstatement of cocaine-induced conditioned place preference. *Neuropharmacology* 64, 464–471. doi: 10.1016/j.neuropharm.2012.06.022

Han, S., Soleiman, M. T., Soden, M. E., Zweifel, L. S., and Palmiter, R. D. (2015). Elucidating an affective pain circuit that creates a threat memory. *Cell* 162, 363–374. doi: 10.1016/j.cell.2015.05.057

Hatfield, T., and McGaugh, J. L. (1999). Norepinephrine infused into the basolateral amygdala posttraining enhances retention in a spatial water maze task. *Neurobiol. Learn. Mem.* 71, 232–239. doi: 10.1006/nlme.1998.3875

Henson, R. N., and Gagnepain, P. (2010). Predictive, interactive multiple memory systems. *Hippocampus* 20, 1315–1326. doi: 10.1002/hipo.20857

Hofmann, S. G., Hüweler, R., MacKillop, J., and Kantak, K. M. (2012). Effects of D-cycloserine on craving to alcohol cues in problem drinkers: Preliminary findings. *Am. J. Drug Alcohol Abuse* 38, 101–107. doi: 10.3109/00952990.2011.600396

Huff, A. E., McGraw, S. D., and Winters, B. D. (2022). Muscarinic (M1) cholinergic receptor activation within the dorsal hippocampus promotes destabilization of strongly encoded object location memories. *Hippocampus* 32, 55–66. doi: 10.1002/hipo.23396

Kafkas, A., and Montaldi, D. (2014). Two separate, but interacting, neural systems for familiarity and novelty detection: A dual-route mechanism. *Hippocampus* 24, 516–527. doi: 10.1002/hipo.22241

Kafkas, A., and Montaldi, D. (2018). How do memory systems detect and respond to novelty? *Neurosci. Lett.* 680, 60–68. doi: 10.1016/j.neulet.2018.01.053

Kamboj, S. K., Joye, A., Das, R. K., Gibson, A. J. W., Morgan, C. J. A., and Curran, H. V. (2012). Cue exposure and response prevention with heavy smokers: A laboratory-based randomised placebo-controlled trial examining the effects of D-cycloserine on cue reactivity and attentional bias. *Psychopharmacology* 221, 273–284. doi: 10.1007/s00213-011-2571-2

Kandel, E. R. (2012). The molecular biology of memory: cAMP, PKA, CRE, CREB-1, CREB-2, and CPEB. *Mol. Brain* 5:14. doi: 10.1186/1756-6606-5-14

Kelly, A., Laroche, S., and Davis, S. (2003). Activation of mitogen-activated protein kinase/extracellular signal-regulated kinase in hippocampal circuitry is required for consolidation and reconsolidation of recognition memory. *J. Neurosci.* 23, 5354–5360. doi: 10.1523/JNEUROSCI.23-12-05354.2003

Kindt, M., Soeter, M., and Vervliet, B. (2009). Beyond extinction: Erasing human fear responses and preventing the return of fear. *Nat. Neurosci.* 12, 256–258. doi: 10.1038/nn.2271

Koob, G. F., and Schulkin, J. (2019). Addiction and stress: An allostatic view. *Neurosci. Biobehav. Rev.* 106, 245–262. doi: 10.1016/j.neubiorev.2018.09.008

Kring, A. M., and Barch, D. M. (2014). The motivation and pleasure dimension of negative symptoms: Neural substrates and behavioral outputs. *Eur. Neuropsychopharmacol.* 24, 725–736. doi: 10.1016/j.euroneuro.2013.06.007

Kwapis, J. L., Alaghband, Y., Keiser, A. A., Dong, T. N., Michael, C. M., Rhee, D., et al. (2020). Aging mice show impaired memory updating in the novel OUL updating paradigm. *Neuropsychopharmacology* 45, 337–346. doi: 10.1038/s41386-019-0438-0

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annu. Rev. Neurosci.* 23, 155–184. doi: 10.1146/annurev.neuro.23.1.155

Lee, J. L. C., Nader, K., and Schiller, D. (2017). An update on memory reconsolidation updating. *Trends Cogn. Sci.* 21, 531–545. doi: 10.1016/j.tics.2017.04.006

Liang, K. C., Juler, R. G., and McGaugh, J. L. (1986). Modulating effects of posttraining epinephrine on memory: Involvement of the amygdala noradrenergic system. *Brain Res.* 368, 125–133. doi: 10.1016/0006-8993(86)91049-8

Liang, K. C., McGaugh, J. L., and Yao, H. Y. (1990). Involvement of amygdala pathways in the influence of post-training intra-amygdala norepinephrine and peripheral epinephrine on memory storage. *Brain Res.* 508, 225–233. doi: 10.1016/0006-8993(90)90400-6

Lin, X., Deng, J., Yuan, K., Wang, Q., Liu, L., Bao, Y., et al. (2021). Neural substrates of propranolol-induced impairments in the reconsolidation of nicotine-associated memories in smokers. *Transl. Psychiatry* 11:441. doi: 10.1038/s41398-021-01566-6

Lisman, J., Grace, A. A., and Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci.* 34, 536–547. doi: 10.1016/j.tins.2011.07.006

Lisman, J. E., and Grace, A. A. (2005). The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron* 46, 703–713. doi: 10.1016/j.neuron.2005.05.002

Liu, J.-F., Tian, J., and Li, J.-X. (2019). Modulating reconsolidation and extinction to regulate drug reward memory. *Eur. J. Neurosci.* 50, 2503–2512. doi: 10.1111/ejn.14072

Lonergan, M., Saumier, D., Tremblay, J., Kieffer, B., Brown, T. G., and Brunet, A. (2016). Reactivating addiction-related memories under propranolol to reduce craving: A pilot randomized controlled trial. *J. Behav. Ther. Exp. Psychiatry* 50, 245–249. doi: 10.1016/j.jbtep.2015.09.012

Lonergan, M. H., Olivera-Figueroa, L. A., Pitman, R. K., and Brunet, A. (2013). Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: A meta-analysis. *J. Psychiatry Neurosci.* 38, 222–231. doi: 10.1503/jpn.120111

Lu, C., Yang, T., Zhao, H., Zhang, M., Meng, F., Fu, H., et al. (2016). Insular cortex is critical for the perception, modulation, and chronification of pain. *Neurosci. Bull.* 32, 191–201. doi: 10.1007/s12264-016-0016-y

Mahler, S. V., and Berridge, K. C. (2012). What and when to "want"? Amygdala-based focusing of incentive salience upon sugar and sex. *Psychopharmacology* 221, 407–426. doi: 10.1007/s00213-011-2588-6

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychol. Rev.* 87, 252–271. doi: 10.1037/0033-295X.87.3.252

Manrique, T., Moroìn, I., Ballesteros, M. A., Guerrero, R. M., Fenton, A. A., and Gallo, M. (2009). Hippocampus, aging, and segregating memories. *Hippocampus* 19, 57–65. doi: 10.1002/hipo.20481

Marissen, M. A. E., Franken, I. H. A., Blanken, P., van den Brink, W., and Hendriks, V. M. (2007). Cue exposure therapy for the treatment of opiate addiction: Results of a randomized controlled clinical trial. *Psychother. Psychosom.* 76, 97–105. doi: 10.1159/000097968

McCall, J. G., Siuda, E. R., Bhatti, D. L., Lawson, L. A., McElligott, Z. A., Stuber, G. D., et al. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *eLife* 6:e18247. doi: 10.7554/eLife.18247

McGaugh, J. L. (2000). Memory–a century of consolidation. *Science* 287, 248–251. doi: 10.1126/science.287.5451.248

McGaugh, J. L. (2013). Making lasting memories: Remembering the significant. *Proc. Natl. Acad. Sci. U.S.A.* 110(Suppl. 2), 10402–10407. doi: 10.1073/pnas.1301209110

Merkow, M. B., Burke, J. F., and Kahana, M. J. (2015). The human hippocampus contributes to both the recollection and familiarity components of recognition memory. *Proc. Natl. Acad. Sci. U.S.A.* 112, 14378–14383. doi: 10.1073/pnas.1513145112

Merlo, E., Milton, A. L., Goozée, Z. Y., Theobald, D. E., and Everitt, B. J. (2014). Reconsolidation and extinction are dissociable and mutually exclusive processes: Behavioral and molecular evidence. *J. Neurosci.* 34, 2422–2431. doi: 10.1523/JNEUROSCI.4001-13.2014

Milekic, M. H., Brown, S. D., Castellini, C., and Alberini, C. M. (2006). Persistent disruption of an established morphine conditioned place preference. *J. Neurosci.* 26, 3010–3020. doi: 10.1523/JNEUROSCI.4818-05.2006

Miranda, M. I., Ramírez-Lugo, L., and Bermúdez-Rattoni, F. (2000). Cortical cholinergic activity is related to the novelty of the stimulus. *Brain Res.* 882, 230–235. doi: 10.1016/s0926-6410(00)00050-1

Moreno-Castilla, P., Guzman-Ramos, K., and Bermudez-Rattoni, F. (2018). "Chapter 28: object recognition and object location recognition memory Ű the role of dopamine and noradrenaline," in *Handbook of behavioral neuroscience*, eds A. Ennaceur and M. A. de Souza Silva (Amsterdam: Elsevier), 403–413. doi: 10.1016/B978-0-12-812012-5.00028-8

Moreno-Castilla, P., Rodriguez-Duran, L. F., Guzman-Ramos, K., Barcenas-Femat, A., Escobar, M. L., and Bermudez-Rattoni, F. (2016). Dopaminergic neurotransmission dysfunction induced by amyloid-β transforms cortical long-term potentiation into long-term depression and produces memory impairment. *Neurobiol. Aging* 41, 187–199. doi: 10.1016/j.neurobiolaging.2016.02.021

Morici, J. F., Bekinschtein, P., and Weisstaub, N. V. (2015). Medial prefrontal cortex role in recognition memory in rodents. *Behav. Brain Res.* 292, 241–251. doi: 10.1016/j.bbr.2015.06.030

Morillas, E., Gómez-Chacón, B., and Gallo, M. (2017). Flavor and object recognition memory impairment induced by excitotoxic lesions of the perirhinal cortex. *Neurobiol. Learn. Mem.* 144, 230–234. doi: 10.1016/j.nlm.2017.08.002

Moron, I., Ballesteros, M. A., Candido, A., and Gallo, M. (2002). Taste aversion learning and aging: A comparison with the effect of dorsal hippocampal lesions in rats. *Physiol. Res.* 51(Suppl. 1), S21–S27.

Morris, R. G. M., Inglis, J., Ainge, J. A., Olverman, H. J., Tulloch, J., Dudai, Y., et al. (2006). Memory reconsolidation: Sensitivity of spatial memory to inhibition of protein synthesis in dorsal hippocampus during encoding and retrieval. *Neuron* 50, 479–489. doi: 10.1016/j.neuron.2006.04.012

Moschak, T. M., Wang, X., and Carelli, R. M. (2018). A neuronal ensemble in the rostral agranular insula tracks cocaine-induced devaluation of natural reward and predicts cocaine seeking. *J. Neurosci.* 38, 8463–8472. doi: 10.1523/JNEUROSCI.1195-18.2018

Myers, K. M., and Carlezon, W. A. (2012). D-cycloserine effects on extinction of conditioned responses to drug-related cues. *Biol. Psychiatry* 71, 947–955. doi: 10.1016/j.biopsych.2012.02.030

Nadel, L., and Hardt, O. (2011). Update on memory systems and processes. *Neuropsychopharmacology* 36, 251–273. doi: 10.1038/npp.2010.169

Nader, K., Schafe, G. E., and Le Doux, J. E. (2000). Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature* 406, 722–726. doi: 10.1038/35021052

Naqvi, N. H., and Bechara, A. (2009). The hidden island of addiction: The insula. *Trends Neurosci.* 32, 56–67. doi: 10.1016/j.tins.2008.09.009

Nguyen, V. T., Breakspear, M., Hu, X., and Guo, C. C. (2016). The integration of the internal and external milieu in the insula during dynamic emotional experiences. *Neuroimage* 124, 455–463. doi: 10.1016/j.neuroimage.2015.08.078

Norris, D. (2017). Short-term memory and long-term memory are still different. *Psychol. Bull.* 143, 992–1009. doi: 10.1037/bul0000108

Osorio-Gómez, D., Bermúdez-Rattoni, F., and Guzmán-Ramos, K. (2019). Artificial taste avoidance memory induced by coactivation of NMDA and β-adrenergic receptors in the amygdala. *Behav. Brain Res.* 376:112193. doi: 10.1016/j.bbr.2019.112193

Osorio-Gómez, D., Bermúdez-Rattoni, F., and Guzmán-Ramos, K. R. (2021). Cortical neurochemical signaling of gustatory stimuli and their visceral consequences during the acquisition and consolidation of taste aversion memory. *Neurobiol. Learn. Mem.* 181:107437. doi: 10.1016/j.nlm.2021.107437

Osorio-Gómez, D., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2016). Differential involvement of glutamatergic and catecholaminergic activity within the amygdala during taste aversion retrieval on memory expression and updating. *Behav. Brain Res.* 307, 120–125. doi: 10.1016/j.bbr.2016.03.038

Osorio-Gómez, D., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2017). Memory trace reactivation and behavioral response during retrieval are differentially modulated by amygdalar glutamate receptors activity: Interaction between amygdala and insular cortex. *Learn. Mem.* 24, 14–23. doi: 10.1101/lm.042895.116

Osorio-Gómez, D., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2018). "6 - Neurobiology of neophobia and its attenuation," in *Food neophobia, woodhead publishing series in food science, technology and nutrition*, ed. S. Reilly (Sawston: Woodhead Publishing), 111–128. doi: 10.1016/B978-0-08-101931-3.00006-9

Osorio-Gómez, D., Guzmán-Ramos, K., and Bermúdez-Rattoni, F. (2022). Dopamine activity on the perceptual salience for recognition memory. *Front. Behav. Neurosci.* 16:963739. doi: 10.3389/fnbeh.2022.963739

Otto, M. W., Pachas, G. N., Cather, C., Hoeppner, S. S., Moshier, S. J., Hearon, B. A., et al. (2019). A placebo-controlled randomized trial of D-cycloserine augmentation of cue exposure therapy for smoking cessation. *Cogn. Behav. Ther.* 48, 65–76. doi: 10.1080/16506073.2018.1476908

Ozawa, T., and Johansen, J. P. (2018). Learning rules for aversive associative memory formation. *Curr. Opin. Neurobiol.* 49, 148–157. doi: 10.1016/j.conb.2018.02.010

Parker, A., Wilding, E., and Akerman, C. (1998). The von restorff effect in visual object recognition memory in humans and monkeys. The role of frontal/perirhinal interaction. *J. Cogn. Neurosci.* 10, 691–703. doi: 10.1162/089892998563103

Paulus, M. P., and Stein, M. B. (2006). An insular view of anxiety. *Biol. Psychiatry* 60, 383–387. doi: 10.1016/j.biopsych.2006.03.042

Peciña, S., and Smith, K. S. (2010). Hedonic and motivational roles of opioids in food reward: Implications for overeating disorders. *Pharmacol. Biochem. Behav.* 97, 34–46. doi: 10.1016/j.pbb.2010.05.016

Pigeon, S., Lonergan, M., Rotondo, O., Pitman, R. K., and Brunet, A. (2022). Impairing memory reconsolidation with propranolol in healthy and clinical samples: A meta-analysis. *J. Psychiatry Neurosci.* 47, E109–E122. doi: 10.1503/jpn.210057

Pina, M. M., Pati, D., Hwa, L. S., Wu, S. Y., Mahoney, A. A., Omenyi, C. G., et al. (2020). The kappa opioid receptor modulates GABA neuron excitability and synaptic transmission in midbrainprojections from the insular cortex. *Neuropharmacology* 165:107831. doi: 10.1016/j.neuropharm.2019.107831

Popik, B., Amorim, F. E., Amaral, O. B., and De Oliveira Alvares, L. (2020). Shifting from fear to safety through deconditioning-update. *eLife* 9:e51207. doi: 10.7554/eLife.51207

Price, K. L., Baker, N. L., McRae-Clark, A. L., Saladin, M. E., Desantis, S. M., Santa Ana, E. J., et al. (2013). A randomized, placebo-controlled laboratory study of the effects of D-cycloserine on craving in cocaine-dependent individuals. *Psychopharmacology* 226, 739–746. doi: 10.1007/s00213-011-2592-x

Quirarte, G. L., Galvez, R., Roozendaal, B., and McGaugh, J. L. (1998). Norepinephrine release in the amygdala in response to footshock and opioid peptidergic drugs. *Brain Res.* 808, 134–140. doi: 10.1016/S0006-8993(98)00795-1

Ranganath, C., and Rainer, G. (2003). Neural mechanisms for detecting and remembering novel events. *Nat. Rev. Neurosci.* 4, 193–202. doi: 10.1038/nrn1052

Ritchie, H., and Roser, M. (2019). *Drug use*. Oxford: Our World in Data.

Rizvi, S. J., Pizzagalli, D. A., Sproule, B. A., and Kennedy, S. H. (2016). Assessing anhedonia in depression: Potentials and pitfalls. *Neurosci. Biobehav. Rev.* 65, 21–35. doi: 10.1016/j.neubiorev.2016.03.004

Robertson, S. D., Plummer, N. W., de Marchena, J., and Jensen, P. (2013). Developmental origins of central norepinephrine neuron diversity. *Nat. Neurosci.* 16, 1016–1023. doi: 10.1038/nn.3458

Robinson, M. J. F., and Franklin, K. B. J. (2010). Reconsolidation of a morphine place preference: Impact of the strength and age of memory on disruption by propranolol and midazolam. *Behav. Brain Res.* 213, 201–207. doi: 10.1016/j.bbr.2010.04.056

Rodríguez-García, G., and Miranda, M. I. (2016). Opposing roles of cholinergic and GABAergic activity in the insular cortex and nucleus basalis magnocellularis during novel recognition and familiar taste memory retrieval. *J. Neurosci.* 36, 1879–1889. doi: 10.1523/JNEUROSCI.2340-15.2016

Rodriguez-Ortiz, C. J., Balderas, I., Garcia-DeLaTorre, P., and Bermudez-Rattoni, F. (2012). Taste aversion memory reconsolidation is independent of its retrieval. *Neurobiol. Learn. Mem.* 98, 215–219. doi: 10.1016/j.nlm.2012.08.002

Rodriguez-Ortiz, C. J., Balderas, I., Saucedo-Alquicira, F., Cruz-Castañeda, P., and Bermudez-Rattoni, F. (2011). Long-term aversive taste memory requires insular and amygdala protein degradation. *Neurobiol. Learn. Mem.* 95, 311–315. doi: 10.1016/j.nlm.2010.12.010

Rodriguez-Ortiz, C. J., and Bermúdez-Rattoni, F. (2017). Determinants to trigger memory reconsolidation: The role of retrieval and updating information. *Neurobiol. Learn. Mem.* 142, 4–12. doi: 10.1016/j.nlm.2016.12.005

Rodriguez-Ortiz, C. J., De la Cruz, V., Gutiérrez, R., and Bermudez-Rattoni, F. (2005). Protein synthesis underlies post-retrieval memory consolidation to a restricted degree only when updated information is obtained. *Learn. Mem.* 12, 533–537. doi: 10.1101/lm.94505

Rodriguez-Ortiz, C. J., Garcia-DeLaTorre, P., Benavidez, E., Ballesteros, M. A., and Bermudez-Rattoni, F. (2008). Intrahippocampal anisomycin infusions disrupt previously consolidated spatial memory only when memory is updated. *Neurobiol. Learn. Mem.* 89, 352–359. doi: 10.1016/j.nlm.2007.10.004

Roozendaal, B. (2002). Stress and memory: Opposing effects of glucocorticoids on memory consolidation and memory retrieval. *Neurobiol. Learn. Mem.* 78, 578–595. doi: 10.1006/nlme.2002.4080

Roozendaal, B., and McGaugh, J. L. (1996). Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiol. Learn. Mem.* 65, 1–8. doi: 10.1006/nlme.1996.0001

Roser, M., Ritchie, H., and Spooner, F. (2021). *Burden of disease*. Oxford: Our World in Data.

Rossato, J. I., Bevilaqua, L. R. M., Myskiw, J. C., Medina, J. H., Izquierdo, I., and Cammarota, M. (2007). On the role of hippocampal protein synthesis in the consolidation and reconsolidation of object recognition memory. *Learn. Mem.* 14, 36–46. doi: 10.1101/lm.422607

Rossato, J. I., Köhler, C. A., Radiske, A., Lima, R. H., Bevilaqua, L. R. M., and Cammarota, M. (2015). State-dependent effect of dopamine D1/D5 receptors inactivation on memory destabilization and reconsolidation. *Behav. Brain Res.* 285, 194–199. doi: 10.1016/j.bbr.2014.09.009

Rossi, M. A., and Stuber, G. D. (2018). Overlapping brain circuits for homeostatic and hedonic feeding. *Cell Metab.* 27, 42–56. doi: 10.1016/j.cmet.2017.09.021

Roullet, P., Vaiva, G., Véry, E., Bourcier, A., Yrondi, A., Dupuch, L., et al. (2021). Traumatic memory reactivation with or without propranolol for PTSD and comorbid MD symptoms: A randomised clinical trial. *Neuropsychopharmacology* 46, 1643–1649. doi: 10.1038/s41386-021-00984-w

Royet, J. P., Gervais, R., and Araneda, S. (1983). Effect of local 6-OHDA and 5,6-DHT injections into the rat olfactory bulb on neophobia and learned aversion to a novel food. *Behav. Brain Res.* 10, 297–309. doi: 10.1016/0166-4328(83)90036-0

Saladin, M. E., Gray, K. M., McRae-Clark, A. L., Larowe, S. D., Yeatts, S. D., Baker, N. L., et al. (2013). A double blind, placebo-controlled study of the effects of post-retrieval propranolol on reconsolidation of memory for craving and cue reactivity in cocaine dependent humans. *Psychopharmacology* 226, 721–737. doi: 10.1007/s00213-013-3039-3

Santa Ana, E. J., Prisciandaro, J. J., Saladin, M. E., McRae-Clark, A. L., Shaftman, S. R., Nietert, P. J., et al. (2015). D-cycloserine combined with cue exposure therapy fails to attenuate subjective and physiological craving in cocaine dependence. *Am. J. Addict.* 24, 217–224. doi: 10.1111/ajad.12191

Santa Ana, E. J., Rounsaville, B. J., Frankforter, T. L., Nich, C., Babuscio, T., Poling, J., et al. (2009). D-Cycloserine attenuates reactivity to smoking cues in nicotine dependent smokers: A pilot investigation. *Drug Alcohol Depend.* 104, 220–227. doi: 10.1016/j.drugalcdep.2009.04.023

Santoyo-Zedillo, M., Rodriguez-Ortiz, C. J., Chavez-Marchetta, G., Bermudez-Rattoni, F., and Balderas, I. (2014). Retrieval is not necessary to trigger reconsolidation of object recognition memory in the perirhinal cortex. *Learn. Mem.* 21, 452–456. doi: 10.1101/lm.035428.114

Saper, C. B. (1982). Convergence of autonomic and limbic connections in the insular cortex of the rat. *J. Comp. Neurol.* 210, 163–173. doi: 10.1002/cne.902100207

Sara, S. J. (2000). Retrieval and reconsolidation: Toward a neurobiology of remembering. *Learn. Mem.* 7, 73–84. doi: 10.1101/lm.7.2.73

Sato, M., Ito, M., Nagase, M., Sugimura, Y. K., Takahashi, Y., Watabe, A. M., et al. (2015). The lateral parabrachial nucleus is actively involved in the acquisition of fear memory in mice. *Mol. Brain* 8:22. doi: 10.1186/s13041-015-0108-z

Schramm, M. J. W., Everitt, B. J., and Milton, A. L. (2016). Bidirectional modulation of alcohol-associated memory reconsolidation through manipulation of adrenergic signaling. *Neuropsychopharmacology* 41, 1103–1111. doi: 10.1038/npp.2015.248

Schultz, W. (2015). Neuronal reward and decision signals: From theories to data. *Physiol. Rev.* 95, 853–951. doi: 10.1152/physrev.00023.2014

Schultz, W. (2016). Dopamine reward prediction error coding. *Dialogues Clin. Neurosci.* 18, 23–32.

Shield, K., Manthey, J., Rylett, M., Probst, C., Wettlaufer, A., Parry, C. D. H., et al. (2020). National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: A comparative risk assessment study. *Lancet Public Health* 5, e51–e61. doi: 10.1016/S2468-2667(19)30231-2

Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. *Neurobiol. Learn. Mem.* 82, 171–177. doi: 10.1016/j.nlm.2004.06.005

Squire, L. R. (2009). Memory and brain systems: 1969–2009. *J. Neurosci.* 29, 12711–12716. doi: 10.1523/JNEUROSCI.3575-09.2009

Squire, L. R., and Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. *Proc. Natl. Acad. Sci. U.S.A.* 93, 13515–13522. doi: 10.1073/pnas.93.24.13515

Starr, C. J., Sawaki, L., Wittenberg, G. F., Burdette, J. H., Oshiro, Y., Quevedo, A. S., et al. (2009). Roles of the insular cortex in the modulation of pain: Insights from brain lesions. *J. Neurosci.* 29, 2684–2694. doi: 10.1523/JNEUROSCI.5173-08.2009

Steketee, J. D., Silverman, P. B., and Swann, A. C. (1989). Forebrain norepinephrine involvement in selective attention and neophobia. *Physiol. Behav.* 46, 577–583. doi: 10.1016/0031-9384(89)90335-1

Tian, S., Pan, S., and You, Y. (2015). Nicotine enhances the reconsolidation of novel object recognition memory in rats. *Pharmacol. Biochem. Behav.* 129, 14–18. doi: 10.1016/j.pbb.2014.11.019

Torregrossa, M. M., and Taylor, J. R. (2013). Learning to forget: Manipulating extinction and reconsolidation processes to treat addiction. *Psychopharmacology* 226, 659–672. doi: 10.1007/s00213-012-2750-9

Tulving, E. (2002). Episodic memory: From mind to brain. *Annu. Rev. Psychol.* 53, 1–25. doi: 10.1146/annurev.psych.53.100901.135114

Uematsu, A., Tan, B. Z., Ycu, E. A., Cuevas, J. S., Koivumaa, J., Junyent, F., et al. (2017). Modular organization of the brainstem noradrenaline system coordinates opposing learning states. *Nat. Neurosci.* 20, 1602–1611. doi: 10.1038/nn.4642

Vaverková, Z., Milton, A. L., and Merlo, E. (2020). Retrieval-dependent mechanisms affecting emotional memory persistence: Reconsolidation, extinction, and the space in between. *Front. Behav. Neurosci.* 14:574358. doi: 10.3389/fnbeh.2020.574358

Villain, H., Benkahoul, A., Drougard, A., Lafragette, M., Muzotte, E., Pech, S., et al. (2016). Effects of propranolol, a β-noradrenergic antagonist, on memory consolidation and reconsolidation in mice. *Front. Behav. Neurosci.* 10:49. doi: 10.3389/fnbeh.2016.00049

Wang, L., Gillis-Smith, S., Peng, Y., Zhang, J., Chen, X., Salzman, C. D., et al. (2018). The coding of valence and identity in the mammalian taste system. *Nature* 558, 127–131. doi: 10.1038/s41586-018-0165-4

Wassum, K. M., Ostlund, S. B., Maidment, N. T., and Balleine, B. W. (2009). Distinct opioid circuits determine the palatability and the desirability of rewarding events. *Proc. Natl. Acad. Sci. U.S.A.* 106, 12512–12517. doi: 10.1073/pnas.0905874106

Watabe, A. M., Ochiai, T., Nagase, M., Takahashi, Y., Sato, M., and Kato, F. (2013). Synaptic potentiation in the nociceptive amygdala following fear learning in mice. *Mol. Brain* 6:11. doi: 10.1186/1756-6606-6-11

Winters, B. D., Tucci, M. C., and DaCosta-Furtado, M. (2009). Older and stronger object memories are selectively destabilized by reactivation in the presence of new information. *Learn. Mem.* 16, 545–553. doi: 10.1101/lm.1509909

Winters, B. D., Tucci, M. C., Jacklin, D. L., Reid, J. M., and Newsome, J. (2011). On the dynamic nature of the engram: Evidence for circuit-level reorganization of object memory traces following reactivation. *J. Neurosci.* 31, 17719–17728. doi: 10.1523/JNEUROSCI.2968-11.2011

Wood, N. E., Rosasco, M. L., Suris, A. M., Spring, J. D., Marin, M.-F., Lasko, N. B., et al. (2015). Pharmacological blockade of memory reconsolidation in posttraumatic stress disorder: Three negative psychophysiological studies. *Psychiatry Res.* 225, 31–39. doi: 10.1016/j.psychres.2014.09.005

Wouda, J. A., Diergaarde, L., Riga, D., van Mourik, Y., Schoffelmeer, A. N. M., and De Vries, T. J. (2010). Disruption of long-term alcohol-related memory reconsolidation: Role of β-adrenoceptors and NMDA receptors. *Front. Behav. Neurosci.* 4:179. doi: 10.3389/fnbeh.2010.00179

Wright, D. S., Bodinayake, K. K., and Kwapis, J. L. (2020). Investigating memory updating in mice using the objects in updated locations task. *Curr. Protoc. Neurosci.* 91:e87. doi: 10.1002/cpns.87

Xue, Y.-X., Deng, J.-H., Chen, Y.-Y., Zhang, L.-B., Wu, P., Huang, G.-D., et al. (2017). Effect of selective inhibition of reactivated nicotine-associated memories with propranolol on nicotine craving. *JAMA Psychiatry* 74, 224–232. doi: 10.1001/jamapsychiatry.2016.3907

Yonelinas, A. P. (2002). The nature of recollection and familiarity: A review of 30 years of research. *J. Mem. Lang.* 46, 441–517. doi: 10.1006/jmla.2002.2864

Yonelinas, A. P., Aly, M., Wang, W.-C., and Koen, J. D. (2010). Recollection and familiarity: Examining controversial assumptions and new directions. *Hippocampus* 20, 1178–1194. doi: 10.1002/hipo.20864

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Assessment and management of pain/nociception in patients with disorders of consciousness or locked-in syndrome: A narrative review

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The assessment and management of pain and nociception is very challenging in patients unable to communicate functionally such as patients with disorders of consciousness (DoC) or in locked-in syndrome (LIS). In a clinical setting, the detection of signs of pain and nociception by the medical staff is therefore essential for the wellbeing and management of these patients. However, there is still a lot unknown and a lack of clear guidelines regarding the assessment, management and treatment of pain and nociception in these populations. The purpose of this narrative review is to examine the current knowledge regarding this issue by covering different topics such as: the neurophysiology of pain and nociception (in healthy subjects and patients), the source and impact of nociception and pain in DoC and LIS and, finally, the assessment and treatment of pain and nociception in these populations. In this review we will also give possible research directions that could help to improve the management of this specific population of severely brain damaged patients.

KEYWORDS

pain, nociception, disorders of consciousness, locked-in syndrome, pain assessment, pain management, theories of pain

1. Introduction

Pain refers to an "*unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" (Raja et al., 2020). Integrating several dimensions (physiological, sensory, cognitive, and emotional aspects), pain is based on subjective experience and therefore, on conscious processing of the stimulus. Like any subjective experience, communication with the patient is the most appropriate way to assess it. In severely brain injured subjects, such as patients with disorders of consciousness (DoC) and locked-in syndrome (LIS), verbal communication is impaired but does not

exclude the possibility that they experience pain. Even more, the absence of behavioral signs of consciousness does not preclude the patient to show (at least a minimum of) cortical activity preservation, suggesting partial preservation of consciousness and pain processing. Therefore, it is important not to neglect the assessment of pain and nociception in these patients with limited or no ability to communicate, regardless of the diagnosis. In the last years, clinicians tended to identify behavioral patterns related to conscious perception of pain, with important ethical and clinical implications in terms of diagnosis, prognosis, and treatment. Nonetheless, the absence of clinical signs of pain does not preclude a conscious (i.e., cortically mediated) pain experience nor a physiological impact of the nociceptive stimuli. Indeed, nociception refers to "*neuronal process allowing the encoding and processing of a noxious stimulus*" (Loeser and Treede, 2008) and while it does not require conscious perception of the stimulus, it leads to changes in the autonomic control of target organs (e.g., changes in heart rate, sweating, bronchial resistance to air flow, and pupil diameter) and behavioral responses (e.g., flexion withdrawal).

Disorders of consciousness could be due to various traumatic (TBI) or non-traumatic (NTBI) brain injuries (e.g., strokes or anoxia). In the United States, 2.5 million people suffer from a TBI each year (288,000 hospitalizations and 56,800 deaths) and some of them will become unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS) patients (Capizzi et al., 2020). In the United States, the prevalence of patients with DoC (adults and children) is estimated between 4,000 and 25,000 for patients in UWS and between 112,000 to 280,000 for patients in MCS (The Multi-Society Task Force on PVS, 1994; Pisa et al., 2014). In Europe, the cases of UWS patients are estimated between 4,362 and 58,160 in a population of 727,000,000 (Ashwal, 2004). The current literature does not allow to give the prevalence of LIS patients on a global or national level. Due to the absence of or impaired communication in these patients, pain assessment and management is a major clinical and ethical issue. DoC include different clinical entities based on cognitive level and motor abilities (see **Figure 1**). For instance, a patient who shows signs of arousal characterized by eye opening periods but no signs of awareness (i.e., only reflexive movement and absence of cortical processes), will be categorized as in UWS (The Multi-Society Task Force on PVS, 1994; Laureys et al., 2010). Patients in a MCS show reproducible, responses without functional communication and have partial cortical processes. They are classified into two main groups based on language preservation: patients in MCS minus (MCS−) showing non-reflexive behaviors (Bruno et al., 2011b; Giacino et al., 2018), and MCS plus (MCS+) who have a preservation of higher level non-reflexive behavior and language abilities (Thibaut et al., 2020). The progress of neuroimaging techniques has also allowed the emergence of new terminologies to classify patients with "atypical" brain activity patterns such as: minimally conscious state star (MCS*, i.e., patients behaviorally diagnosed with UWS but preserving residual brain activity congruent with MCS diagnosis at rest or during a passive or active paradigm; Thibaut et al., 2021), covert cortical processing (CCP or higher-order cortex motor dissociation – HMD, i.e., patient behaviorally diagnosed in a coma, UWS, or MCS− but retaining brain activity upon passive task; Edlow et al., 2017), cognitive motor dissociation (CMD, i.e., patient behaviorally diagnosed in a coma, UWS, or MCS− but retaining brain activity upon active tasks; Schiff, 2015). Finally, when a patient regains functional communication or functional use of objects, he or she is considered to be emerging from MCS (Di Perri et al., 2016). LIS is not considered as a DoC but could be misdiagnosed with coma and UWS (Cistaro et al., 2018). This condition results from a lesion in the corticospinal and corticobulbar pathways of the brainstem due to vascular pathology, traumatic brain injury, masses in the ventral pons, infection, or demyelination (Das et al., 2021). LIS patients suffer from limbs, head, and face paralysis (i.e., quadriparesis) as well as verbalization/vocalization, breathing, and coordination impairments. LIS patients can communicate using eyelid blinks, vertical eye movements, or head movements (i.e., yes/no communication code or letter spelling communication; Lugo et al., 2015). EEG-based brain–computer interfaces also allow LIS patients to communicate through brain signals (Annen et al., 2020). So far, there has been limited scientific research on pain processing in LIS. However, according to a European survey of health professionals, 90% of them considered that patients in LIS are able to feel pain and need to be treated (Demertzi et al., 2014). For patients with DoC, according to a survey, 96% of health professionals believed that MCS patients can feel pain, compared to 56% believing that UWS patients can do so (Demertzi et al., 2009). Nevertheless, as explained above, some behaviorally unresponsive patients can still have a cortical activity preservation suggesting covert consciousness (and potentially a preservation of pain processing). It is therefore important to set up pain assessment tools and treatments that are independent of the clinical diagnosis to avoid mismanagement.

This manuscript aims at reviewing the current knowledge about the assessment and management of pain and nociception in patients with DoC and LIS. We will first give an overview of the physiology of pain and nociception. We will then look more specifically at the possible sources and impact of pain in these populations. Finally, we will describe the tools and treatments currently in place for the assessment and management of pain and nociception for this patient population. This narrative review is based on systematic reviews, meta-analyses, original articles, and case studies.

2. Neurophysiology of pain and nociception

In order to understand the difference between pain and nociception and to comprehend to what extent severely brain-damaged patients process nociceptive inputs and pain, we must first look at the neurophysiology of these two phenomena. When nociceptive stimulation occurs, following tissue damage for example, a signal will be generated at the endings of the nociceptive Aδ (i.e., thinly myelinated fibers responsible for faster signal transmission, mediate nociceptive inputs but also non-nociceptive heat and cold stimuli) and C-fibers (i.e., non-myelinated, polymodal nociceptors that are sensitive to chemical, mechanical, and thermal stimuli, including nociceptive hot – >48°C – and noxious cold – <11°C). These fibers synapse at the level of the dorsal horn with the second nociceptive neuron that continues its path into the spinothalamic tract to the thalamus (for the majority of the fibers). After the thalamus, the signal

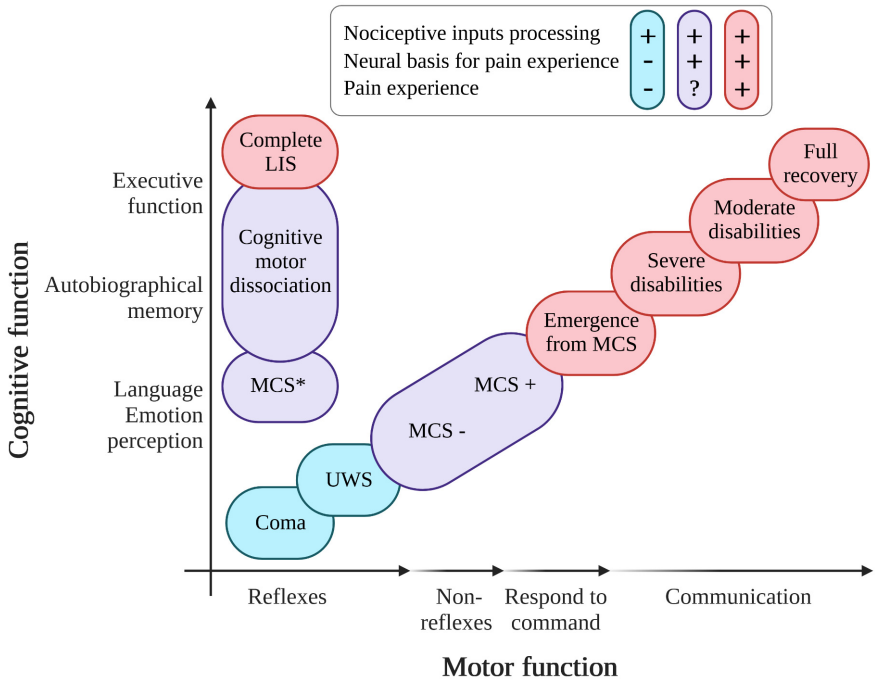

FIGURE 1
Variation in diagnosis of patients with pathological states of consciousness according to the level of recovery of cognitive and motor functions. UWS, unresponsive wakefulness syndrome; MCS, minimally conscious state; LIS, locked-in syndrome; in red, patients able to process nociceptive inputs and able to experience pain; in blue, patients processing nociceptive inputs but without evidence of pain experience; in purple, patients able to process nociceptive inputs and having the (probable) neural basis for pain experience (created with BioRender.com, based on Thibaut et al. (2019) and recent empirical literature).

arrives at several cortical areas [i.e., the primary and secondary somatosensory cortex and the insula and the anterior cingulate cortex (ACC)]. All these cortical and subcortical structures and their connections form a network which is activated following a painful stimulus. In this review, we will use the term "pain-related neuromatrix" to refer to these brain regions activated following a noxious stimulus. However, it is important to note that this network is not only related to pain processing but has been identified more as a salience detection network (Melzack and Wall, 1965; Ingvar, 1999; Brown et al., 2018). This supports the multidimensional aspect of pain sensation, already highlighted by Melzack and Wall (1965), and subsequently confirmed by neuroimaging studies: pain is not the result of the activation of a single specific region but of a network (Mouraux et al., 2011; Mouraux and Iannetti, 2018). The pain-related neuromatrix can be divided in two parts comprising: (1) the lateral system, involved in the sensory dimension of nociceptive stimulus processing (i.e., localization, duration, and intensity) which includes the lateral thalamic nucleus, the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), and the insula and the posterior parietal cortex; and (2) the medial system, related to the affective dimension of pain and comprising the medial thalamic nucleus, the prefrontal cortex, the ACC, the posterior cingulate cortex (PCC), and the posterior medial cortex (Bushnell et al., 1999; Hofbauer et al., 2001). These regions (i.e., prefrontal cortex, thalamus, and ACC) are also part of the external and internal networks of consciousness which underlines the importance of these brain areas in the conscious perception of pain. The insula also has an important role in the affective processing of pain because it mediates the signal between the posterior insula (lateral system) and the rostral part of the ACC (medial system) (Coghill et al., 1999; Peyron et al., 2002). According to neuroimaging studies in healthy subjects during acute pain stimulation, the cortical and subcortical regions most involved in pain signal processing are S2, the insula and the ACC [for a review refer to Peyron et al. (2000)]. The use of hypnosis [i.e., a state of consciousness involving attentional focus and reduced peripheral attention, characterized by an increased ability to respond to suggestion (Elkins et al., 2015)] with analgesic suggestions leads to a decrease of brain activity in the ACC, and makes it possible to modulate the affective dimension of pain [for a review refer to Thompson (2019)]. The use of hypnosis has also been shown to be effective in relieving chronic pain. Indeed, in a 1997 study, a positive correlation between the perception of painful sensation and cerebral activity of the ACC was demonstrated (Rainville, 1997). Conversely, when the ACC and the insula are activated just before a nociceptive stimulation, an increase in pain perception is observed (Boly et al., 2007). Altogether, the literature shows that the ACC has an important role in modulating pain perception, notably by interacting with regions of the limbic system like the amygdala, the thalamus, and the hippocampus (Moriarty, 2011; Calabrò et al., 2017). These subcortical and limbic structures participate in the balance of activity between the fronto-temporo-parietal cortex (involved in consciousness; Demertzi et al., 2013; Di Perri et al., 2013, 2016) and the autonomic nervous system.

The ascending pathways described above activate descending pathways responsible for modulating the transmission of peripheral

information. Indeed, the descending pathways (cholinergic and serotonergic) to the dorsal horn of the spinal cord are sensitive to peripheral stimuli and not only to nociceptive stimuli. There are also tonic facilitation and inhibition phenomena that originate in the brainstem and respond to peripheral or non-peripheral stimuli (Dunckley, 2005). The activation of these descending pathways starts in the cortex (i.e., in the insula and ACC) and extends through the hypothalamus and the amygdala to finally be transmitted to the brainstem in the PAG, the nucleus of the tractus solitarius and the rostral ventral medulla (Brown et al., 2018). This will result in an inhibition of neurons from the superficial dorsal horn relaying information carried by C-fiber to the deep dorsal horn (**Figure 2**). The suppression of the C-fibers signal will then facilitate the transmission of sensory-discriminative information conducted by the A-fibers (Heinricher et al., 2009). The hypothalamus, the amygdala and the PAG are also responsible for behavioral changes related to acute pain stimulation (Veinante et al., 2013). An fMRI study of awake subjects undergoing acute thermal pain stimulation has shown a decrease of brain activity in the hypothalamus and amygdala as well as an increase brain activity in the lateral PAG (Robertson et al., 2022). The lateral PAG is involved in the selection of appropriate defensive behaviors in response to the nociceptive stimulus [i.e., increase in motor, autonomic, and endocrine activity, as well as alertness, and inhibitory control of this pain (Bandler et al., 2000)] and is regulated by a number of regions including the hypothalamus and the amygdala. A lesion in these different ascending and descending pathways therefore may lead to a dysfunction in the processing of nociceptive stimuli and pain control (i.e., which can result in the phenomenon of central sensitization).

The conscious perception of pain is supported by the activation of the regions evoked above and the functional connectivity between these different regions and the thalamus (Baars et al., 2003; Dehaene and Changeux, 2011). However, even if some of these regions are essential for pain sensation and sensibility, others will play a subtler role and their lesion may not always lead to any noticeable change in terms of pain perception. As explained above, the pain-related neuromatrix, although well established in the scientific literature, is still subject to debate, not least because the regions of this pain-related neuromatrix are more broadly involved in multimodal processing and not specific to pain processes (Mouraux et al., 2011; Mouraux and Iannetti, 2018). A recent opinion paper discussed the idea that pain perception may originate from the brainstem and not only from the cortex. The authors based this assumption in part on the fact that cortical stimulation of specific regions of the pain-related neuromatrix does not induce pain, unlike other sensory modalities (e.g., primary auditory or visual cortex stimulation evokes respectively sound and light). Few studies have nevertheless shown that the electrical stimulation of regions such as the parietal operculum, the posterior insula, and the ventral caudal nucleus of the thalamus could induce pain sensation (Lenz et al., 1993; Mazzola et al., 2006; Bergeron et al., 2021). However, a lesion of the insula does not make the sensation of pain disappear (Libet, 1973; Mazzola et al., 2006; Afif et al., 2008; Isnard et al., 2011). On the contrary, some patients who have suffered a cortical lesion (i.e., central post-stroke patients) experience an increased sensation of pain (Boivie et al., 1989; Andersen et al., 1995). As pain is necessary for survival, these authors suggest that its conscious perception must have been in place before the expansion of the cerebral cortex and therefore be located in the brainstem. Many brainstem nuclei are involved in nociceptive signal processing [for a review refer to Napadow et al. (2019)]. fMRI in humans show that, upon acute cutaneous or visceral stimulation, the PAG, nucleus cuneiformis, ventral tegmental area, substantia nigra, parabrachial complex, and dorsolateral pons regions of the brainstem become activated (Dunckley, 2005; Fairhurst et al., 2007; Sprenger et al., 2011). The spinal trigeminal nucleus located at the level of the medulla and caudal pons is activated during painful stimulation in the orofacial region (Nash et al., 2009). The brainstem also seems to be involved in the phenomenon of conditioned pain modulation. For instance, inhibition of orofacial pain *via* painful stimulation of another area (such as the leg) results in a reduction of the fMRI signal in the dorsal reticular nucleus, dorsolateral pons, and spinal trigeminal nucleus (Youssef et al., 2016). PAG and rostral ventral medulla also appear to be necessary for the temporal summation of pain in connection with the phenomenon of nociceptive wind-up [i.e., facilitation of neural discharges caused by repetitive stimulation of primary afferent C-fibers, involved in central sensitization (Mendell, 2022) in humans and animals with chronic pain (Van Oosterwijck et al., 2013; O'Brien et al., 2018)]. The study of the functionality of these different brainstem nuclei is challenging, especially in neuroimaging studies due to the location of these elongated and small cross-sectional nuclei, their proximity to cardiorespiratory noise sources. The role of these nuclei in pain processing has yet to be studied in LIS and DoC, however, these severely brain-injured patients may present cerebral deformations that make the analysis of robust neuroimaging data difficult.

3. Source and impact of pain and nociception in DoC and LIS

Due to their physical condition and the clinical environment in which they find themselves, patients with DoC and LIS may experience various types of nociceptive insults. For instance, acute nociceptive events can occur after injuries (e.g., fracture, wounds, and soft tissue/solid organ injuries) or during daily care (e.g., catheterization, surgery, or physiotherapy). If pain is present after those injuries, it will act as a protective and adaptive signal for the integrity of the body (Craig, 2003) whereas chronic pain loses the role of warning signal (Varrassi et al., 2010). Chronic pain is persistent and/or recurrent pain lasting for more than 3 months and can result in functional and emotional changes such as depression or anxiety (Grichnick and Ferrante, 1991; Merskey and Bogduk, 1994; Turk et al., 2011). It can be due to muscle contractions, pressure sores, peripheral nerve injury, pain network disruption leading to allodynia, central sensitization, neuropathic pain, or spastic paresis [for a review see Zasler et al. (2022)]. Central sensitization results from a dysfunction of the descending central control system and corresponds to an "*increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input*" (Loeser and Treede, 2008). Neuropathic pain is defined by the International Association for the Study of Pain as a type of "*pain caused by a lesion or disease of the somatosensory nervous system*" as opposed to nociceptive pain occurring following nociceptor stimulation. Neuropathic pain

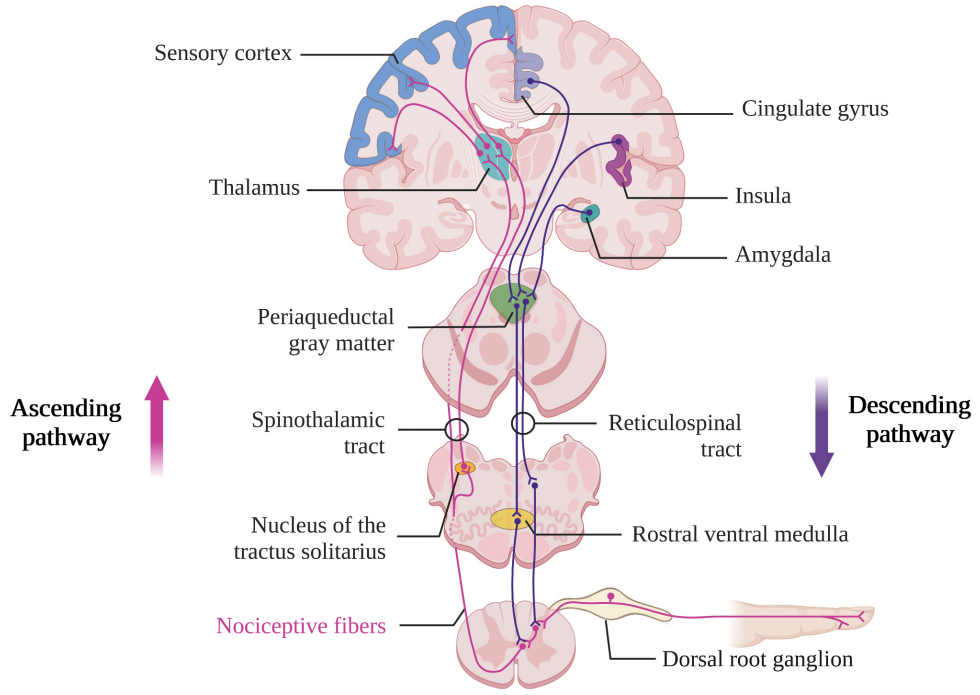

FIGURE 2
Ascending and descending nociceptive pathways (created with BioRender.com). Based on Brown et al. (2018).

can be of central or peripherical origin depending on the lesion localization (Raja et al., 2020). At present, neuropathic pain may be identified by diagnostic testing [e.g., using questionnaires such as the DN4 (Bouhassira et al., 2005)], sensory testing coupled with self-report or neuroimaging (to locate the lesion). However, the use of questionnaires requires functional communication to express subjective experience and therefore cannot be used in patients with DoC. The difficulty of assessing this type of pain in DoC patients has so far not been addressed by any study. Regarding spastic paresis, a recent study showed that the majority (83%) of patients with DoC experience pain during physiotherapy sessions (Bonin et al., 2022b). This result can be explained in part by the high prevalence of spastic paresis in this population, ranging from 59 to 96% (Martens et al., 2017; Thibaut et al., 2021; Zhang et al., 2021; Bonin et al., 2022a,b). In addition to limiting patients' motor responses, leading to misdiagnosis (Monti et al., 2010; Cruse et al., 2011), spastic paresis also appears to be related to the presence of nociception phenomena. Indeed, when looking at the scores of behavioral scales which respectively assess nociception and spastic paresis, it seems that both variables are positively correlated especially in wrist and finger muscles (Bonin et al., 2022a). This can greatly affect the patient's ability to respond to commands and perform other motor-related tasks on which most of the Coma Recovery Scale-Revised [CRS-R, gold standard to assess the level of consciousness in DoC patients (Giacino et al., 2004)] items are based. Due to the fact that LIS patients are bedridden for long periods of time and therefore have limited mobility, they will develop pain mainly in the lower and upper limbs instead of the head, the back, and the abdomen (Bonin et al., 2022a). They will also be prone to develop spastic paresis, which can lead to persistent discomfort in the long run (Cairns and Stein, 2002; Pistoia et al., 2015). A 2022 survey investigated the presence and management of pain in this specific LIS population. The results highlighted that half of the LIS patients surveyed have pain but do not communicate about it and 92% of these patients suffer from chronic pain (Bonin et al., 2022c). Nociception may also have an influence on the autonomic nervous system, provoking an imbalance between sympathetic and parasympathetic activity (Lee et al., 2020). This can have hemodynamic consequences (e.g., increase in blood pressure, tachycardia, and increased heart rate variability), or influence other target organs of the autonomic nervous system (pupils and their diameter, sweat glands, and skin conductance) [for a review see Lee et al. (2020)]. Although no studies exist on this topic in patients with DoC or LIS, it can be assumed that repetitive and/or long-term autonomic nervous system imbalance due to acute or chronic nociception or pain could have consequences for the patient's wellbeing, and could lead to systemic complications (Leo et al., 2016). For instance, it has been shown that, in moderate to severe traumatic brain injured (TBI) patients, autonomic nervous system dysfunction is correlated with an increase in morbidity (Purkayastha et al., 2019).

The perception of pain can vary according to different factors. Numerous studies carried out over the last few decades have revealed gender differences in terms of prevalence, perception and treatment of pain [for a review see Pieretti et al. (2016)]. Although women seem to report signs of pain more often than men, experimental studies on healthy subjects show mix results depending on the type of stimulation (i.e., mechanical, electrical, thermal, ischemic, and chemical) and the type of investigated parameter [e.g., duration and intensity of the pain sensation or pain tolerance or sensitivity (Labus et al., 2008; Racine et al., 2012)]. However, to our knowledge, no study has investigated

gender differences in terms of pain perception in DoC and LIS patients. In LIS patients, the position (lying/sitting) can increase or decrease the pain sensation, depending on each individual (Bonin et al., 2022c). Pain has a direct influence on patients' quality of life such as sleep quality, cognitive abilities, and emotion (Bonin et al., 2022c). Previous studies showed that the majority of patients with chronic pain have sleep disorders and that poor sleep quality can increase pain perception (O'Brien et al., 2011; Rousseau et al., 2015; Frohnhofen, 2018; Bonin et al., 2022c). In addition, the impact of pain on sleep quality can alter the level of arousal, as well as motivation in patients with DoC or in LIS. In this way, their ability to express signs of consciousness may be impeded, hence compromising the clinical diagnosis (Lanzillo et al., 2016; Estraneo et al., 2022). Consequently, the implementation of treatment to alleviate pain could have a positive impact on sleep quality and allow an improvement in the patients' level of arousal/vigilance during clinical examinations. Deleterious effects of pain on cognitive abilities (i.e., increase of tiredness and mood swings, and decrease of memory and concentration) and emotional regulation has been observed in patients with LIS (Bonin et al., 2022c). Other surveys found that some patients in LIS claim experiencing anxiety, depression or suicidal thoughts (Bergés et al., 2007; Rousseau et al., 2015). Furthermore, a past study has found an anti-correlated relationship between perceived pain and life satisfaction (Skevington, 1998; León-Carrión et al., 2002). Several variables can be related to the decrease of life satisfaction in patients with LIS such as the loss of mobility during recreational activities or language impairment/speech production (as communication seems to play a key role in the preservation of the quality of life in those patients) (Bruno et al., 2011a; Demertzi et al., 2014). These results underline the importance of identifying the sources of potential pain by using appropriate tools, to propose patient-tailored management.

4. Pain and nociception assessment and management in DoC and LIS

4.1. Assessments

4.1.1. Behavioral scales

There are many behavioral scales allowing the assessment of pain in non-communicative patients, such as the Neonatal Infant Pain Scales (NIPS; Lawrence et al., 1993), the Faces, Legs, Activity, Cry, Consolability pain scale (FLACC; Merkel et al., 1997) or the Children and Infants Post-operative Pain Scale (CHIPPS; Buttner and Finke, 2000) that assess pain in newborn, infants or adolescent. Other scales include the Pain Assessment In Dementia Scale for patient with dementia (PAINAD; Warden et al., 2003) and the Checklist of Non-verbal Pain Indicator to assess pain in cognitively impaired older adults (CNPI; Feldt, 2000). None of these scales are specific to severely brain-injured patients with DoC and LIS. The Nociception Coma Scale (NCS) has been developed to fill this gap (Schnakers et al., 2010) and consists in four subscales assessing motor, verbal and visual responses, as well as facial expression. It allows to disentangle reflex (e.g., groaning or oral reflex movements) from higher-level behaviors (e.g., pain localization and cry or intelligible verbalization). The visual subscale is the only subscale of the NCS that does not show significant changes between a noxious and a non-noxious condition. As its absence does not alter the sensitivity of the assessment, it was eventually removed to give the Nociception Coma Scale-Revised [NCS-R; Chatelle et al. (2012) total score ranging from 0 to 9]. The NCS-R is sensitive to the level of consciousness, with patients in MCS having higher NCS scores than patients in UWS, and allows the distinction between noxious and non-noxious stimulation (Chatelle et al., 2012, 2014b, 2018). A neuroimaging study in DoC using labeled Fluoro-Deoxy-Glucose (FDG)-PET found a positive correlation between brain activity in the ACC and NCS-R scores, suggesting that these scores are related to a cortical processing of pain (Chatelle et al., 2014a). This scale might also give an indication on the probability of recovering consciousness. Indeed, in a recent study, 76% of the patients in UWS who evolved to MCS showed significant behavioral changes at the NCS-R and NCS 1 week before the new diagnosis. Threshold for prediction has been determined for the NCS-R and the NCS and showed high predictive accuracies (Cortese et al., 2021). However, the NCS provides a better classification of patients likely to evolved to MCS than the NCS-R due to the presence of the visual scale (i.e., visual pursuit and fixation are among the first signs of consciousness observed in patient recovering from a UWS). In clinical practice, mechanical stimulation (i.e., pressure on the nail) is used to perform the assessment by the NCS-R. One study highlighted that the pain threshold following mechanical stimulation (i.e., pressure on the nailbed with an algometer) was lower in patients with DoC than in healthy subjects (Sattin et al., 2017). However, this stimulation technique has very high inter-rater variability. If not performed using an algometer, it allows limited control of the stimulus intensity. Another study conducted in 2019 showed that the use of personalized stimuli, determined on a case-by-case basis by the clinical team during patient mobilizations, resulted in higher scores on the NCS-R compared to standardized stimuli (Formisano et al., 2020). This could allow a case-by-case assessment depending on the patient, particularly in prolonged DoC patients suffering from pain during mobilization at the moment of care (Bonin et al., 2020, 2022b). The NCS-R is a relevant behavioral tool for pain assessment in non-communicative brain-damaged patients [for a review on psychometric values refer to Vink et al. (2017)], as NCS-R scores appear to be related to cortical processing of pain and nociception.

A 2012 study tried to determine an NCS-R cut-off score allowing discrimination between noxious and non-noxious stimulation, but the result was not confirmed in a later study (Chatelle et al., 2012, 2018). Chatelle et al.'s (2018) study determined an NCS-R cut-off score of 2 as being related to nociception (i.e., obtainable by reflex behaviors such as flexion withdrawal or oral reflex movement). Nevertheless, the presence of these reflex behaviors does not necessarily imply a conscious perception of pain. Finally, a recent study based on neuroimaging data (i.e., FDG-PET), determined a conservative NCS-R cut-off score of 5 as being specific to a cortical processing of pain and allowing the detection of covert consciousness (e.g., MCS*). The study highlights brain metabolism differences between "FDG-PET confirmed UWS" patients (i.e., patient diagnosed as UWS with the CRS-R and with a global hypometabolism), patients with potential pain (i.e., UWS and MCS patients with NCS-R score $\geq$5) and healthy subjects at both global and regional levels (i.e., left insula – involved in the processing of the sensory and affective dimension

of pain) (Bonin et al., 2020). Although this cut-off score is very conservative, it has a low sensitivity, which means that patients with a score of less than 5 should not be overlooked as they may still suffer and need appropriate treatment.

Studies involving nurses working with DoC patients confirm the ease of use and clinical relevance of this scale in assessing signs of pain in this population (Vink et al., 2014; Poulsen et al., 2019). Nonetheless, respondents considered that the use of a cut-off score underestimates the number of patients in pain and suggested that the use of physiological measures to complement the behavioral assessment should be favored (Poulsen et al., 2019). In cases of severe spastic paresis or intubation/anarthria, the facial expression subscale of the NCS-R is the only subscale on which the clinician can rely (Garuti et al., 2014; Thibaut et al., 2015). However, some facial expressions assessed by the NCS-R such as groaning or grimacing are not only associated with nociception but can be signs of agitation (Corrigan, 1989; Bogner et al., 2015). A study investigating the clinical relevance of the NCS-R in tracheostomized DoC patients showed that both the total score and the verbal subscore of the scale were decreased in DoC patients with tracheostomy compared to DoC patients without tracheostomy (Lejeune et al., 2020). However, the presence of a tracheostomy had no impact on the sensitivity and specificity of the cut-off score of 2. The authors recommend that the NCS-R should still be used in these patients but that the presence of a tracheostomy should be specified and taken into account in the assessment. Together, these studies confirm the experimental and clinical utility of the NCS-R in the assessment of pain in patients with DoC (Chatelle et al., 2016). As a corollary, these studies emphasize the need for clear guidelines regarding its use.

For appropriate daily management of pain, it appears that the NCS-R is not sufficient alone. The clinical assessment of pain should be based on a multi-modal approach that also considers (neuro)physiological markers wherever possible. Behavioral scales also involving physiological markers have recently been created, such as the Pain Assessment Scale (PAS), devoted to the assessment of patients with acquired brain injuries (Poulsen et al., 2016). It consists of 27 items, divided into four sections, and assessing physiological/autonomic responses, body language, verbal communication, and behavior during potentially painful manipulations. Preliminary results from this study show that half of the assessed items (7 of which were physiological markers) obtained very good inter-rater agreement, suggesting that some of them could be included in a new pain scale. Then, based on these results, the Brain Injury Nociception Assessment Measure (BINAM) was developed to measure nociception intensity in patients with severe brain injury who are unable to communicate (Whyte et al., 2020; for a comparison of the different scales refer to **Supplementary Table 1**). It consists of 10 items assessing both behavioral (e.g., facial expression and presence of tears) and physiological (e.g., respiration rate and skin temperature) parameters related to the processing of a nociceptive stimulus. The scores are independent of the diagnosis or state of agitation of the patients and appear to be sensitive to pain-inducing conditions (e.g., physiotherapy) as well as analgesic treatments (Whyte et al., 2020). However, studies are still needed to validate its clinical utility. The NCS-R is in fact the only behavioral scale recommended by the guidelines of the American Academy of Neurology (Giacino et al., 2018).

Regarding patients in LIS, in most cases, communication through eye movements or the use of Brain Computer Interface (BCI) technology is possible. Therefore, pain is assessed using communication codes (e.g., yes/no communication code *via* blinking, or alphabetic code) or/and visual analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = most severe pain). In spite of these systems, some patients in LIS do not communicate about their pain. In a 2022 survey, 52% of the painful patients declare that they do not inform the clinical teams about their pain (Bonin et al., 2022c) and only 28% of them use a communication code to communicate their pain. Other means of communication such as crying or wincing were also used by the patients but might be confounded with reflexive behavior. These results demonstrate how important it is for the clinical team to assess the signs of acute and chronic pain on a daily basis, through the use of communication codes or BCI techniques (Annen et al., 2020).

4.1.2. Neuroimaging

Patients with DoC suffer from fronto-parietal network activity and functional connectivity dysfunction, which could lead to a disturbance in pain and nociception processing. However, neuroimaging studies carried out in this population have shown that some brain regions are preserved (see **Figure 3**; Laureys et al., 2002; Boly et al., 2008). Indeed, when nociceptive electrical stimulation (i.e., stimulation intensity judged as highly unpleasant to painful in healthy subject) is administered to MCS patients, the cortical activation pattern is close to that observed in healthy subjects and LIS patients, especially in the secondary somatosensory cortex, the ACC and the insula (Boly et al., 2008). Functional connectivity within the pain-related neuromatrix is also preserved in these patients (Kupers et al., 2005). Although if the activation of the pain-related neuromatrix is more lateralized and with a smaller spatial range, these results suggest that patients in MCS are able to consciously process pain. In contrast, in UWS patients, nociceptive electrical stimulation results in an isolated activation of the primary somatosensory cortex with an absence of functional connectivity with other regions involved in pain (Laureys et al., 2002). However, in 2003, a Positron Emission Tomography-$H_2{}^{15}O$ activation study, tracking regional cerebral blood flow response to an external stimulus or task was performed in seven patients in UWS. After a nociceptive electrical stimulation, an increase in cerebral blood flow in the primary and secondary somatosensory cortices and in the ipsilateral posterior insula was observed (Kassubek et al., 2003). Another study using fMRI showed that during nociceptive electrical stimulation, 50% of patients in UWS have activation of the sensory network and 30% an activation of the affective network (Markl et al., 2013). These results suggest that residues of the pain processing network remain active in some patients considered as "unconscious" from a behavioral point of view. In these cases, the re-assessment of the diagnosis should be considered in patients who do not fit the criteria of a "real" UWS but rather those of MCS*.

4.1.3. Neurophysiology

Event-related potentials (ERPs) evaluates the integrity of the central and peripheral sensory pathways within the nervous system (Koenig and Kaplan, 2015). For instance, somatosensory evoked potentials (SEPs), brainstem auditory evoked potentials (BAEPs),

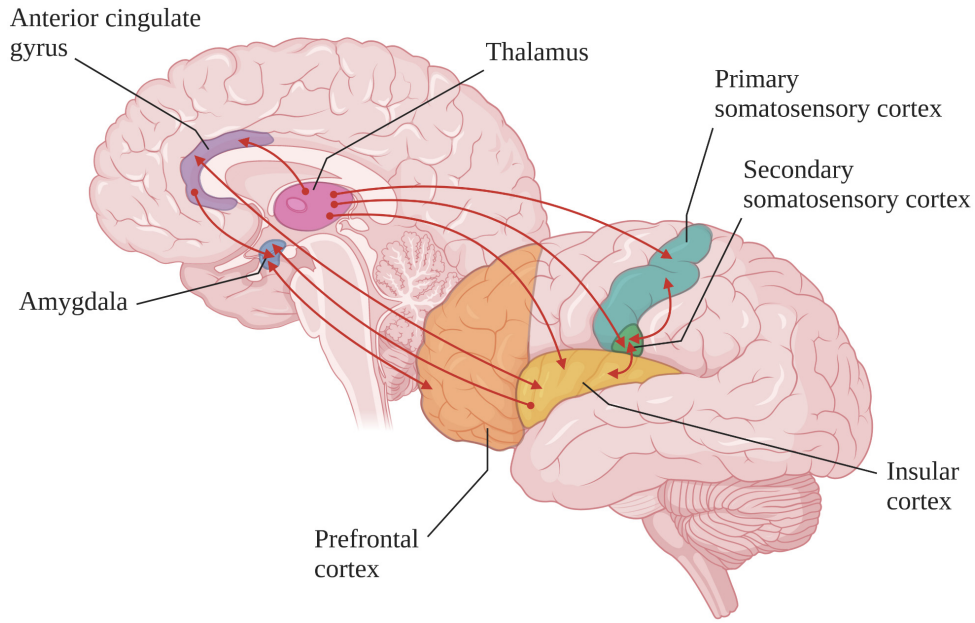

FIGURE 3
Cortical and subcortical regions involved in the pain-related neuromatrix (created with BioRender.com). In healthy subjects and MCS or LIS patients the functional connections (red lines) are preserved whereas in "true" UWS patients the somatosensory cortex is activated in isolation [based on Bouhassira et al. (2005) and Bagnato et al. (2021)].

and visual evoked potentials (VEPs) are used as prognostics tools in acute comatose patients, with the absence of ERPs at the cortical level being associated to a poor outcome (André-Obadia et al., 2018; Rollnik, 2019; Bagnato et al., 2021). It is possible to detect SEP at the cortical level in comatose patients following a noxious stimulation. Some studies have highlighted that the presence of SEPs following median nerve electrical stimulation may appear to be predictive of a good neurological outcome in comatose patients, characterized by a score of 1 (i.e., conscious with normal functions) or 2 (i.e., conscious with moderate disability) at the Glasgow-Pittsburgh Cerebral Performance Categories (Zanatta et al., 2012, 2015; Markl et al., 2013). However, SEPs support the assessment of the functioning of the somatosensory system which, unlike the other ERPs mentioned above, includes several modalities. Indeed, SEPs assesses both Aδ (i.e., encoding thermal nociceptive and non-nociceptive inputs) and Aβ fiber pathways (i.e., encoding sensitivity to pressure or vibration), and therefore reflect the processing of the stimulus by the both spinothalamic and lemniscal pathway. In contrast, laser evoked potentials (LEPs) are specifically used to study nociceptive signal processing by looking at the integrity of the spinothalamic pathway. They are intimately linked to the stimulation of Aδ and C nociceptive fibers (i.e., encoding sensitivity to non-noxious hot and cold, as well as pain) (Treede et al., 2003). Stimulation of Aδ and C fibers can be done separately depending on the method used. One study showed that, in some UWS patients, it was possible to observe LEPs at the cortical level during C-fiber stimulation even in the absence of LEPs related to Aδ-fiber stimulation (Naro et al., 2015). On the other hand, the reverse does not seem to be achievable, which underlines the importance of including the C-fiber stimulation in the assessment of LEPs in UWS patients. However, the results of this study must be interpreted with caution as selective C-fiber stimulation in DoC patients is very difficult to achieve without a strictly temperature-controlled laser or without the patient's cooperation in reporting his or her sensations. The LEPs recording consists of an early component N1, a late vertex components N2–P2 and an endogenous component P3 (only evoked during attentional tasks; Treede et al., 2003). Several studies have highlighted the presence of the N1 and N2-P2 complex at the cortical level in some patients with UWS (de Tommaso et al., 2013, 2015). However, cortical reactivity to nociceptive stimuli (characterized by prolonged N2 and P2 latencies) was decreased in these patients compared to healthy subjects, suggesting impaired functional connectivity. A case study also found a significant relationship between N2-P2 amplitude and the CRS-R scores in DoC patients. In this study, N1 and N2-P2 complexes were observed in MCS patients and only in one UWS patient but with a high CRS-R and NCS-R score (De Salvo et al., 2015). Coupled with SEPs, LEPs also detects potential lesions of the spinothalamic pathways in the dorsal brainstem. A lesion in this region impairs LEPs response while keeping SEPs intact (Treede et al., 2003). In the study of de Tommaso et al. (2015), the authors also studied the responses to auditory, visual and electrical (non-noxious) stimulation and found negative-positive complexes similar to the responses obtained after noxious laser stimulation. This confirms that a noxious stimulus will activate the same brain regions as another type of sensory stimulus (de Tommaso et al., 2015). Moreover, the presence of LEPs seems to be associated with cortical arousal in response to salient nociceptive stimuli (i.e., potentially dangerous stimulus) rather than with conscious pain processing.

4.1.4. Physiological markers

Another way to study nociception that is widely implemented in the clinic is the measurement of physiological markers.

Numerous brain areas forming the pain-related neuromatrix are also involved in modulating autonomic nervous system activity by integrating nociceptive and visceral information in the dorsal horn, insular cortex, amygdala, nucleus of the tractus solitarius, PAG, ACC, thalamus, hypothalamus, and *via* the neurons of Lamina 1 in the dorsal horn (Benarroch, 2001, 2006; Leone et al., 2006; Hohenschurz-Schmidt et al., 2020). This highly specialized organization of nociceptive information in these brain areas may play a major role in the development of an autonomic, affective, and emotional responses to pain (Benarroch, 2001, 2006; Leone et al., 2006; Cortelli et al., 2013; Hohenschurz-Schmidt et al., 2020). Processing of the nociceptive signal leads to homeostatic changes like heart rate variability (HRV), skin conductance or pupillary dilatation reflex (PDR). These physiological markers can therefore be a good index of the autonomic nervous system reactivity following nociceptive stimulation. Nociceptive pathways also have bidirectional interaction with the neuro-endocrine immune system, leading to a humoral response with potential consequences on recovery such as chronic pain (i.e., neuropathic or inflammatory pain) or stress response to surgery. Indeed, in addition to being sensitive to chemical, thermal, and mechanical stimuli, nociceptors are also able to detect immune mediators (e.g., cytokines, lipids, and grow factors) as well as certain pathogens (Basbaum et al., 2009; Chiu et al., 2012, 2016). Following the activation of nociceptors by these different agents, the signal is transmitted to the central nervous system to induce pain [e.g., microglia and T cells are involved in central sensitization (Ji et al., 2014)]. In response to this stimulation, the nociceptors will release neuropeptides that regulate the immune response [for a review refer to Baral et al. (2019)]. The study of interactions between pain and immune pathways is still poorly developed in DoC and LIS patients. A better understanding of these mechanisms in these specific patient populations could lead to new treatments for chronic neuropathic or inflammatory pain.

The most studied physiological marker to evaluate pain in DoC is HRV, which corresponds to changes in the time interval between successive heartbeats. It can provide information about the sympathetic/parasympathetic balance. This is a non-invasive measurement using an electrocardiographic (ECG) recording which takes only a few minutes (Palma and Benarroch, 2014; Riganello et al., 2018). The calculation is based on the interval between the R peaks of the QRS complex extracted from the ECG signal and analysis can be performed in the time or frequency-domain or using non-linear methods [for a review see Laborde et al. (2017)]. Numerous studies in healthy subjects as well as in different patients populations have demonstrated the link between pain/nociception and HRV [for a review refer to Forte et al. (2022)]. The changes in HRV observed during nociceptive stimulation, are not dependent on the method of stimulation since variations in heart rate have been observed after thermal, mechanical, and electrical nociceptive stimulation (Sclocco et al., 2016; Cotton et al., 2018; Courtois et al., 2020). In anesthesia, the HRV measurement is also used in the calculation of the Analgesia-Nociception Index (ANI) in order to control the nociception/anti-nociception balance (De jonckheere et al., 2015). Other studies in healthy subjects or patients able to communicate have also shown an association between HRV and subjective measures of pain such as pain thresholds or pain tolerance (Leźnicka et al., 2017; Paccione et al., 2022). Noteworthy, some studies have failed to find a link between pain stimulation/subjective pain measure and HRV. It has been shown that this physiological marker can also be used as an indication of nociception in patients with DoC. Recent studies found a higher HRV complexity in patients in MCS compared to patients in UWS during nociceptive stimulation (Tobaldini et al., 2018; Riganello et al., 2019). Indeed, a lower HRV complexity index was observed after noxious compared to non-noxious stimulation only in patients in UWS. This decrease in HRV complexity in patients with UWS reflects adaptation difficulties and lower reactivity to nociceptive stimulation (Tobaldini et al., 2018; Riganello et al., 2019; Venturella et al., 2019). In the study by Venturella et al. (2019), nociceptive stimulus processing in patients in UWS was also related to higher delta parietal activation [i.e., involved in attention and perception processing (Güntekin and Başar, 2016)], lower left frontal alpha activation (i.e., left frontal alpha activity related to information inhibition processes), and an increase of galvanic skin response (GSR). These results suggest that nociceptive stimulation can generate a cortical and autonomic response in behaviorally unresponsive patients.

The GSR (also referred to as electrodermal activity or skin conductance) is a biological electrical activity of the skin linked to the activity of the sweat glands which are controlled by the sympathetic system. It is a non-invasive technique allowing the investigation of emotional response following auditory or nociceptive stimulation (Gomez and Danuser, 2004; Khalfa et al., 2008). Studies using the number of skin conductance fluctuations and the normalized skin conductance level in healthy subjects showed that these measures could disentangle noxious stimulation (i.e., heat, mechanical, and cold stimulation) from other sympathetic stimuli (i.e., stimulation by noise and painful images). Indeed, the authors noticed that these measures during noxious stimulation were greater than during other stimulations and correlated with the subjective measure of pain using self-reported pain scale (Günther et al., 2016; Sugimine et al., 2020). Regarding patients with DoC, a study used the GSR and HRV entropy to investigate the autonomic response related to trace conditioning learning in patients in UWS after nociceptive stimulation. Patients in UWS with high GSR showed behavioral signs overlapping with the diagnosis of MCS 4 weeks after the experiment (Cortese et al., 2020). Measurement of GSR to assess the response to nociceptive stimulation during conditional learning may be an additional tool to improve the assessment of patients with DoC.

Finally, the pupillary dilatation reflex (PDR), whose variation results from the balance between the ortho- and parasympathetic tone, represents a promising tool to objectify nociception in DoC. The PDR is used to detect pain in brain-injured patients. It is also sensitive to opioids and allows the assessment of the nociception-anti-nociception balance during general anesthesia (De jonckheere et al., 2015). In the absence of intercurrent factors, PDR may be due to either sympathetic stimulation (e.g., in awake patient) or parasympathetic inhibition (e.g., in anesthetized patient). It is important to note that PDR is also sensitive to tactile stimuli and increased attention/cognitive load or emotional/cognitive arousal (Gusso et al., 2021). This suggests that PDR, related to nociceptive stimulus processing, can be divided into two stages: an excitation stage related to the strength of the stimulus, and an exploration stage related to the emotional processing of the stimulus (Bradley et al., 2008; Gusso et al., 2021). The use of pupillometry to detect the

processing of nociceptive stimulus has not been studied in patients with DoC yet. The use of pupillometry to detect the processing of nociceptive stimulus has not been studied in patients with DoC yet. It would be interesting to investigate this topic in future studies, taking care to control for potential confounding factors due to the environment (e.g., change in brightness) or patient's condition (e.g., presence of eyelid disorder, ptosis or pupil disorder, and mydriasis/myosis).

4.2. Treatments for pain

Pain prevention in patients with DoC still needs improvement. Indeed, a recent pilot clinical trial found that, although the majority of patients showed signs of pain during mobilization, only 33% of them were treated for pain before inclusion in the study (Bonin et al., 2022b). In order to reduce pain in severe brain-damaged patients, both pharmacological and non-pharmacological treatments can be used (**Figure 4**).

Even if, in clinical practice, the administration of pharmacological treatment is common, it is very important to pay attention to the nature and the dose of these treatments. There are three levels of analgesics: level 1 corresponds to non-opioid medications (e.g., acetaminophen), level 2 to weak opioids (e.g., tramadol) and level 3 to strong opioids (e.g., morphine) (Ventafridda et al., 1985). By preventing the release of acetylcholine in the thalamus, high-doses of opioids may decrease arousal and thus have an impact on the diagnosis as well (Brown et al., 2018). In contrast, the use of an optimal dose of analgesic medications can decrease pain while preserving patients' level of arousal and consciousness (Chatelle et al., 2016; Lanzillo et al., 2016; Whyte et al., 2020). In an open label study by Chatelle et al. (2016), a decrease in the NCS-R total scores and subscores was observed after analgesic treatment administration (ranging from level 1 to level 3 analgesic medications, depending on patient needs), independently from the diagnosis and etiology. This decrease in NCS-R scores did not lead to a deleterious change in the level of consciousness, with some patients even showing an improvement. Another study showed an increase in the level of consciousness after the administration of an analgesic treatment in patients with DoC who demonstrate severe spastic paresis (Lanzillo et al., 2016). Nonetheless, these results were not replicated in a recent trial by Bonin et al. (2022b) designed to evaluate the effects of analgesic treatment on nociception and pain signs during physiotherapy. This absence of results suggests either a lack of sensitivity of the NCS-R in detecting behavioral changes related to analgesic administration during physiotherapy or a lack of effectiveness of the treatments used. This disparity in outcomes can be related to the fact that Chatelle et al. (2016) conducted an open label research on patients with acute DoC, whereas Bonin et al. (2022b) performed a randomized double-blind placebo-control trial on patients with chronic DoC. Therefore, the lack of improvement in NCS-R scores might be attributed to the ineffectiveness of interventions during the chronic phase or potential bias during the assessment. Indeed, acute and chronic DoC have different pain profiles (i.e., chronic DoC are more prone to develop spastic paresis or neuropathic pain and are thus more resistant to analgesic therapies). Another study performed in a large sample of patients with TBI showed that BINAM scores were also sensitive to the administration of a non-opioid analgesic medication (Whyte et al., 2020). These studies indicate that the use of appropriate analgesia could reduce the risk of misdiagnosis and that the monitoring of pain (i.e., NCS-R and BINAM) as well as arousal/consciousness (i.e., assessed using the CRS-R) is necessary to set a good balance between pain relief and side effects of these treatments. Regarding pain treatment in LIS patients, a recent study highlighted that the majority of the surveyed patients were receiving pain killers (73% non-opioids, 20% non-inflammatory, and 13% weak opioids; Bonin et al., 2022c). In this study, 36% of the surveyed patients were suspected of having neuropathic pain. The first-line treatments for this type of pain are antidepressants and antiepileptics (Foley, 2003). Some of these patients (12%) were indeed being treated with these two types of drugs, but it was not clear from the information collected in the study whether it was given specifically for neuropathic pain or for other reasons. It is also possible to relieve patients' pain indirectly by acting on the source of the pain. For instance, several studies found beneficial effects of intrathecal baclofen on reducing spastic paresis as well as on improving consciousness recovery (Francois et al., 2001; Shrestha et al., 2011). By decreasing spastic paresis, these approaches could facilitate consciousness recovery by improving motor function and/or reducing pain (Pistoia et al., 2015; Lanzillo et al., 2016).

As explained above, pharmacological treatments often induce side effects that can impact the behavioral responses of patients during evaluations. Therefore, being able to propose non-pharmacological treatments seems essential to manage pain in these patients. The use of invasive brain stimulation techniques such as deep brain stimulation on the PAG and the rostral ventromedial medulla or motor cortex stimulation have proven to be effective in the treatment of chronic pain but remain difficult to implement in patients with DoC (Bittar et al., 2005; Cruccu et al., 2007; Lima and Fregni, 2008; Fontaine et al., 2009). Although less effective than invasive stimulation, a possible alternative to these methods would be the use of non-invasive stimulation techniques such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation (Klein et al., 2015; Lefaucheur et al., 2017). The effectiveness of physiotherapy or aerobic exercises (in combination with other methods) has also shown beneficial effects for pain management in LIS patients (Rice et al., 2019). Regarding other non-pharmacological approaches, and according to Bonin et al.'s (2022c) survey, only a minority of LIS patients have ever tried methods such as osteopathy, acupuncture, or electromagnetic therapy and none have tried hypnosis, relaxation, or meditation. None of these methods have been specifically investigated in patients with LIS, while some techniques could be of particular interest for these patients. Although used in the clinical setting on other pathologies, some of the methods are still controversial. Osteopathy, for instance, shows different results depending on the type of pain. A systematic review investigating osteopathy on musculoskeletal pain did not provide convincing evidence of efficacy in treating such pain (Posadzki and Ernst, 2011). However, another systematic review focusing on chronic low back pain found osteopathy to be effective in relieving it (Dal Farra et al., 2021). A recent meta-analysis showed that acupuncture can be effective in some cases of chronic pain such as musculoskeletal, headache, and osteoarthritis pain (Vickers et al., 2018). A study in

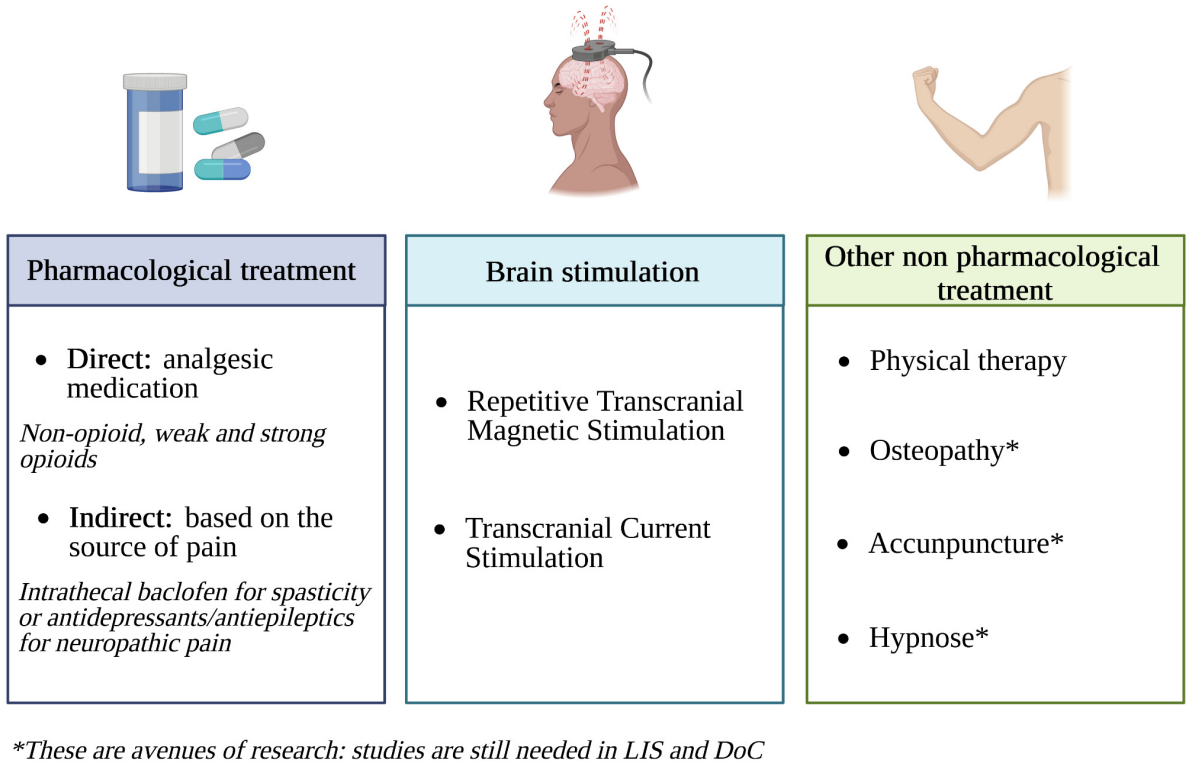

FIGURE 4
Pain treatment options in DoC and LIS patients (created with BioRender.com). Based on Posadzki and Ernst (2011), Klein et al. (2015), Chatelle et al. (2016), Vickers et al. (2018), Rice et al. (2019), Bicego et al. (2021), and de Pedro Negri et al. (2022).

mice also showed the effectiveness of this technique in relieving allodynia and improving emotional/cognitive dysfunction caused by neuropathic pain (Jang et al., 2021). Regarding electromagnetic therapy, systematic reviews of patients with musculoskeletal or chronic pelvic pain have shown that this method could be effective, but further studies are needed to examine the use of more standardized protocols (Paolucci et al., 2020; de Pedro Negri et al., 2022). Studies focusing on the use of hypnosis in healthy subjects and patients with acute or chronic pain highlighted a modulation of pain perception during the hypnotic state (Rainville, 1997; Vanhaudenhuyse et al., 2018; Bicego et al., 2021). A multiple-case study found that self-hypnosis could also be a useful tool to improve the quality of life of patients suffering from phantom limb pain (i.e., sensation of pain in a limb that has been amputated) by reducing the intensity of the pain, whether sensory or affective (Bicego et al., 2022). The reduction of pain sensation induced by hypnosis allows decreasing the doses of analgesics usually administered to these patients and thus improves their level of arousal and quality of life. The use of this technique in LIS patients, by avoiding side effects such as fatigue, could allow them to make the most of their communication tools. Meditation is an approach that has not yet been studied in LIS patients. However, experts in meditation show a decrease in pain sensitivity associated with an increase in brain activity in regions involved in pain processing, and a decrease in brain activity in regions involved in emotional processing and executive functions (Grant et al., 2011; Gard et al., 2012). It is hypothesized that the decrease in cognitive and emotional processing of the nociceptive stimulus may facilitate the association of the noxious stimulus with a neutral rather than unpleasant valence.

5. Reflections and future directions

Regarding the assessment of pain and nociception in patients with DoC or LIS, there are currently no clear guidelines and no clinical consensus. When performing neuroimaging analyses, it is relevant to mention that differences in terms of structures and physiological properties may exist between a severe brain-injured patient and a healthy subject. Therefore, it is essential to perform a multimodal assessment, not only based on neuroimaging but also on pain-related behaviors and physiological changes [(i.e., increase of heart rate and respiratory rhythm, and skin conductance (Cowen et al., 2015; Devalle et al., 2018; Riganello et al., 2019)] to improve pain assessment and indirectly the diagnosis of these patients. From a behavioral perspective, opinions still differ among researchers and clinicians regarding some behaviors that could be reflective of cortical processing (Poulsen et al., 2019). This is particularly the case for facial expression such as grimacing and crying. Indeed, even if grimacing is considered as an indicator of pain, the Multi-Society Task Force on Permanent Vegetative State does not consider it as a necessary sign of conscious perception, as it can occur reflexively through subcortical pathways in the thalamus and limbic system (The Multi-Society Task Force on PVS, 1994). Patients showing no sign of consciousness except for grimaces to nociceptive stimuli can therefore be diagnosed as being

in UWS. Moreover, some patients in LIS suffer from cortical lesions. This impacts their cognitive functions by impairing, for example, the recognition of negative facial expressions, or leading to the development of pathological laughter and crying which may distort the assessment of pain (Leonard et al., 2019). Many pain scales take into account the assessment of facial expressions in a more or less developed way (Feldt, 2000; Gélinas et al., 2006; Chanques et al., 2009; Chatelle et al., 2012). However, the facial expression assessment is clinically scored based on gross observation of facial movements in response to a noxious stimulation. A better characterization of facial expressions could be an interesting avenue of research to improve the behavioral assessment of these patients. For instance, the use of the facial action coding system could be developed in these patients. This system allows the coding of different types of emotions (including pain) based on the anatomical analysis of facial movements. It can distinguish 46 different action units produced by a single muscle or a combination of muscles (Kunz et al., 2007, 2008; Bartlett et al., 2014).

Numerous studies have highlighted the relevance of measuring neurophysiological parameters in the assessment of pain and nociception (Riganello et al., 2019; Cortese et al., 2020). At present, very few studies have investigated the clinical utility of GSR and PDR in the assessment of pain in DoC. This is mainly due to the fact that these measures are not suitable for all types of DoC patients, some of whom may suffer from ptosis often associated with the presence of myosis (i.e., pupil constriction) or other pupillary reactivity disorders, which makes it difficult to measure PDR. In addition, it is important to note that there is a gap between research and practice. The scientific literature on LEPs is well developed, but in practice, this technique is more complicated to implement in a systematic way. The device allowing LEP measurement is an expensive non-portable system, difficult to use in a clinical setting, especially with a sensitive population such as patients with DoC. Other less costly and easier to use techniques assessing the integrity of the spinothalamic pathways are used in other populations and deserve to be investigated in patients with DoC and LIS. For instance, pinprick-evoked potentials (PEPs, mechanical stimulation) are useful to assess the functional integrity of mechano-nociceptive pathways and detect central sensitization (Iannetti et al., 2013; Rosner et al., 2020; van den Broeke et al., 2020) but could be difficult to use in non-collaborative population such as DoC patients. Then, cool-evoked potentials (CEPs, thermal stimulation) allow the evaluation of the integrity of the spinothalamic pathways by stimulating Aδ-fibers and participate in the diagnosis of neuropathic pain without inducing pain (De Keyser et al., 2018; Leone et al., 2019). Finally, contact heat-evoked potentials (CHEPs, thermal stimulation) are also used to specifically assess the nociceptive component of a stimulus. These new generation of thermal cutaneous stimulators (i.e., thermodes) are portable and easier alternatives to LEPs for the recording of robust nociceptive (heat) and non-nociceptive (cold) responses in patients with DoC (De Schoenmacker et al., 2021; Lejeune et al., 2022). The aforementioned techniques could allow better understanding of nociception processing and facilitate neuropathic pain detection in patients with DoC and LIS, which is currently understudied. In the future, the NCS-R could be improved by integrating new physiological parameters like other recently developed scales, such as the BINAM for TBI patients or the PAS. Moreover, the measurement of physiological parameters could facilitate the assessment of the nociception/anti-nociception balance after analgesic administration. Indeed, to monitor the effects of analgesics administered during general anesthesia, anesthesiologists can use different types of tools measuring the activity of the autonomic nervous system (De jonckheere et al., 2015). The above-mentioned ANI, for instance, is based on HRV analysis and allows the measurement of the relative parasympathetic tone. Its score ranges from 0 to 100, a low score meaning that the patient is able to process nociceptive stimulus. The Surgical Pleth Index (SPI) is rather based on the measurement of the orthosympathetic hemodynamic response to noxious stimulation, and uses normalized heartbeat intervals (HBIs) and plethysmography wave amplitude for its calculation (Rogobete et al., 2021). The PDR and the GSR are also used in anesthesia to assess the sympathetic tone but have not yet been studied in detail in patients with DoC and LIS. The functional near-infrared spectroscopy (fNIRS) applied to pain detection could also be an avenue of future research to investigate. It is a non-invasive, low cost, easy-to-use, and portable brain imaging technique that allows to measure cortical hemoglobin concentration changes (Barati et al., 2017; Lopez-Martinez et al., 2019). Studies in healthy subjects have shown that fNIRS can provide an objective and robust assessment of pain by measuring changes in hemoglobin in the sensorimotor and prefrontal cortex (Yücel et al., 2015). Its application for pain detection has also been studied in sensitive and non-communicative patient populations such as infants and critically ill patients (Ranger and Gélinas, 2014; Yuan et al., 2022). The fNIRS is also used in patient with DoC to improve diagnosis but there is not, to our knowledge, any study specifically related to the detection of pain in this population (Rupawala et al., 2018). This measurement technique could also be an avenue to develop in post-coma patients given its low cost, ease of use and portability.

In the future, it would also be essential to develop non-pharmacological therapies in order to limit the use of analgesics and thus avoid the side effects such as fatigue or decreased vigilance. Few studies have looked at the effects of music therapy on the level of consciousness of UWS and MCS patients and have shown that it is a safe and effective method that can improve functional outcomes of patients [for a meta-analyses refer to Li et al. (2020)]. The effect of this technique on pain perception in LIS and DoC patients has not, to our knowledge, been studied yet. However, studies carried out in other patient populations have shown interesting effects (by reducing anxiety for instance) which suggest that this may be an interesting avenue to investigate in future research (Lin et al., 2020; Santiváñez-Acosta et al., 2020; Dallı et al., 2022; Seyffert et al., 2022).

This review focuses mainly on the physical pain that DoC and LIS patients may experience. However, LIS patients may also suffer from emotional pain such as depression or anxiety (Bergés et al., 2007; Rousseau et al., 2015; Bonin et al., 2022c). More studies are still needed to better characterize this type of suffering and its impact on patients' daily lives in order to propose appropriate pharmacological (e.g., antidepressants and anxiolytics) and complementary (e.g., hypnosis and meditation) treatments.

6. Conclusion

There are still many unknowns in the assessment, management and treatment of pain in DoC and LIS patients. The NCS-R remains

the most appropriate way to assess pain in patients with DoC but could be improved by considering the inclusion of physiological parameters in their behavioral assessment. The measurement of pain and nociception should be done with a multimodal approach, also taking into account (neuro)physiological and neuroimaging data as complementary measures. It is known that some behavioral UWS patients may show preservation of cortical areas involved in nociceptive signal processing. Then, pain assessment and analgesic treatments should be applied in a more systematic way, and most importantly, independently of patient's clinical diagnosis. In particular, titration of analgesic agents should be implemented to determine the optimal dose of the medications. The NCS-R and the BINAM represent relevant assessment tools to find a balance between reduced pain and preserved level of consciousness following analgesic treatment. For the moment, the guidelines of the American Academy of Neurology recommend the use of the NCS-R to assess pain in patient with DoC but these guidelines still need to be developed further and refined (Giacino et al., 2018). Regarding patients in LIS, even if they do not communicate their pain spontaneously, it is important to actively and regularly make an assessment through the use of simple communication codes. When signs of pain are detected, it is essential to identify the source of the physical and emotional pain to be able to propose appropriate treatments, both pharmacological and non-pharmacological.

Author contributions

EB: conceptualization, research, references formatting, writing, and editing. AT: conceptualization, supervision, review and editing, visualization, and resources. NL, ES, VB, CM, OG, and SL: review and resources. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

Afif, A., Hoffmann, D., Minotti, L., Benabid, A., and Kahane, P. (2008). Middle short gyrus of the insula implicated in pain processing. *Pain* 138, 546–555. doi: 10.1016/j.pain.2008.02.004

Andersen, G., Vestergaard, K., Ingeman-Nielsen, M., and Jensen, T. (1995). Incidence of central post-stroke pain. *Pain* 61, 187–193. doi: 10.1016/0304-3959(94)00144-4

André-Obadia, N., Zyss, J., Gavaret, M., Lefaucheur, J., Azabou, E., Boulogne, S., et al. (2018). Recommendations for the use of electroencephalography and evoked potentials in comatose patients. *Neurophysiol. Clin.* 48, 143–169. doi: 10.1016/j.neucli.2018.05.038

Annen, J., Laureys, S., and Gosseries, O. (2020). Brain-computer interfaces for consciousness assessment and communication in severely brain-injured patients. *Handb. Clin. Neurol.* 168, 137–152. doi: 10.1016/B978-0-444-63934-9.00011-1

Ashwal, S. (2004). Pediatric vegetative state: epidemiological and clinical issues. *Neuropsychol. Rehabil.* 19, 349–360. doi: 10.3233/NRE-2004-19412

Baars, B., Ramsøy, T., and Laureys, S. (2003). Brain, conscious experience and the observing self. *Trends Neurosci.* 26, 671–675. doi: 10.1016/j.tins.2003.09.015

Bagnato, S., Prestandrea, C., D'Agostino, T., Boccagni, C., and Rubino, F. (2021). Somatosensory evoked potential amplitudes correlate with long-term consciousness recovery in patients with unresponsive wakefulness syndrome. *Clin. Neurophysiol.* 132, 793–799. doi: 10.1016/j.clinph.2021.01.006

Bandler, R., Keay, K., Floyd, N., and Price, J. (2000). Central circuits mediating patterned autonomic activity during active vs. passive emotional coping. *Brain Res. Bull.* 53, 95–104. doi: 10.1016/S0361-9230(00)00313-0

Baral, P., Udit, S., and Chiu, I. (2019). Pain and immunity: implications for host defence. *Nat. Rev. Immunol.* 19, 433–447. doi: 10.1038/s41577-019-0147-2

Barati, Z., Zakeri, I., and Pourrezaei, K. (2017). Functional near-infrared spectroscopy study on tonic pain activation by cold pressor test. *Neurophoton* 4:015004. doi: 10.1117/1.NPh.4.1.015004

Bartlett, M., Littlewort, G., Frank, M., and Lee, K. (2014). Automatic decoding of facial movements reveals deceptive pain expressions. *Curr. Biol.* 24, 738–743. doi: 10.1016/j.cub.2014.02.009

Basbaum, A., Bautista, D., Scherrer, G., and Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell* 139, 267–284. doi: 10.1016/j.cell.2009.09.028

Benarroch, E. (2001). Pain-autonomic interactions: a selective review. *Clin. Auton. Res.* 11, 343–349. doi: 10.1007/BF02292765

Benarroch, E. (2006). Pain-autonomic interactions. *Neurol. Sci.* 27, 130–133. doi: 10.1007/s10072-006-0587-x

Bergeron, D., Obaid, S., Fournier-Gosselin, M., Bouthillier, A., and Nguyen, D. (2021). Deep brain stimulation of the posterior insula in chronic pain: a theoretical framework. *Brain Sci.* 11:639. doi: 10.3390/brainsci11050639

Bergés, I., Ottenbacher, K., Kuo, Y., Smith, P., Smith, D., and Ostir, G. (2007). Satisfaction with quality of life poststroke: effect of sex differences in pain response. *Arch. Phys. Med. Rehabil.* 88, 413–417. doi: 10.1016/j.apmr.2006.12.022

Bicego, A., Delmal, P., Ledoux, D., Faymonville, M., Noordhout, B., Cerasoli, A., et al. (2022). Self-hypnosis for phantom limb pain: a multiple-case study. *OBM Integr. Complement. Med.* 7, 1–28. doi: 10.21926/obm.icm.2203040

Bicego, A., Monseur, J., Collinet, A., Donneau, A., Fontaine, R., Libbrecht, D., et al. (2021). Complementary treatment comparison for chronic pain management: a randomized longitudinal study. *PLoS One* 16:e0256001. doi: 10.1371/journal.pone.0256001

Bittar, R., Kar-Purkayastha, I., Owen, S., Bear, R., Green, A., Wang, S., et al. (2005). Deep brain stimulation for pain relief: a meta-analysis. *J. Clin. Neurosci.* 12, 515–519. doi: 10.1016/j.jocn.2004.10.005

Bogner, J., Barrett, R., Hammond, F., Horn, S., Corrigan, J., Rosenthal, J., et al. (2015). Predictors of agitated behavior during inpatient rehabilitation for traumatic brain injury. *Arch. Phys. Med. Rehabil.* 96, 274–281. doi: 10.1016/j.apmr.2015.04.020

Boivie, J., Leijon, G., and Johansson, I. (1989). Central post-stroke pain — a study of the mechanisms through analyses of the sensory abnormalities. *Pain* 37, 173–185. doi: 10.1016/0304-3959(89)90128-0

Boly, M., Balteau, E., Schnakers, C., Degueldre, C., Moonen, G., Luxen, A., et al. (2007). Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc. Natl. Acad. Sci. U.S.A.* 104, 12187–12192. doi: 10.1073/pnas.0611404104

Boly, M., Faymonville, M., Schnakers, C., Peigneux, P., Lambermont, B., Phillips, C., et al. (2008). Perception of pain in the minimally conscious state with PET activation: an observational study. *Lancet Neurol.* 7, 1013–1020. doi: 10.1016/S1474-4422(08)70219-9

Bonin, E., Binda Fossati, M., Chatelle, C., Martens, G., Martial, C., Briand, M., et al. (2022a). Pain and spastic features in chronic DOC patient: a cross-sectional retrospective study. *Ann. Phys. Rehabil. Med.* 65:101566. doi: 10.1016/j.rehab.2021.101566

Bonin, E., Binda Fossati, M., Filippini, M., Bornheim, S., Lejeune, N., O'Brien, A., et al. (2022b). Evaluation of the effect of analgesic treatment on signs of nociception-related behaviors during physiotherapy in patients with disorders of consciousness: a pilot crossover randomized controlled trial. *Pain* 163, e349–e356. doi: 10.1097/j.pain.0000000000002367

Bonin, E., Delsemme, Z., Blandin, V., Alnagger, N., Faymonville, M., Faymonville, M., et al. (2022c). French survey on pain perception and management in patients with locked-in syndrome. *Diagnostics.* 12:769. doi: 10.3390/diagnostics12030769

Bonin, E., Lejeune, N., Thibaut, A., Cassol, H., Antonopoulos, G., Wannez, S., et al. (2020). Nociception coma scale revised allows to identify patients with preserved neural basis for pain experience. *J. Pain.* 21, 742–750. doi: 10.1016/j.jpain.2019.11.004

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., et al. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 114, 29–36. doi: 10.1016/j.pain.2004.12.010

Bradley, M., Miccoli, L., Escrig, M., and Lang, P. (2008). The pupil as a measure of emotional arousal and autonomic activation. *Psychophysiology* 45, 602–607. doi: 10.1111/j.1469-8986.2008.00654.x

Brown, E., Pavone, K., and Naranjo, M. (2018). Multimodal general anesthesia: theory and practice. *Anesth. Analgesia* 127, 1246–1258. doi: 10.1213/ANE.0000000000003668

Bruno, M., Bernheim, J., Ledoux, D., Pellas, F., Demertzi, A., and Laureys, S. (2011a). A survey on self-assessed well-being in a cohort of chronic locked-in syndrome patients: happy majority, miserable minority. *BMJ Open* 1:e000039. doi: 10.1136/bmjopen-2010-000039

Bruno, M., Vanhaudenhuyse, A., Thibaut, A., Moonen, G., and Laureys, S. (2011b). From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J. Neurol.* 258, 1373–1384. doi: 10.1007/s00415-011-6114-x

Bushnell, M., Duncan, G., Hofbauer, R., Ha, B., Chen, J., and Carrier, B. (1999). Pain perception: is there a role for primary somatosensory cortex? *Proc. Natl. Acad. Sci. U.S.A.* 96, 7705–7709. doi: 10.1073/pnas.96.14.7705

Buttner, W., and Finke, W. (2000). Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. *Pediatr. Anesth.* 10, 303–318. doi: 10.1046/j.1460-9592.2000.00530.x

Cairns, K., and Stein, J. (2002). Motor function improvement following intrathecal baclofen pump placement in a patient with locked-in syndrome. *Am. J. Phys. Med. Rehabil.* 81, 307–309. doi: 10.1097/00002060-200204000-00013

Calabrò, R., Naro, A., Manuli, A., Leo, A., De Luca, R., Lo Buono, V., et al. (2017). Pain perception in patients with chronic disorders of consciousness: what can limbic system tell us? *Clin. Neurophysiol.* 128, 454–462. doi: 10.1016/j.clinph.2016.12.011

Capizzi, A., Woo, J., and Verduzco-Gutierrez, M. (2020). Traumatic brain injury. *Med. Clin. North Am.* 104, 213–238. doi: 10.1016/j.mcna.2019.11.001

Chanques, G., Payen, J., Mercier, G., de Lattre, S., Viel, E., Jung, B., et al. (2009). Assessing pain in non-intubated critically ill patients unable to self report: an adaptation of the behavioral pain scale. *Intens. Care Med.* 35, 2060–2067. doi: 10.1007/s00134-009-1590-5

Chatelle, C., De Val, M., Catano, A., Chaskis, C., Seeldrayers, P., Laureys, S., et al. (2016). Is the nociception coma scale-revised a useful clinical tool for managing pain in patients with disorders of consciousness? *Clin. J. Pain* 32, 321–326. doi: 10.1097/AJP.0000000000000259

Chatelle, C., Hauger, S., Martial, C., Becker, F., Eifert, B., Boering, D., et al. (2018). Assessment of nociception and pain in participants in an unresponsive or minimally conscious state after acquired brain injury: the relation between the coma recovery scale–revised and the nociception coma scale–revised. *Arch. Phys. Med. Rehabil.* 99, 1755–1762. doi: 10.1016/j.apmr.2018.03.009

Chatelle, C., Majerus, S., Whyte, J., Laureys, S., and Schnakers, C. (2012). A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. *J. Neurol. Neurosurg. Psychiatry* 83, 1233–1237. doi: 10.1136/jnnp-2012-302987

Chatelle, C., Thibaut, A., Bruno, M., Boly, M., Bernard, C., Hustinx, R., et al. (2014a). Nociception coma scale–revised scores correlate with metabolism in the anterior cingulate cortex. *Neurorehabil. Neural Repair* 28, 149–152. doi: 10.1177/1545968313503220

Chatelle, C., Thibaut, A., Gosseries, O., Bruno, M., Demertzi, A., Bernard, C., et al. (2014b). Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. *Front. Hum. Neurosci.* 8:917. doi: 10.3389/fnhum.2014.00917

Chiu, I., Pinho-Ribeiro, F., and Woolf, C. (2016). Pain and infection: pathogen detection by nociceptors. *Pain* 157, 1192–1193. doi: 10.1097/j.pain.0000000000000559

Chiu, I., von Hehn, C., and Woolf, C. (2012). Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat. Neurosci.* 15, 1063–1067. doi: 10.1038/nn.3144

Cistaro, A., Lo Banco, G., Fania, P., Margotti, S., Vigneri, S., Geraci, C., et al. (2018). Locked-in syndrome and 18F-fluorodeoxyglucose-positron emission tomography/computed tomography: observations from a case of basilar artery thrombosis. *Indian J. Nucl. Med.* 33, 65–67.

Coghill, R., Sang, C., Maisog, J., and Iadarola, M. (1999). Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J. Neurophysiol.* 82, 1934–1943. doi: 10.1152/jn.1999.82.4.1934

Corrigan, J. (1989). Development of a scale for assessment of agitation following traumatic brain injury. *J. Clin. Exp. Neuropsychol.* 11, 261–277. doi: 10.1080/01688638908400888

Cortelli, P., Giannini, G., Favoni, V., Cevoli, S., and Pierangeli, G. (2013). Nociception and autonomic nervous system. *Neurol. Sci.* 34, 41–46. doi: 10.1007/s10072-013-1391-z

Cortese, D., Riganello, F., Arcuri, F., Lucca, L., Tonin, P., Schnakers, C., et al. (2020). The trace conditional learning of the noxious stimulus in UWS patients and its prognostic value in a GSR and HRV entropy study. *Front. Hum. Neurosci.* 14:97. doi: 10.3389/fnhum.2020.00097

Cortese, M., Arcuri, F., Nemirovsky, I., Lucca, L., Tonin, P., Soddu, A., et al. (2021). Nociceptive response is a possible marker of evolution in the level of consciousness in unresponsive wakefulness syndrome patients. *Front. Neurosci.* 15:771505. doi: 10.3389/fnins.2021.771505

Cotton, V., Low, L., Villemure, C., and Bushnell, M. (2018). Unique autonomic responses to pain in yoga practitioners. *Psychosom. Med.* 80, 791–798. doi: 10.1097/PSY.0000000000000587

Courtois, I., Gholamrezaei, A., Jafari, H., Lautenbacher, S., Van Diest, I., Van Oudenhove, L., et al. (2020). Respiratory hypoalgesia? The effect of slow deep breathing on electrocutaneous, thermal, and mechanical pain. *J. Pain* 21, 616–632. doi: 10.1016/j.jpain.2019.10.002

Cowen, R., Stasiowska, M., Laycock, H., and Bantel, C. (2015). Assessing pain objectively: the use of physiological markers. *Anaesthesia* 70, 828–847. doi: 10.1111/anae.13018

Craig, A. D. (2003). A new view of pain as a homeostatic emotion. *Trends Neurosci.* 26, 303–307. doi: 10.1016/S0166-2236(03)00123-1

Cruccu, G., Aziz, T., Garcia-Larrea, L., Hansson, P., Jensen, T., Lefaucheur, J., et al. (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur. J. Neurol.* 14, 952–970. doi: 10.1111/j.1468-1331.2007.01916.x

Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T., Fernández-Espejo, D., Pickard, J., et al. (2011). Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 378, 2088–2094. doi: 10.1016/S0140-6736(11)61224-5

Dal Farra, F., Risio, R., Vismara, L., and Bergna, A. (2021). Effectiveness of osteopathic interventions in chronic non-specific low back pain: a systematic review and meta-analysis. *Complement. Ther. Med.* 56:102616. doi: 10.1016/j.ctim.2020.102616

Dallı, Ö, Yıldırım, Y., Aykar, F., and Kahveci, F. (2022). The effect of music on delirium, pain, sedation and anxiety in patients receiving mechanical ventilation in the intensive care unit. *Intens. Crit. Care Nurs.* 75:103348. doi: 10.1016/j.iccn.2022.103348

Das, J., Anosike, K., and Asuncion, R. (2021). *Locked-in syndrome*. Treasure Island, FL: StatPearls Publishing.

De jonckheere, J., Bonhomme, V., Jeanne, M., Boselli, E., Gruenewald, M., Logier, R., et al. (2015). Physiological signal processing for individualized anti-nociception management during general anesthesia: a review. *Yearb. Med. Inform.* 24, 95–101. doi: 10.15265/IY-2015-004

De Keyser, R., van den Broeke, E., Courtin, A., Dufour, A., and Mouraux, A. (2018). Event-related brain potentials elicited by high-speed cooling of the skin: a robust and non-painful method to assess the spinothalamic system in humans. *Clin. Neurophysiol.* 129, 1011–1019. doi: 10.1016/j.clinph.2018.02.123

de Pedro Negri, A., Ruiz Prieto, M., Díaz-Mohedo, E., and Martín-Valero, R. (2022). Efficacy of magnetic therapy in pain reduction in patients with chronic pelvic pain: a systematic review. *Int. J. Environ. Res. Public Health* 19:5824. doi: 10.3390/ijerph19105824

De Salvo, S., Naro, A., Bonanno, L., Russo, M., Muscarà, N., Bramanti, P., et al. (2015). Assessment of nociceptive system in vegetative and minimally conscious state by using laser evoked potentials. *Brain Inj.* 29, 1467–1474. doi: 10.3109/02699052.2015.1071430

De Schoenmacker, I., Berry, C., Blouin, J., Rosner, J., Hubli, M., Jutzeler, C., et al. (2021). An intensity matched comparison of laser- and contact heat evoked potentials. *Sci. Rep.* 11:6861. doi: 10.1038/s41598-021-85819-w

de Tommaso, M., Navarro, J., Lanzillotti, C., Ricci, K., Buonocunto, F., Livrea, P., et al. (2015). Cortical responses to salient nociceptive and not nociceptive stimuli in vegetative and minimal conscious state. *Front. Hum. Neurosci.* 9:17. doi: 10.3389/fnhum.2015.00017

de Tommaso, M., Navarro, J., Ricci, K., Lorenzo, M., Lanzillotti, C., Colonna, F., et al. (2013). Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. *Brain Inj.* 27, 962–972. doi: 10.3109/02699052.2013.775507

Dehaene, S., and Changeux, J. (2011). Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227. doi: 10.1016/j.neuron.2011.03.018

Demertzi, A., Jox, R., Racine, E., and Laureys, S. (2014). A European survey on attitudes towards pain and end-of-life issues in locked-in syndrome. *Brain Inj.* 28, 1209–1215. doi: 10.3109/02699052.2014.920526

Demertzi, A., Racine, E., Bruno, M., Ledoux, D., Gosseries, O., Vanhaudenhuyse, A., et al. (2013). Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. *Neuroethics* 6, 37–50. doi: 10.1007/s12152-011-9149-x

Demertzi, A., Schnakers, C., Ledoux, D., Chatelle, C., Bruno, M., Vanhaudenhuyse, A., et al. (2009). Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. *Progr. Brain Res.* 177, 329–338. doi: 10.1016/S0079-6123(09)17722-1

Devalle, G., Castiglioni, P., Arienti, C., Abbate, C., Mazzucchi, A., Agnello, L., et al. (2018). Cardio-respiratory autonomic responses to nociceptive stimuli in patients with disorders of consciousness. *PLoS One* 13:e0201921. doi: 10.1371/journal.pone.0201921

Di Perri, C., Bahri, M., Amico, E., Thibaut, A., Heine, L., Antonopoulos, G., et al. (2016). Neural correlates of consciousness in patients who have emerged from a minimally conscious state: a cross-sectional multimodal imaging study. *Lancet Neurol.* 15, 830–842. doi: 10.1016/S1474-4422(16)00111-3

Di Perri, C., Bastianello, S., Bartsch, A., Pistarini, C., Maggioni, G., Magrassi, L., et al. (2013). Limbic hyperconnectivity in the vegetative state. *Neurology* 81, 1417–1424. doi: 10.1212/WNL.0b013e3182a43b78

Dunckley, P. A. (2005). Comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. *J. Neurosci.* 25, 7333–7341. doi: 10.1523/JNEUROSCI.1100-05.2005

Edlow, B., Chatelle, C., Spencer, C., Chu, C., Bodien, Y., O'Connor, K., et al. (2017). Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain* 140, 2399–2414. doi: 10.1093/brain/awx176

Elkins, G., Barabasz, A., Council, J., and Spiegel, D. (2015). Advancing research and practice: the revised APA division 30 definition of hypnosis. *Int. J. Clin. Exp. Hypn.* 63, 1–9. doi: 10.1080/00207144.2014.961870

Estraneo, A., Magliacano, A., Fiorenza, S., Formisano, R., Grippo, A., Angelakis, E., et al. (2022). Risk factors for 2-year mortality in patients with prolonged disorders of consciousness: an international multicentre study. *Eur. J. Neurol.* 29, 390–399. doi: 10.1111/ene.15143

Fairhurst, M., Wiech, K., Dunckley, P., and Tracey, I. (2007). Anticipatory brainstem activity predicts neural processing of pain in humans. *Pain* 128, 101–110. doi: 10.1016/j.pain.2006.09.001

Feldt, K. (2000). The checklist of nonverbal pain indicators (CNPI). *Pain Manag. Nurs.* 1, 13–21. doi: 10.1053/jpmn.2000.5831

Foley, K. (2003). Opioids and chronic neuropathic pain. *N. Engl. J. Med.* 348, 1279–1281. doi: 10.1056/NEJMe030014

Fontaine, D., Hamani, C., and Lozano, A. (2009). Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature: clinical article. *J. Neurosurg.* 110, 251–256. doi: 10.3171/2008.6.17602

Formisano, R., Contrada, M., Aloisi, M., Ferri, G., Schiattone, S., Iosa, M., et al. (2020). Nociception coma scale with personalized painful stimulation versus standard stimulus in non-communicative patients with disorders of consciousness. *Neuropsychol. Rehabil.* 30, 1893–1904. doi: 10.1080/09602011.2019.1614464

Forte, G., Troisi, G., Pazzaglia, M., Pascalis, V., and Casagrande, M. (2022). Heart rate variability and pain: a systematic review. *Brain Sci.* 12, 1–25. doi: 10.3390/brainsci12020153

Francois, B., Vacher, P., Roustan, J., Salle, J., Vidal, J., Moreau, J., et al. (2001). Intrathecal baclofen after traumatic brain injury: early treatment using a new technique to prevent spasticity. *J. Trauma* 50, 158–161. doi: 10.1097/00005373-200101000-00035

Frohnhofen, H. (2018). Pain and sleep: a bidirectional relationship. *Zeitschr. Gerontol. Geriatr.* 51, 871–874. doi: 10.1007/s00391-018-01461-8

Gard, T., Holzel, B., Sack, A., Hempel, H., Lazar, S., Vaitl, D., et al. (2012). Pain attenuation through mindfulness is associated with decreased cognitive control and increased sensory processing in the brain. *Cereb. Cortex.* 22, 2692–2702. doi: 10.1093/cercor/bhr352

Garuti, G., Reverberi, C., Briganti, A., Massobrio, M., Lombardi, F., and Lusuardi, M. (2014). Swallowing disorders in tracheostomised patients: a multidisciplinary/multiprofessional approach in decannulation protocols. *Multidiscip. Respir. Med.* 9:36. doi: 10.4081/mrm.2014.371

Gélinas, C., Fillion, L., Puntillo, K., Viens, C., Fortier, M., and Francisco, S. (2006). Validation of the critical-care pain observation tool in adult patients. *Am. J. Crit. Care.* 15:9. doi: 10.1037/t33641-000

Giacino, J., Kalmar, K., and Whyte, J. (2004). The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility11No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the authors or upon any organization with which the authors are associated. *Arch. Phys. Med. Rehabil.* 85, 2020–2029. doi: 10.1016/j.apmr.2004.02.033

Giacino, J., Katz, D., Schiff, N., Whyte, J., Ashman, E., Ashwal, S., et al. (2018). Practice guideline update recommendations summary: disorders of consciousness. *Arch. Phys. Med. Rehabil.* 99, 1699–1709. doi: 10.1016/j.apmr.2018.07.001

Gomez, P., and Danuser, B. (2004). Affective and physiological responses to environmental noises and music. *Int. J. Psychophysiol.* 53, 91–103. doi: 10.1016/j.ijpsycho.2004.02.002

Grant, J., Courtemanche, J., and Rainville, P. (2011). A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. *Pain* 152, 150–156. doi: 10.1016/j.pain.2010.10.006

Grichnick, K., and Ferrante, F. (1991). The difference between acute and chronic pain. *Mt. Sinai J. Med.* 58, 217–220.

Güntekin, B., and Başar, E. (2016). Review of evoked and event-related delta responses in the human brain. *Int. J. Psychophysiol.* 103, 43–52. doi: 10.1016/j.ijpsycho.2015.02.001

Günther, A., Schandl, A., Berhardsson, J., Bjärtå, A., Wållgren, M., Sundin, Ö, et al. (2016). Pain rather than induced emotions and ICU sound increases skin conductance variability in healthy volunteers. *Acta Anaesthesiol. Scand.* 60, 1111–1120. doi: 10.1111/aas.12751

Gusso, M., Serur, G., and Nohama, P. (2021). Pupil reactions to tactile stimulation: a systematic review. *Front. Neurosci.* 15:610841. doi: 10.3389/fnins.2021.610841

Heinricher, M., Tavares, I., Leith, J., and Lumb, B. (2009). Descending control of nociception: specificity, recruitment and plasticity. *Brain Res. Rev.* 60, 214–225. doi: 10.1016/j.brainresrev.2008.12.009

Hofbauer, R., Rainville, P., Duncan, G., and Bushnell, M. (2001). Cortical representation of the sensory dimension of pain. *J. Neurophysiol.* 86, 402–411. doi: 10.1152/jn.2001.86.1.402

Hohenschurz-Schmidt, D., Calcagnini, G., Dipasquale, O., Jackson, J., Medina, S., O'Daly, O., et al. (2020). Linking pain sensation to the autonomic nervous system: the role of the anterior cingulate and periaqueductal gray resting-state networks. *Front. Neurosci.* 14:147. doi: 10.3389/fnins.2020.00147

Iannetti, G., Baumgärtner, U., Tracey, I., Treede, R., and Magerl, W. (2013). Pinprick-evoked brain potentials: a novel tool to assess central sensitization of nociceptive pathways in humans. *J. Neurophysiol.* 110, 1107–1116. doi: 10.1152/jn.00774.2012

Ingvar, M. (1999). Pain and functional imaging. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 354, 1347–1358. doi: 10.1098/rstb.1999.0483

Isnard, J., Magnin, M., Jung, J., Mauguière, F., and Garcia-Larrea, L. (2011). Does the insula tell our brain that we are in pain? *Pain* 152, 946–951. doi: 10.1016/j.pain.2010.12.025

Jang, J., Song, E., Do, Y., Ahn, S., Oh, J., Hwang, T., et al. (2021). Acupuncture alleviates chronic pain and comorbid conditions in a mouse model of neuropathic pain: the involvement of DNA methylation in the prefrontal cortex. *Pain* 162, 514–530. doi: 10.1097/j.pain.0000000000002031

Ji, R., Xu, Z., and Gao, Y. (2014). Emerging targets in neuroinflammation-driven chronic pain. *Nat. Rev. Drug Discov.* 13, 533–548. doi: 10.1038/nrd4334

Kassubek, J., Juengling, F., Els, T., Spreer, J., Herpers, M., Krause, T., et al. (2003). Activation of a residual cortical network during painful stimulation in long-term postanoxic vegetative state: a 15O–H2O PET study. *J. Neurol. Sci.* 212, 85–91. doi: 10.1016/S0022-510X(03)00106-0

Khalfa, S., Roy, M., Rainville, P., Dalla Bella, S., and Peretz, I. (2008). Role of tempo entrainment in psychophysiological differentiation of happy and sad music? *Int. J. Psychophysiol.* 68, 17–26. doi: 10.1016/j.ijpsycho.2007.12.001

Klein, M., Treister, R., Raij, T., Pascual-Leone, A., Park, L., Nurmikko, T., et al. (2015). Transcranial magnetic stimulation of the brain: guidelines for pain treatment research. *Pain* 156, 1601–1614. doi: 10.1097/j.pain.0000000000000210

Koenig, M., and Kaplan, P. (2015). Clinical applications for EPs in the ICU. *J. Clin. Neurophysiol.* 32, 472–480. doi: 10.1097/WNP.0000000000000215

Kunz, M., Chatelle, C., Lautenbacher, S., and Rainville, P. (2008). The relation between catastrophizing and facial responsiveness to pain. *Pain* 140, 127–134. doi: 10.1016/j.pain.2008.07.019

Kunz, M., Scharmann, S., Hemmeter, U., Schepelmann, K., and Lautenbacher, S. (2007). The facial expression of pain in patients with dementia. *Pain* 133, 221–228. doi: 10.1016/j.pain.2007.09.007

Kupers, R., Faymonville, M., and Laureys, S. (2005). The cognitive modulation of pain: hypnosis- and placebo-induced analgesia. *Progr. Brain Res.* 150, 251–69. doi: 10.1016/S0079-6123(05)50019-0

Laborde, S., Mosley, E., and Thayer, J. (2017). Heart rate variability and cardiac vagal tone in psychophysiological research – recommendations for experiment planning, data analysis, and data reporting. *Front. Psycholo.* 8:213. doi: 10.3389/fpsyg.2017.00213

Labus, J., Naliboff, B., Fallon, J., Berman, S., Suyenobu, B., Bueller, J., et al. (2008). Sex differences in brain activity during aversive visceral stimulation and its expectation in patients with chronic abdominal pain: a network analysis. *Neuroimage* 41, 1032–1043. doi: 10.1016/j.neuroimage.2008.03.009

Lanzillo, B., Loreto, V., Calabrese, C., Estraneo, A., Moretta, P., and Trojano, L. (2016). Does pain relief influence recovery of consciousness? A case report of a patient treated with ziconotide. *Eur. J. Phys. Rehabil. Med.* 52:4.

Laureys, S., Celesia, G., Cohadon, F., Lavrijsen, J., León-Carrión, J., Sannita, W., et al. (2010). Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med.* 8:68. doi: 10.1186/1741-7015-8-68

Laureys, S., Faymonville, M., Peigneux, P., Damas, P., Lambermont, B., Del Fiore, G., et al. (2002). Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage* 17, 732–741. doi: 10.1006/nimg.2002.1236

Lawrence, J., Alcock, D., McGrath, P., Kay, J., MacMurray, S., and Dulberg, C. (1993). The development of a tool to assess neonatal pain. *Neonatal Netw.* 12, 59–66.

Lee, I., Necka, E., and Atlas, L. (2020). Distinguishing pain from nociception, salience, and arousal: how autonomic nervous system activity can improve neuroimaging tests of specificity. *Neuroimage* 33, 423–424. doi: 10.1016/j.neuroimage.2019.116254

Lefaucheur, J., Antal, A., Ayache, S., Benninger, D., Brunelin, J., Cogiamanian, F., et al. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin. Neurophysiol.* 128, 56–92. doi: 10.1016/j.clinph.2016.10.087

Lejeune, N., Petrossova, E., Frahm, S., and Mouraux, A. (2022). High-speed heating of the skin using a contact thermode elicits comparable brain responses to those elicited by a CO2-laser device. *Clin. Neurophysiol.* 146, 1–9. doi: 10.1016/j.clinph.2022.11.008

Lejeune, N., Thibaut, A., Martens, G., Martial, C., Wannez, S., Laureys, S., et al. (2020). Can the nociception coma scale-revised be used in patients with a tracheostomy? *Arch. Phys. Med. Rehabil.* 101, 1064–1067. doi: 10.1016/j.apmr.2019.09.020

Lenz, F., Seike, M., Richardson, R., Lin, Y., Baker, F., Khoja, I., et al. (1993). Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. *J. Neurophysiol.* 70, 200–212. doi: 10.1152/jn.1993.70.1.200

Leo, A., Naro, A., Cannavò, A., Pisani, L., Bruno, R., Salviera, C., et al. (2016). Could autonomic system assessment be helpful in disorders of consciousness diagnosis? A neurophysiological study. *Exp. Brain Res.* 234, 2189–2199. doi: 10.1007/s00221-016-4622-8

Leonard, M., Renard, F., Harsan, L., Pottecher, J., Braun, M., Schneider, F., et al. (2019). Diffusion tensor imaging reveals diffuse white matter injuries in locked-in syndrome patients. *PLoS One* 14:e0213528. doi: 10.1371/journal.pone.0213528

León-Carrión, J., van Eeckhout, P., Domínguez-Morales M del, R., and Pérez-Santamaría, F. (2002). Survey: the locked-in syndrome: a syndrome looking for a therapy. *Brain Inj.* 16, 571–582. doi: 10.1080/02699050110119781

Leone, C., Dufour, A., Di Stefano, G., Fasolino, A., Di Lionardo, A., La Cesa, S., et al. (2019). Cooling the skin for assessing small-fibre function. *Pain* 160, 1967–1975. doi: 10.1097/j.pain.0000000000001584

Leone, M., Proietti Cecchini, A., Mea, E., Tullo, V., Curone, M., and Bussone, G. (2006). Neuroimaging and pain: a window on the autonomic nervous system. *Neurol. Sci.* 27, 134–137. doi: 10.1007/s10072-006-0588-9

Leźnicka, K., Pawlak, M., Białecka, M., Safranow, K., and Cięszczyk, P. (2017). Pain perception and cardiovascular system response among athletes playing contact sports. *Res. Sports Med.* 25, 290–299. doi: 10.1080/15438627.2017.1314288

Li, X., Li, C., Hu, N., and Wang, T. (2020). Music interventions for disorders of consciousness: a systematic review and meta-analysis. *J. Neurosci. Nurs.* 52, 146–151. doi: 10.1097/JNN.0000000000000511

Libet, B. (1973). "Electrical stimulation of cortex in human subjects, and conscious sensory aspects," in *Handbook of sensory physiology*, ed. A. Iggo (Berlin: Springer), 743–790. doi: 10.1007/978-3-642-65438-1_20

Lima, M., and Fregni, F. (2008). Motor cortex stimulation for chronic pain. *Neurology* 70, 2329–2337. doi: 10.1212/01.wnl.0000314649.38527.93

Lin, C., Hwang, S., Jiang, P., and Hsiung, N. (2020). Effect of music therapy on pain after orthopedic surgery—a systematic review and meta-analysis. *Pain Pract.* 20, 422–436. doi: 10.1111/papr.12864

Loeser, J., and Treede, R. (2008). The Kyoto protocol of IASP basic pain terminology. *Pain* 137, 473–477. doi: 10.1016/j.pain.2008.04.025

Lopez-Martinez, D., Peng, K., Lee, A., Borsook, D., and Picard, R. (2019). *Pain detection with fNIRS-measured brain signals: a personalized machine learning approach using the wavelet transform and bayesian hierarchical modeling with dirichlet process priors. arXiv [Preprint]*. Available online at: http://arxiv.org/abs/1907.12830 (accessed February 9, 2023). doi: 10.1109/ACIIW.2019.8925076

Lugo, Z., Bruno, M., Gosseries, O., Demertzi, A., Heine, L., Thonnard, M., et al. (2015). Beyond the gaze: communicating in chronic locked-in syndrome. *Brain Inj.* 29, 1056–1061. doi: 10.3109/02699052.2015.1004750

Markl, A., Yu, T., Vogel, D., Müller, F., Kotchoubey, B., and Lang, S. (2013). Brain processing of pain in patients with unresponsive wakefulness syndrome. *Brain Behav.* 3, 95–103. doi: 10.1002/brb3.110

Martens, G., Laureys, S., and Thibaut, A. (2017). Spasticity management in disorders of consciousness. *Brain Sci.* 7:162. doi: 10.3390/brainsci7120162

Mazzola, L., Isnard, J., and Mauguière, F. (2006). Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses. *Cereb. Cortex.* 16, 960–968. doi: 10.1093/cercor/bhj038

Melzack, R., and Wall, P. (1965). Pain mechanisms: a new theory. *Science* 150, 971–979. doi: 10.1126/science.150.3699.971

Mendell, L. (2022). The path to discovery of windup and central sensitization. *Front. Pain Res.* 3:833104. doi: 10.3389/fpain.2022.833104

Merkel, S., Shayevitz, J., Voepel-Lewis, T., and Malviya, S. (1997). The FLACC: a behavorial scale for scoring postoperative pain in young children. *Pediatr. Nurs.* 23, 293–297.

Merskey, H., and Bogduk, N. (1994). *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms*, 2nd Edn. Seattle, WA: IASP Press.

Monti, M., Vanhaudenhuyse, A., Coleman, M., Boly, M., Pickard, J., Tshibanda, L., et al. (2010). Willful modulation of brain activity in disorders of consciousness. *N. Engl. J. Med.* 362, 579–589. doi: 10.1056/NEJMoa0905370

Moriarty, O. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Progr. Neurobiol.* 93, 385–404. doi: 10.1016/j.pneurobio.2011.01.002

Mouraux, A., and Iannetti, G. (2018). The search for pain biomarkers in the human brain. *Brain* 141, 3290–3307. doi: 10.1093/brain/awy281

Mouraux, A., Diukova, A., Lee, M., Wise, R., and Iannetti, G. D. (2011). A multisensory investigation of the functional significance of the "pain matrix.". *Neuroimage* 54, 2237–2249. doi: 10.1016/j.neuroimage.2010.09.084

Napadow, V., Sclocco, R., and Henderson, L. (2019). Brainstem neuroimaging of nociception and pain circuitries. *Pain Rep.* 4:e745. doi: 10.1097/PR9.0000000000000745

Naro, A., Leo, A., Bramanti, P., and Calabrò, R. (2015). Moving toward conscious pain processing detection in chronic disorders of consciousness: anterior cingulate cortex neuromodulation. *The J. Pain* 16, 1022–1031. doi: 10.1016/j.jpain.2015.06.014

Nash, P., Macefield, V., Klineberg, I., Murray, G., and Henderson, L. (2009). Differential activation of the human trigeminal nuclear complex by noxious and non-noxious orofacial stimulation. *Hum. Brain Map.* 30, 3772–3782. doi: 10.1002/hbm.20805

O'Brien, A., Deitos, A., Triñanes Pego, Y., Fregni, F., and Carrillo-de-la-Peña, M. (2018). Defective endogenous pain modulation in fibromyalgia: a meta-analysis of temporal summation and conditioned pain modulation paradigms. *J. Pain* 19, 819–836. doi: 10.1016/j.jpain.2018.01.010

O'Brien, E., Waxenberg, L., Gremillion, H., and Robinson, M. (2011). Intraindividual variability in daily sleep and pain ratings among chronic pain patients: bidirectional association and the role of negative mood. *Clin. J. Pain* 27:9. doi: 10.1097/AJP.0b013e318208c8e4

Paccione, C., Bruehl, S., My Diep, L., Rosseland, L., Stubhaug, A., and Jacobsen, H. (2022). The indirect impact of heart rate variability on cold pressor pain tolerance and intensity through psychological distress in individuals with chronic pain: the Tromsø Study. *Pain Rep.* 7:e970. doi: 10.1097/PR9.0000000000000970

Palma, J., and Benarroch, E. (2014). Neural control of the heart: recent concepts and clinical correlations. *Neurology* 83, 261–271. doi: 10.1212/WNL.0000000000000605

Paolucci, T., Pezzi, L., Centra, A., Giannandrea, N., Bellomo, R., and Saggini, R. (2020). Electromagnetic field therapy: a rehabilitative perspective in the management of musculoskeletal pain – a systematic review. *J. Pain Res.* 13, 1385–1400. doi: 10.2147/JPR.S231778

Peyron, R., Frot, M., Schneider, F., Garcia-Larrea, L., Mertens, P., Barral, F., et al. (2002). Role of operculoinsular cortices in human pain processing: converging evidence from PET, fMRI, dipole modeling, and intracerebral recordings of evoked potentials. *Neuroimage* 17, 1336–1346. doi: 10.1006/nimg.2002.1315

Peyron, R., Laurent, B., and García-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol. Clin.* 30, 263–288. doi: 10.1016/S0987-7053(00)00227-6

Pieretti, S., Giannuario, A., Giovannandrea, R., Marzoli, F., Piccaro, G., Minosi, P., et al. (2016). Gender differences in pain and its relief. *Ann. Ist. Super. Sanità.* 52, 184–189.

Pisa, F., Biasutti, E., Drigo, D., and Barbone, F. (2014). The prevalence of vegetative and minimally conscious states. *J. Head Trauma Rehabil.* 29, E23–E30. doi: 10.1097/HTR.0b013e3182a4469f

Pistoia, F., Sacco, S., Sarà, M., Franceschini, M., and Carolei, A. (2015). Intrathecal baclofen: effects on spasticity, pain, and consciousness in disorders of consciousness and locked-in syndrome. *Current Pain Headache Rep.* 19:466. doi: 10.1007/s11916-014-0466-8

Posadzki, P., and Ernst, E. (2011). Osteopathy for musculoskeletal pain patients: a systematic review of randomized controlled trials. *Clin. Rheumatol.* 30, 285–291. doi: 10.1007/s10067-010-1600-6

Poulsen, I., Balle, M., and Givard, K. (2019). Nociception coma scale–revised: nurses' experience in clinical practice. *Pain Manag. Nurs.* 20, 592–598. doi: 10.1016/j.pmn.2019.02.003

Poulsen, I., Brix, P., Andersen, S., Westergaard, L., and Guldager, R. (2016). Pain assessment scale for patients with disorders of consciousness: a preliminary validation study. *J. Neurosci. Nurs.* 48, 124–131. doi: 10.1097/JNN.0000000000000206

Purkayastha, S., Stokes, M., and Bell, K. (2019). Autonomic nervous system dysfunction in mild traumatic brain injury: a review of related pathophysiology and symptoms. *Brain Inj.* 33, 1129–1136. doi: 10.1080/02699052.2019.1631488

Racine, M., Tousignant-Laflamme, Y., Kloda, L., Dion, D., Dupuis, G., and Choinière, M. (2012). A systematic literature review of 10 years of research on sex/gender and experimental pain perception – Part 1: are there really differences between women and men? *Pain* 153, 602–618. doi: 10.1016/j.pain.2011.11.025

Rainville, P. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 277, 968–971. doi: 10.1126/science.277.5328.968

Raja, S., Carr, D., Cohen, M., Finnerup, N., Flor, H., Gibson, S., et al. (2020). The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. *Pain* 161, 1976–1982. doi: 10.1097/j.pain.0000000000001939

Ranger, M., and Gélinas, C. (2014). Innovating in pain assessment of the critically ill: exploring cerebral near-infrared spectroscopy as a bedside approach. *Pain Manag. Nurs.* 15, 519–529. doi: 10.1016/j.pmn.2012.03.005

Rice, D., Nijs, J., Kosek, E., Wideman, T., Hasenbring, M., Koltyn, K., et al. (2019). Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. *J. Pain* 20, 1249–1266. doi: 10.1016/j.jpain.2019.03.005

Riganello, F., Chatelle, C., Schnakers, C., and Laureys, S. (2019). Heart rate variability as an indicator of nociceptive pain in disorders of consciousness? *J. Pain Symptom Manag.* 57, 47–56. doi: 10.1016/j.jpainsymman.2018.09.016

Riganello, F., Larroque, S., Bahri, M., Heine, L., Martial, C., Carrière, M., et al. (2018). A heartbeat away from consciousness: heart rate variability entropy can discriminate disorders of consciousness and is correlated with resting-state fmri brain connectivity of the central autonomic network. *Front. Neurol.* 9:769. doi: 10.3389/fneur.2018.00769

Robertson, R., Crawford, L., Meylakh, N., Macey, P., Macefield, V., Keay, K., et al. (2022). Regional hypothalamic, amygdala, and midbrain periaqueductal gray matter recruitment during acute pain in awake humans: a 7-Tesla functional magnetic resonance imaging study. *Neuroimage* 259:119408. doi: 10.1016/j.neuroimage.2022.119408

Rogobete, A., Bedreag, O., Papurica, M., Popovici, S., Bratu, L., Rata, A., et al. (2021). Multiparametric monitoring of hypnosis and nociception-antinociception balance during general anesthesia—a new era in patient safety standards and healthcare management. *Medicina* 57:132. doi: 10.3390/medicina57020132

Rollnik, J. (2019). Clinical neurophysiology of neurologic rehabilitation. *Handb. Clin. Neurol.* 161, 187–194. doi: 10.1016/B978-0-444-64142-7.00048-5

Rosner, J., Scheuren, P., Stalder, S., Curt, A., and Hubli, M. (2020). Pinprick evoked potentials—reliable acquisition in healthy human volunteers. *Pain Med.* 21, 736–746. doi: 10.1093/pm/pnz126

Rousseau, M., Baumstarck, K., Alessandrini, M., Blandin, V., Billette de Villemeur, T., and Auquier, P. (2015). Quality of life in patients with locked-in syndrome: evolution over a 6-year period. *Orphanet J. Rare Dis.* 10:88. doi: 10.1186/s13023-015-0304-z

Rupawala, M., Dehghani, H., Lucas, S., Tino, P., and Cruse, D. (2018). Shining a light on awareness: a review of functional near-infrared spectroscopy for prolonged disorders of consciousness. *Front. Neurol.* 9:350. doi: 10.3389/fneur.2018.00350

Santiváñez-Acosta, R., Tapia-López, E., de las, N., and Santero, M. (2020). Music therapy in pain and anxiety management during labor: a systematic review and meta-analysis. *Medicina* 56:526. doi: 10.3390/medicina56100526

Sattin, D., Morganti, L., De Torres, L., Dolce, G., Arcuri, F., Estraneo, A., et al. (2017). Care pathways models and clinical outcomes in disorders of consciousness. *Brain Behav.* 7:e00740. doi: 10.1002/brb3.740

Schiff, N. (2015). Cognitive motor dissociation following severe brain injuries. *JAMA Neurol.* 72, 1413–1415. doi: 10.1001/jamaneurol.2015.2899

Schnakers, C., Chatelle, C., Vanhaudenhuyse, A., Majerus, S., Ledoux, D., Boly, M., et al. (2010). The nociception coma scale: a new tool to assess nociception in disorders of consciousness. *Pain* 148, 215–219. doi: 10.1016/j.pain.2009.09.028

Sclocco, R., Beissner, F., Desbordes, G., Polimeni, J., Wald, L., Kettner, N., et al. (2016). Neuroimaging brainstem circuitry supporting cardiovagal response to pain: a combined heart rate variability/ultrahigh-field (7 T) functional magnetic resonance imaging study. *Philos. Trans. R. Soc. A Math. Phys. Eng. Sci.* 374, 1–17. doi: 10.1098/rsta.2015.0189

Seyffert, S., Moiz, S., Coghlan, M., Balozian, P., Nasser, J., Rached, E., et al. (2022). Decreasing delirium through music listening (DDM) in critically ill, mechanically ventilated older adults in the intensive care unit: a two-arm, parallel-group, randomized clinical trial. *Trials* 23:576. doi: 10.1186/s13063-022-06448-w

Shrestha, P., Malla, H., Pant, B., and Taira, T. (2011). Intrathecal baclofen therapy in severe head injury, first time in Nepal, a technique suitable for underdeveloped countries. *Asian J. Neurosurg.* 6, 49–51. doi: 10.4103/1793-5482.85638

Skevington, S. (1998). Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. *Pain* 76, 395–406. doi: 10.1016/S0304-3959(98)00072-4

Sprenger, C., Bingel, U., and Büchel, C. (2011). Treating pain with pain: supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. *Pain* 152, 428–439. doi: 10.1016/j.pain.2010.11.018

Sugimine, S., Saito, S., and Takazawa, T. (2020). Normalized skin conductance level could differentiate physical pain stimuli from other sympathetic stimuli. *Sci. Rep.* 10:10950. doi: 10.1038/s41598-020-67936-0

The Multi-Society Task Force on PVS (1994). Medical aspects of the persistent vegetative state. *N. Engl. J. Med.* 330, 1499–1508. doi: 10.1056/NEJM199405263302107

Thibaut, A., Bodien, Y., Laureys, S., and Giacino, J. (2020). Minimally conscious state "plus": diagnostic criteria and relation to functional recovery. *J. Neurol.* 267, 1245–1254. doi: 10.1007/s00415-019-09628-y

Thibaut, A., Chatelle, C., Wannez, S., Deltombe, T., Stender, J., Schnakers, C., et al. (2015). Spasticity in disorders of consciousness A behavioral study. *Eur. J. Phys. Rehabil. Med.* 51, 389–397.

Thibaut, A., Panda, R., Annen, J., Sanz, L., Naccache, L., Martial, C., et al. (2021). Preservation of brain activity in unresponsive patients identifies MCS star. *Ann. Neurol.* 90, 89–100. doi: 10.1002/ana.26095

Thibaut, A., Schiff, N., Giacino, J., Laureys, S., and Gosseries, O. (2019). Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol.* 18, 600–614. doi: 10.1016/S1474-4422(19)30031-6

Thompson, T. (2019). The effectiveness of hypnosis for pain relief: a systematic review and meta-analysis of 85 controlled experimental trials. *Neurosci. Biobehav. Rev.* 99, 298–310. doi: 10.1016/j.neubiorev.2019.02.013

Tobaldini, E., Toschi-Dias, E., Trimarchi, P., Brena, N., Comanducci, A., Casarotto, S., et al. (2018). Cardiac autonomic responses to nociceptive stimuli in patients with chronic disorders of consciousness. *Clin. Neurophysiol.* 129, 1083–1089. doi: 10.1016/j.clinph.2018.01.068

Treede, R., Lorenz, J., and Baumgärtner, U. (2003). Clinical usefulness of laser-evoked potentials. *Clin. Neurophysiol.* 33, 303–314. doi: 10.1016/j.neucli.2003.10.009

Turk, D., Wilson, H., and Cahana, A. (2011). Treatment of chronic non-cancer pain. *Lancet* 377, 2226–2235. doi: 10.1016/S0140-6736(11)60402-9

van den Broeke, E., de Hemptinne, P., Mercken, M., Torta, D., Lambert, J., and Mouraux, A. (2020). Central sensitization of nociceptive pathways demonstrated by

robot-controlled pinprick-evoked brain potentials. *Clin. Neurophysiol.* 131, 2491–2498. doi: 10.1016/j.clinph.2020.06.020

Van Oosterwijck, J., Nijs, J., Meeus, M., and Paul, L. (2013). Evidence for central sensitization in chronic whiplash: a systematic literature review: systematic review: central sensitization in chronic WAD. *Eur. J. Pain* 17, 299–312. doi: 10.1002/j.1532-2149.2012.00193.x

Vanhaudenhuyse, A., Gillet, A., Malaise, N., Salamun, I., Grosdent, S., Maquet, D., et al. (2018). Psychological interventions influence patients' attitudes and beliefs about their chronic pain. *J. Tradit. Complement. Med.* 8, 296–302. doi: 10.1016/j.jtcme.2016.09.001

Varrassi, G., Müller-Schwefe, G., Pergolizzi, J., Orónska, A., Morlion, B., Margarit, C., et al. (2010). Pharmacological treatment of chronic pain – the need for CHANGE. *Curr. Med. Res. Opin.* 26, 1231–1245. doi: 10.1185/03007991003689175

Veinante, P., Yalcin, I., and Barrot, M. (2013). The amygdala between sensation and affect: a role in pain. *J. Mol. Psychiatry* 1:9. doi: 10.1186/2049-9256-1-9

Ventafridda, V., Saita, L., Ripamonti, C., and De Conno, F. (1985). WHO guidelines for the use of analgesics in cancer pain. *Int. J. Tissue React.* 7, 93–96.

Venturella, I., Crivelli, D., Fossati, M., Fiorillo, F., and Balconi, M. (2019). EEG and autonomic responses to nociceptive stimulation in disorders of consciousness. *J. Clin. Neurosci.* 60, 101–106. doi: 10.1016/j.jocn.2018.09.020

Vickers, A., Vertosick, E., Lewith, G., MacPherson, H., Foster, N., Sherman, K., et al. (2018). Acupuncture for chronic pain: update of an individual patient data meta-analysis. *J. Pain* 19, 455–474. doi: 10.1016/j.jpain.2017.11.005

Vink, P., Eskes, A., Lindeboom, R., van den Munckhof, P., and Vermeulen, H. (2014). Nurses assessing pain with the nociception coma scale: interrater reliability and validity. *Pain Manag. Nurs.* 15, 881–887. doi: 10.1016/j.pmn.2014.01.004

Vink, P., Lucas, C., Maaskant, J., van Erp, W., Lindeboom, R., and Vermeulen, H. (2017). Clinimetric properties of the nociception coma scale (-Revised): a systematic review. *Eur. J. Pain* 21, 1463–1474. doi: 10.1002/ejp.1063

Warden, V., Hurley, A., and Volicer, L. (2003). Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale. *J. Am. Med. Direct. Assoc.* 4, 9–15. doi: 10.1097/01.JAM.0000043422.31640.F7

Whyte, J., Poulsen, I., Ni, P., Eskildsen, M., and Guldager, R. (2020). Development of a measure of nociception for patients with severe brain injury. *Clin. J. Pain* 36, 281–288. doi: 10.1097/AJP.0000000000000811

Youssef, A., Macefield, V., and Henderson, L. (2016). Pain inhibits pain; human brainstem mechanisms. *Neuroimage* 124, 54–62. doi: 10.1016/j.neuroimage.2015.08.060

Yuan, I., Nelson, O., Bar, G., Zhang, B., Topjian, A., DiMaggio, T., et al. (2022). Functional near-infrared spectroscopy to assess pain in neonatal circumcisions. *Paediatr. Anaesth.* 32, 404–412. doi: 10.1111/pan.14326

Yücel, M., Aasted, C., Petkov, M., Borsook, D., Boas, D., and Becerra, L. (2015). Specificity of hemodynamic brain responses to painful stimuli: a functional near-infrared spectroscopy study. *Sci. Rep.* 5:9469. doi: 10.1038/srep09469

Zanatta, P., Linassi, F., Mazzarolo, A., Aricò, M., Bosco, E., Bendini, M., et al. (2015). Pain-related somato sensory evoked potentials: a potential new tool to improve the prognostic prediction of coma after cardiac arrest. *Crit. Care* 19:403. doi: 10.1186/s13054-015-1119-y

Zanatta, P., Messerotti Benvenuti, S., Baldanzi, F., Bendini, M., Saccavini, M., Tamari, W., et al. (2012). Pain-related somatosensory evoked potentials and functional brain magnetic resonance in the evaluation of neurologic recovery after cardiac arrest: a case study of three patients. *Scand. J. Trauma Resuscitation Emerg. Med.* 20:22. doi: 10.1186/1757-7241-20-22

Zasler, N., Formisano, R., and Aloisi, M. (2022). Pain in persons with disorders of consciousness. *Brain Sci.* 12:300. doi: 10.3390/brainsci12030300

Zhang, B., Karri, J., O'Brien, K., DiTommaso, C., Kothari, S., and Li, S. (2021). Spasticity management in persons with disorders of consciousness. *Phys. Med. Rehabil.* 13, 657–665. doi: 10.1002/pmrj.12458

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Cerebellar control of thalamocortical circuits for cognitive function: A review of pathways and a proposed mechanism

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There is general agreement that cerebrocerebellar interactions *via* cerebellothalamocortical pathways are essential for a cerebellar cognitive and motor functions. Cerebellothalamic projections were long believed target mainly the ventral lateral (VL) and part of the ventral anterior (VA) nuclei, which project to cortical motor and premotor areas. Here we review new insights from detailed tracing studies, which show that projections from the cerebellum to the thalamus are widespread and reach almost every thalamic subnucleus, including nuclei involved in cognitive functions. These new insights into cerebellothalamic pathways beyond the motor thalamus are consistent with the increasing evidence of cerebellar cognitive function. However, the function of cerebellothalamic pathways and how they are involved in the various motor and cognitive functions of the cerebellum is still unknown. We briefly review literature on the role of the thalamus in coordinating the coherence of neuronal oscillations in the neocortex. The coherence of oscillations, which measures the stability of the phase relationship between two oscillations of the same frequency, is considered an indicator of increased functional connectivity between two structures showing coherent oscillations. Through thalamocortical interactions coherence patterns dynamically create and dissolve functional cerebral cortical networks in a task dependent manner. Finally, we review evidence for an involvement of the cerebellum in coordinating coherence of oscillations between cerebral cortical structures. We conclude that cerebellothalamic pathways provide the necessary anatomical substrate for a proposed role of the cerebellum in coordinating neuronal communication between cerebral cortical areas by coordinating the coherence of oscillations.

KEYWORDS

cerebellum, cognition, communication through coherence (CTC), cerebrocerebellar communication, cerebellothalamic tract, corticothalamic circuits

Introduction

A defining characteristic of cerebral cortical function is interaction between multiple cerebral cortex areas forming a temporary task-specific functional network [e.g., (Damasio, 1989; Vaadia et al., 1995; Mesulam, 1998; Ayzenshtat et al., 2010)]. The formation and resolution of such task specific network involves precisely coordinated modulation of functional connectivity, defined as periods of increased correlation of neuronal activity (Aertsen et al., 1989; Vaadia et al., 1995). How functional connectivity is modulated at time scales compatible with normal brain function is not fully understood but evidence suggests a crucial role of the thalamus in coordinating functional connectivity between cerebral cortical areas in a task dependent manner (Ketz et al., 2015; Nakajima and Halassa, 2017; Schmitt et al., 2017). The term functional connectivity in essence describes the temporal correlation of neuronal activity between two structures measured as spike activity, local field potentials or using BOLD signals (Aertsen et al., 1989; Buckner et al., 2013). In a seminal publication, Pascal Fries proposed a mechanism for controlling functional connectivity between brain structures through the modulation of coherence of their neuronal oscillations (Fries, 2005), a mechanism he termed "communication through coherence" (CTC). Coherence of oscillations is a measure of how stable the phase relation between two oscillations of similar frequency is. Typically, coherence values change in a task dependent manner. One of the best studied examples of task related coherence increases occurs between the prefrontal cortex and dorsal hippocampus during decision making in spatial memory tasks (Benchenane et al., 2010; Gordon, 2011; Liu et al., 2022). The concept of communication through coherence has since received substantial support from experiments showing that coherence changes do indeed correlate with changes in the effectiveness of neuronal signal (i.e., spike) transmission (e.g., McAfee et al., 2018) and that changes in coherence are linked to specific behaviors, with memory and working memory related behaviors amongst the most thoroughly studied (Fell and Axmacher, 2011; Gordon, 2011; Brincat and Miller, 2015; Liu et al., 2022).

The concept of CTC thus provides an intriguing neuronal mechanism for modulating information flow and integration through the modulation of functional connectivity. Coherence and synchrony between cerebral cortical areas is known to critically depend on the thalamus and thalamocortical connectivity (Destexhe et al., 1999; Jones, 2001; Habas et al., 2009; Browning et al., 2015; Ketz et al., 2015; Mitchell, 2015; Hallock et al., 2016; Nakajima and Halassa, 2017). What is unknown, however, is how changes in coherence are controlled. Besides its massive interconnection with the cerebral cortex, the thalamus is also the key relay station for interactions between the cerebellum and the cerebral cortex (Allen and Tsukahara, 1974; Angaut et al., 1985; Habas et al., 2019). New anatomical studies have revealed that projections from the cerebellum to the thalamus are far richer and more widespread than previously believed and include numerous thalamic nuclei involved in cognitive functions (Habas et al., 2019; Fujita et al., 2020; Pisano et al., 2021). Considering the crucial role of the thalamus in modulating coherence and synchrony between cerebral cortical areas (Destexhe et al., 1999; Jones, 2001; Habas et al., 2009; Browning et al., 2015; Ketz et al., 2015; Mitchell, 2015; Hallock et al., 2016; Nakajima and Halassa, 2017), cerebellothalamic projections provide a robust interface for the cerebellum modulate thalamic activity and thus shape thalamocortical interactions. Here we review (1) evidence for the role of the thalamus in coordinating synchrony and functional connectivity between cerebral cortical areas, (2) recent literature that revealed rich projections from the cerebellum to nearly all subnuclei of the thalamus and (3) the evidence of a cerebellar involvement in coordinating coherence of oscillations in the cerebral cortex. We will focus on cerebellothalamic pathways that are likely to be involved in spatial working memory and will review a proposed new function of the cerebellum in the task-dependent coordination of functional connectivity between the medial prefrontal cortex (mPFC) and the dorsal hippocampus. The mediodorsal nucleus (MD) and nucleus reuniens (RE) of the thalamus deserve particular attention in this context due to their dense reciprocal connections to the prefrontal cortex and the reported role of the RE in coordinating coherence between the mPFC and hippocampus (Vertes et al., 2007; Browning et al., 2015; Ito et al., 2015; Ketz et al., 2015; Mitchell, 2015).

Cerebellothalamic pathways to support sensorimotor and cognitive functions

The thalamus can be divided into two major regions–the dorsal region, containing anterior, lateral, medial, and posterior groups of nuclei, and the ventral region, made up of the thalamic reticular nucleus (TRN). The dorsal region is made of both glutaminergic projections and GABAergic interneurons, that receive input broadly from the cortex, subcortical structures, areas of the brainstem, and the cerebellum and project to localized areas of the cortex and striatum. The TRN only receives collateral projections from thalamocortical and corticothalamic neurons involved in somatosensory, sensory, and motor processes and provides exclusively GABAergic input to the dorsal thalamus (Habas et al., 2019). Traditional views associated the cerebellum solely with sensorimotor and vestibular functions and the pathways from the cerebellum to the thalamus were thought to be limited to projections from the cerebellar nuclei (CN) to the ventral or motor thalamus–specifically to the ventrolateral (VL) and parts of the ventral anterior (VA) nuclei. Recent comprehensive tracing studies have revealed far more extensive connections between the CN and the thalamus, including thalamic nuclei involved in cognitive functions (Bohne et al., 2019; Fujita et al., 2020; Pisano et al., 2021).

Bohne et al. (2019) confirmed dense projections between the fastigial, interposed, and dentate cerebellar nuclei and VL but also found new projections in the laterodorsal thalamic nucleus. Tracing experiments by Fujita et al. (2020) discovered broad connections between the fastigial nucleus of the cerebellum to several subnuclei throughout the thalamus, including the MD, VL, VM, and centrolateral (CL), and parafascicular nuclei. Pisano et al. (2021) performed a detailed study of

cerebellothalamocortical pathways using trans-synaptic tracing methods. Their results also show CN projections to multiple thalamic nuclei outside of the ventral thalamus, including the MD, TRN, lateral posterior nucleus, lateral and medial geniculate nuclei, and zona incerta. Tracing experiments primarily targeted the dentate, with some expression in the interposed and fastigial nuclei. Retrograde tracing studies found axons from both the dentate and interposed nuclei in the TRN.

These findings that cerebellar projections from all three cerebellar nuclei target the thalamic nuclei involved in cognitive functions such as the MD, CL, and TRN align well with the now substantial evidence of cerebellar cognitive and affective functions (Schmahmann, 2004; Ito, 2008; Buckner, 2013; Liu et al., 2022). Detailed physiological studies of the different cerebellothalamic pathways furthermore revealed substantial pathway-specific differences in cerebellar influence on thalamic target neurons. While it was known that cerebellothalamic projections were excitatory, it turns out that the impact cerebellar projections have on postsynaptic thalamic neurons varies greatly between thalamic target nuclei (Gornati et al., 2018). Gornati et al. (2018) investigated projections from the interposed nucleus to the VL, VM, and CL thalamic nuclei and found significant differences in the sizes and density of synaptic terminals and the amplitude of postsynaptic responses. For example, glutamatergic projection terminals from the CN to the VL thalamus were significantly higher in density, displayed more complex synaptic interactions, and resulted in greater excitatory post-synaptic potentials than CN projections to the CL. Different cerebellothalamic pathways also differ in the way cerebellar-receiving thalamic neurons affect neuronal activity in their respective cerebral cortical target areas. VL thalamus has been associated with parvalbumin-positive neurons, which are found more densely in sensorimotor cortices, hippocampal, and retrohippocampal regions and are associated with spatial navigation and sensorimotor skills (Miao et al., 2017; Gornati et al., 2018; Bjerke et al., 2021). Cerebellar-receiving VL nucleus cells can also be categorized as "driver" inputs to the cortex, which further indicates a role in information processing and ongoing activity adaptation. While cerebellar projections to the VM and CL nuclei did not display significant synaptic differences from each other, the thalamocortical projections from the VM and CL nuclei are markedly different from those of the ventrolateral thalamic nuclei both in projection patterns and binding protein (Gornati et al., 2018). For example, VM and CL thalamic nuclei contain higher densities of calbindin-positive neurons and project to brain regions involved in behavior and emotion, including the infralimbic cortex, ventral tegmental area, anterior cingulate cortex, midbrain raphe nuclei, and periaqueductal gray (Van der Werf et al., 2002; Bjerke et al., 2021).

Taken together these findings show that cerebellothalamocortical pathways seem to involve most if not all of the thalamic nuclei, fitting with the rich repertoire of cerebellar motor, cognitive and affective functions. Our understanding of the physiological properties and differences between these pathways is in its infancy and an in depth investigation is essential to any attempt at understanding cerebellar contribution to brain functions.

Sensorimotor functions

Sensory feedback continuously informs motor planning, and the cerebellar contribution mostly from the medial and interposed nuclei to this ongoing process provides a concrete example of its influence on motor cortical areas *via* the thalamus, which can be evaluated through effective execution of movements. Looking to the vibrissal system of rodents as a well-characterized model system where sensory input and motor output can be ascertained, the effect of sensory feedback on motor planning is made apparent by changes in whisking behavior as an animal encounters a tactile stimulus. Rodents tend to perform slow, low-amplitude sweeps with their whiskers in familiar environments, but then transition to rapid high-amplitude sweeps in a novel environment or when a novel stimulus is encountered (Arkley et al., 2014). For this behavioral adaptation to be effective however, there must be a mechanism for streams of sensory information to reach cortices responsible for motor planning and execution.

There are three (non-mutually exclusive) mechanisms established in functional and neuroanatomical descriptions of the rodent vibrissal system that allow sensory information to reach the motor cortex. First, a direct pathway between whisker sensory cortex (vS1) and the facial nuclei for whisker retraction allows for sensory input during whisker protraction to directly initiate retraction behavior (Matyas et al., 2010). This primes the system for more rapid protraction and active sensing when there is an object in the vibrissal field to be explored. Second, vS1 activates motor cortices for whisker retraction *via* cortico-cortical projections (Matyas et al., 2010; Mao et al., 2011), after vS1 itself is excited by tactile input. And third, neurons of cerebellar crus I and II integrate sensory and motor information streams *via* pontine and trigeminocerebellar mossy fiber inputs, and convey this combined sensorimotor information to whisker motor cortex (vM1) by way of the VL thalamic nuclei (Proville et al., 2014).

Importantly, experiments have shown that both the second and third mechanisms rely on cerebellar modulation of thalamic activity for effective somatomotor integration. In the less-obvious case of cortico-cortical communication between vS1 and vM1, synchronous rhythms between structures that promote this form of communication require an intact cerebellum (Popa et al., 2013; Lindeman et al., 2021). Using various methods to inhibit the cerebellar nuclei, it has been shown that cerebellar inactivation reduces the firing rate in motor thalamic neurons (Popa et al., 2013), decreases gamma-rhythmic coherence between vS1 and vM1 (Popa et al., 2013; Lindeman et al., 2021), and impairs the ability of animal to adapt whisking strategies appropriately in a changing sensory context (Proville et al., 2014).

Execution of head, limb, eye, or truncal movements may rely on different or additional pathways for sensory feedback in motor planning, but the available evidence suggests that cerebellothalamocortical pathways are crucial for the planning and execution of these movements as well. Each of these somatic regions exhibit robust representation within the cerebellum (Grodd et al., 2001; Manni and Petrosini, 2004;

Grimaldi and Manto, 2012), with evidence of integrated sensory and motor representations (Wiestler et al., 2011). Somatic areas exhibit robust correlation with corresponding regions of the motor cortex (Buckner et al., 2011; Saadon-Grosman et al., 2022), which are connected *via* thalamic nuclei. Therefore, the cerebellar contribution to motor planning in other somatic domains is likely to be similar in principle to the mechanisms outlined here, albeit more complex with the execution of more complex movements in a more spatially complex environment.

Cognitive functions

In the following two sections we will discuss the roles of the MD thalamic nucleus and the nucleus reuniens (RE) in shaping cerebral cortical activity and cognitive function. The MD nucleus prominently projects to the mPFC, an area of cerebral cortex widely associated with cognitive function (Guldin et al., 1981) and these projections allow patterns of prefrontal activity to persist when task-relevant information needs to be held in mind. The RE has been shown to play a key role in coordinating the coherence of neuronal oscillations, and hence the functional connectivity, between the medial prefrontal cortex and the hippocampus (Hallock et al., 2016) which is critical for spatial working memory (SWM) and navigation.

Mediodorsal nucleus

As a general rule, thalamic activity directs the flow of information to and throughout the neocortex. For lower sensory cortical areas, the role of the thalamus is manifest as a sort of sensory relay station, where thalamic impulses modulate excitability at appropriate times and convey specific sensory information to cortical neurons. For higher-order areas like the PFC, the thalamus conveys no specific information, but instead seems to modulate the tone of cortical neurons in a manner that is topographically selective and precisely timed for the gating and maintenance of task-relevant information (Mitchell, 2015; Schmitt et al., 2017; Honjoh et al., 2018). The mediodorsal (MD) thalamic nucleus is interconnected with the prefrontal cortex in mammals (Guldin et al., 1981; Ray and Price, 1993; Kuramoto et al., 2017), and the timing of MD activity affects the flow of information on two different timescales. First, on the order of hundreds of milliseconds, increased MD activity signals that sensory information is being presented which is relevant to gain a future reward. On the timescale of milliseconds, sustained MD activity drives fast interneuron rhythms while disinhibiting principal neurons (Anastasiades et al., 2020), promoting communication between principal neurons that signal coherently with the inhibitory rhythm. The result, as demonstrated by Schmitt et al. (2017) is thalamic activity that promotes precisely timed communication between cortical neurons that are tuned to common information, which is thought to help sustain the neuronal representation of that information during a delay period.

How the MD is activated on the broader timescale in an appropriate manner for a given task has not yet been fully explored. Some of this thalamic recruitment is thought to occur as a top-down phenomenon, initiated by the PFC itself when conscious effort is made to maintain information in mind for decision-making. The cerebellum is well positioned to assist in the task-relevant modulation of MD as well, and likely plays a role that is mechanistically similar to how it promotes functional connectivity within the sensorimotor system. In rodents, the fastigial nuclei project to the lateral MD thalamic nuclei (Fujita et al., 2020), which in turn project to the prelimbic prefrontal cortex to modulate inter-neuronal communication (Divac et al., 1993; Kuramoto et al., 2017). Functional circuit mapping techniques in rodents have shown that projections to the cerebellum (*via* the pons) from the prelimbic PFC predominantly terminate within the lateral vermis (Watson et al., 2009), which in turn project to the fastigial nuclei to close the circuit (Fujita et al., 2020). Given the known anatomy, the cerebellum could have a supportive role in recruiting the MD nuclei in response to PFC activity. Additionally, the vermal cortex that provides input to the fastigial nuclei may serve as a substrate for potential predictive activation of MD in the appropriate sensory context, but further information is needed as to what sources of input converge in the vermis.

In humans, the prefrontal cortices and neocerebellum are selectively expanded in comparison to rodents (Balsters et al., 2010), and primates show more numerous and extensive pathways connecting the cerebellum, thalamic nuclei, and prefrontal cortex. In human imaging studies, MD shows a broader functional relationship with the cerebellar hemispheres, which is notably diminished in patients with schizophrenia (Anticevic et al., 2014).

Nucleus Reuniens

We focus on the mPFC and hippocampus because several independent studies have shown that SWM requires the coordinated activity of the mPFC and dorsal hippocampus (Churchwell and Kesner, 2011; Gordon, 2011). Simultaneous electrophysiological recordings in the mPFC and hippocampus during performance of SWM tasks have shown that the decision process is associated with an increase in the coherence of theta oscillations between the mPFC and dorsal hippocampus (Jones and Wilson, 2005; Hyman et al., 2010; Benchenane et al., 2011; Gordon, 2011; Liu et al., 2022). A comparison of correct and incorrect decisions revealed that mPFC-hippocampal theta coherence reached higher values during correct compared to incorrect decisions, supporting a functional role of coherence in this task (Jones and Wilson, 2005; Hyman et al., 2010; Liu et al., 2022). Coherence of neuronal oscillations does not impact brain function unless it affects changes in spike activity within the communicating regions. It is important to note that in the context of SWM two studies measured both spike activity and local field potential (LFP) coherence and showed that an increase in coherence was accompanied by an increase in entrainment of mPFC spike activity to the phase of the coherent mPFC-hippocampal theta oscillations (Jones and Wilson, 2005; Hyman et al., 2010). For additional examples of experimental support an influence of coherence on

spike activity see also (Jones and Wilson, 2005; Siegel et al., 2008; Bosman et al., 2012; Brunet et al., 2014; Sigurdsson and Duvarci, 2016; Bonnefond et al., 2017; Palmigiano et al., 2017; McAfee et al., 2018). Thus, changes in coherence between the mPFC and hippocampus are strongly implicated in SWM. The thalamic nuclei involved in controlling mPFC-hippocampal coherence could thus serve as the interface for cerebellar contributions to SWM decision making which involves cerebellar lobulus simplex as recently reported in mice performing a SWM task (Liu et al., 2022).

When considering the influence of the cerebellar cortex on mPFC-hippocampal coherence during SWM decision making, the RE is a possible key thalamic nucleus involved in the modulation of that coherence. Neurons in the RE receive excitatory inputs from the prelimbic and infralimbic areas of mPFC and in turn send dense excitatory projections to dorsal CA1 region of the hippocampus (Vertes et al., 2007). While direct ventral hippocampal projections to mPFC had already been established (Ferino et al., 1987; Carr and Sesack, 1996) this tracing study showed that hippocampal-prefrontal connectivity was in fact reciprocal *via* the RE. Additional tracing studies have also identified populations of RE cells that send collaterals to both mPFC and hippocampus (Hoover and Vertes, 2007; Varela et al., 2014), establishing bidirectional connectivity between mPFC and RE. The functional implications of this pathway have since been further explored in the context of working memory (Hallock et al., 2013; Ito et al., 2015).

Dolleman-van et al. (2019) and Griffin (2021) wrote comprehensive reviews about the role of RE in coordinating hippocampal-prefrontal interactions during working memory. One report central to both these reviews was a study from Ito et al. (2015) which showed that neurons in the mPFC, RE, and CA1 in rats exhibited trajectory-dependent firing in a continuous alternation task using a modified T-maze. Trajectory-dependent firing is a key component to spatial navigation in that it contains predictive information about future positions as well as instantaneous position, which is crucial to establishing a "goal path." Permanent inactivation of RE *via* lesions significantly impaired trajectory-dependent firing in CA1. Transient optogenetic inactivation of RE neurons also led to a significant decrease of trajectory-dependent firing in CA1. This study shows that projections from mPFC to CA1 *via* RE are crucial for trajectory-dependent firing in CA1 and provides additional evidence for the role of thalamic nuclei in coordinating long-range communication between cortical regions (Ito et al., 2015).

In addition to RE's role in facilitating trajectory-dependent firing, new work has shown that RE contributes to the coordination and stabilization of neuronal assemblies within mPFC and hippocampus (Angulo-Garcia et al., 2020). In experiments using anesthetized rats and *in vivo* electrophysiology, it was shown that assemblies of RE neurons activate sequentially during "up states" of slow LFP oscillations, which preceded activation of mPFC assemblies. "Up states" are defined as the periods from the peak to the trough of the filtered slow oscillation LFP signal. Chemogenetic inactivation of RE disrupted mPFC assembly onset during up states as well as hippocampal assemblies present during sharp wave ripples. The authors suggest that RE may be necessary to stabilize mPFC and hippocampal cell assemblies. This report provides further evidence that RE is a functional hub for prefrontal-hippocampal interactions (Angulo-Garcia et al., 2020).

We currently know little about cerebellar projections to RE. The most detailed recent tracing studies suggest that projections exist but might be sparse (Fujita et al., 2020; Pisano et al., 2021). More focused studies are required to determine the extent and physiological effectiveness of cerebellar influence on the RE.

Summary

Understanding the broad involvement of the cerebellum in motor, affective and cognitive brain function it is essential to gain a detailed understanding of the pathways that connect the cerebellum with the cerebral cortex *via* the thalamus. We have reviewed rich new evidence showing that cerebellar projections from all three cerebellar nuclei seem to reach most, if not all nuclei of the thalamus and that each of these pathways may have unique physiological properties in terms of cerebellar influence on thalamic neurons and in terms of the influence of cerebellar receiving thalamic neurons on the cerebral cortex. Clearly, in order to understand the role of the cerebellum in its various functions that require cerebrocerebellar interactions, the cerebellothalamocortical pathways must be a major focus of future investigations.

Author contributions

DH developed the concept of the review. DH, MF, BC, SM, and YL jointly wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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References

Aertsen, A. M. H. J., Gerstein, G. L., Habib, M. D., and Palm, G. (1989). Dynamics of neuronal firing correlation: Modulation of "effective connectivity". *J. Neurophysiol.* 61, 900–917.

Allen, G. I., and Tsukahara, N. (1974). Cerebrocerebellar communication systems. *Physiol. Rev.* 54, 957–1006.

Anastasiades, P. G., Collins, D. P., and Carter, A. G. (2020). Mediodorsal and ventromedial thalamus engage distinct L1 circuits in the prefrontal cortex. *Neuron* 109, 314–330.e4. doi: 10.1016/j.neuron.2020.10.031

Angaut, P., Cicirata, F., and Serapide, F. (1985). Topographic organization of the cerebellothalamic projections in the rat. An autoradiographic study. *Neuroscience* 15, 389–401. doi: 10.1016/0306-4522(85)90221-0

Angulo-Garcia, D., Ferraris, M., Ghestem, A., Nallet-Khosrofian, L., Bernard, C., and Quilichini, P. P. (2020). Cell assemblies in the cortico-hippocampal-reuniens network during slow oscillations. *J. Neurosci.* 40, 8343–8354. doi: 10.1523/JNEUROSCI.0571-20.2020

Anticevic, A., Yang, G., Savic, A., Murray, J. D., Cole, M. W., Repovs, G., et al. (2014). Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis history. *Schizophr. Bull.* 40, 1227–1243. doi: 10.1093/schbul/sbu100

Arkley, K., Grant, R. A., Mitchinson, B., and Prescott, T. J. (2014). Strategy change in vibrissal active sensing during rat locomotion. *Curr. Biol.* 24, 1507–1512. doi: 10.1016/j.cub.2014.05.036

Ayzenshtat, I., Meirovithz, E., Edelman, H., Werner-Reiss, U., Bienenstock, E., Abeles, M., et al. (2010). Precise spatiotemporal patterns among visual cortical areas and their relation to visual stimulus processing. *J. Neurosci.* 30, 11232–11245.

Balsters, J. H., Cussans, E., Diedrichsen, J., Phillips, K. A., Preuss, T. M., Rilling, J. K., et al. (2010). Evolution of the cerebellar cortex: The selective expansion of prefrontal-projecting cerebellar lobules. *Neuroimage* 49, 2045–2052. doi: 10.1016/j.neuroimage.2009.10.045

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., et al. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. *Neuron* 66, 921–936. doi: 10.1016/j.neuron.2010.05.013

Benchenane, K., Tiesinga, P. H., and Battaglia, F. P. (2011). Oscillations in the prefrontal cortex: A gateway to memory and attention. *Curr. Opin. Neurobiol.* 21, 475–485. doi: 10.1016/j.conb.2011.01.004

Bjerke, I. E., Yates, S. C., Laja, A., Witter, M. P., Puchades, M. A., Bjaalie, J. G., et al. (2021). Densities and numbers of calbindin and parvalbumin positive neurons across the rat and mouse brain. *iScience* 24:101906. doi: 10.1016/j.isci.2020.101906

Bohne, P., Schwarz, M. K., Herlitze, S., and Mark, M. D. (2019). A new projection from the deep cerebellar nuclei to the hippocampus via the ventrolateral and laterodorsal thalamus in mice. *Front. Neural Circuits* 13:51. doi: 10.3389/fncir.2019.00051

Bonnefond, M., Kastner, S., and Jensen, O. (2017). Communication between brain areas based on nested oscillations. *eNeuro* 4:ENEURO.0153-16.2017. doi:10.1523/ENEURO.0153-16.2017

Bosman, C. A., Schoffelen, J. M., Brunet, N., Oostenveld, R., Bastos, A. M., Womelsdorf, T., et al. (2012). Attentional stimulus selection through selective synchronization between monkey visual areas. *Neuron* 75, 875–888. doi: 10.1016/j.neuron.2012.06.037

Brincat, S. L., and Miller, E. K. (2015). Frequency-specific hippocampal-prefrontal interactions during associative learning. *Nat. Neurosci.* 18, 576–581. doi: 10.1038/nn.3954

Browning, P. G., Chakraborty, S., and Mitchell, A. S. (2015). Evidence for mediodorsal thalamus and prefrontal cortex interactions during cognition in macaques. *Cereb. Cortex* 25, 4519–4534. doi: 10.1093/cercor/bhv093

Brunet, N. M., Bosman, C. A., Vinck, M., Roberts, M., Oostenveld, R., Desimone, R., et al. (2014). Stimulus repetition modulates gamma-band synchronization in primate visual cortex. *Proc. Natl. Acad. Sci. U.S.A.* 111, 3626–3631. doi: 10.1073/pnas.1309714111

Buckner, R. L. (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron* 80, 807–815. doi:10.1016/j.neuron.2013.10.044

Buckner, R. L., Krienen, F. M., and Yeo, B. T. (2013). Opportunities and limitations of intrinsic functional connectivity MRI. *Nat. Neurosci.* 16, 832–837. doi: 10.1038/nn.3423

Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., and Yeo, B. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *J. Neurophysiol.* 106, 2322–2345. doi: 10.1152/jn.00339.2011

Carr, D. B., and Sesack, S. R. (1996). Hippocampal afferents to the rat prefrontal cortex: Synaptic targets and relation to dopamine terminals. *J. Comp. Neurol.* 369, 1–15. doi: 10.1002/(SICI)1096-9861(19960520)369:1<1::AID-CNE1>3.0.CO;2-7

Churchwell, J. C., and Kesner, R. P. (2011). Hippocampal-prefrontal dynamics in spatial working memory: Interactions and independent parallel processing. *Behav. Brain Res.* 225, 389–395. doi: 10.1016/j.bbr.2011.07.045

Damasio, A. R. (1989). Time-locked multiregional retroactivation: A systems-level proposal for the neural substrates of recall and recognition. *Cognition* 33, 25–62. doi: 10.1016/0010-0277(89)90005-x

Destexhe, A., Contreras, D., and Steriade, M. (1999). Cortically-induced coherence of a thalamic-generated oscillation. *Neuroscience* 92, 427–443. doi: 10.1016/s0306-4522(99)00024-x

Divac, I., Mogensen, J., Petrovic-Minic, B., Zilles, K., and Regidor, J. (1993). Cortical projections of the thalamic mediodorsal nucleus in the rat. Definition of the prefrontal cortex. *Acta Neurobiol. Exp. (Wars)* 53, 425–429.

Dolleman-van, M. J., der Weel, A. L., Griffin, H. T. Ito, Shapiro, M. L., Witter, M. P., Vertes, R. P., et al. (2019). The nucleus reuniens of the thalamus sits at the nexus of a hippocampus and medial prefrontal cortex circuit enabling memory and behavior. *Learn. Mem.* 26, 191–205. doi: 10.1101/lm.048389.118

Fell, J., and Axmacher, N. (2011). The role of phase synchronization in memory processes. *Nat. Rev. Neurosci.* 12, 105–118. doi: 10.1038/nrn2979

Ferino, F., Thierry, A. M., and Glowinski, J. (1987). Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex in the rat. *Exp. Brain Res.* 65, 421–426. doi: 10.1007/BF00236315

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends Cogn. Sci.* 9, 474–480.

Fujita, H., Kodama, T., and du Lac, S. (2020). Modular output circuits of the fastigial nucleus for diverse motor and nonmotor functions of the cerebellar vermis. *Elife* 9:e58613. doi: 10.7554/eLife.58613

Gordon, J. A. (2011). Oscillations and hippocampal-prefrontal synchrony. *Curr. Opin. Neurobiol.* 21, 486–491. doi: 10.1016/j.conb.2011.02.012

Gornati, S. V., Schafer, C. B., Eelkman Rooda, O. H. J., Nigg, A. L., De Zeeuw, C. I., and Hoebeek, F. E. (2018). Differentiating cerebellar impact on thalamic nuclei. *Cell Rep.* 23, 2690–2704. doi: 10.1016/j.celrep.2018.04.098

Griffin, A. L. (2021). The nucleus reuniens orchestrates prefrontal-hippocampal synchrony during spatial working memory. *Neurosci. Biobehav. Rev.* 128, 415–420. doi: 10.1016/j.neubiorev.2021.05.033

Grimaldi, G., and Manto, M. (2012). Topography of cerebellar deficits in humans. *Cerebellum* 11, 336–351. doi: 10.1007/s12311-011-0247-4

Grodd, W., Hulsmann, E., Lotze, M., Wildgruber, D., and Erb, M. (2001). Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. *Hum. Brain Mapp.* 13, 55–73.

Guldin, W. O., Pritzel, M., and Markowitsch, H. J. (1981). Prefrontal cortex of the mouse defined as cortical projection area of the thalamic mediodorsal nucleus. *Brain Behav. Evol.* 19, 93–107. doi: 10.1159/000121636

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C. F., Menon, V., et al. (2009). Distinct cerebellar contributions to intrinsic connectivity networks. *J. Neurosci.* 29, 8586–8594.

Habas, C., Manto, M., and Cabaraux, P. (2019). The cerebellar thalamus. *Cerebellum* 18, 635–648. doi: 10.1007/s12311-019-01019-3

Hallock, H. L., Wang, A., and Griffin, A. L. (2016). Ventral midline thalamus is critical for hippocampal-prefrontal synchrony and spatial working memory. *J. Neurosci.* 36, 8372–8389. doi: 10.1523/JNEUROSCI.0991-16.2016

Hallock, H. L., Wang, A., Shaw, C. L., and Griffin, A. L. (2013). Transient inactivation of the thalamic nucleus reuniens and rhomboid nucleus produces deficits of a working-memory dependent tactile-visual conditional discrimination task. *Behav. Neurosci.* 127, 860–866. doi: 10.1037/a0034653

Honjoh, S., Sasai, S., Schiereck, S. S., Nagai, H., Tononi, G., and Cirelli, C. (2018). Regulation of cortical activity and arousal by the matrix cells of the ventromedial thalamic nucleus. *Nat. Commun.* 9:2100. doi: 10.1038/s41467-018-04497-x

Hoover, W. B., and Vertes, R. P. (2007). Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Struct. Funct.* 212, 149–179. doi: 10.1007/s00429-007-0150-4

Hyman, J. M., Zilli, E. A., Paley, A. M., and Hasselmo, M. E. (2010). Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front. Integr. Neurosci.* 4:2. doi: 10.3389/neuro.07.002.2010

Ito, H. T., Zhang, S. J., Witter, M. P., Moser, E. I., and Moser, M. B. (2015). A prefrontal-thalamo-hippocampal circuit for goal-directed spatial navigation. *Nature* 522, 50–55. doi: 10.1038/nature14396

Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nat. Rev. Neurosci.* 9, 304–313. doi: 10.1038/nrn2332

Jones, E. G. (2001). The thalamic matrix and thalamocortical synchrony. *Trends Neurosci.* 24, 595–601. doi: 10.1016/s0166-2236(00)01922-6

Jones, M. W., and Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3:e402. doi: 10.1371/journal.pbio.0030402

Ketz, N. A., Jensen, O., and O'Reilly, R. C. (2015). Thalamic pathways underlying prefrontal cortex-medial temporal lobe oscillatory interactions. *Trends Neurosci.* 38, 3–12. doi: 10.1016/j.tins.2014.09.007

Kuramoto, E., Pan, S., Furuta, T., Tanaka, Y. R., Iwai, H., Yamanaka, A., et al. (2017). Individual mediodorsal thalamic neurons project to multiple areas of the rat prefrontal cortex: A single neuron-tracing study using virus vectors. *J. Comp. Neurol.* 525, 166–185. doi: 10.1002/cne.24054

Lindeman, S., Kros, L., Hong, S., Mejias, J. F., Romano, V., Negrello, M., et al. (2021). Cerebellar Purkinje cells can differentially modulate coherence between sensory and motor cortex depending on region and behavior. *Proc. Natl. Acad. Sci. U.S.A.* 118, e2015292118. doi: 10.1073/pnas.2015292118

Liu, Y., McAfee, S. S., Van Der Heijden, M. E., Dhamala, M., Sillitoe, R. V., and Heck, D. H. (2022). Causal evidence for a role of cerebellar lobulus simplex in prefrontal-hippocampal interaction in spatial working memory decision-making. *Cerebellum* 21, 762–775. doi: 10.1007/s12311-022-01383-7

Manni, E., and Petrosini, L. (2004). A century of cerebellar somatotopy: A debated representation. *Nat. Rev. Neurosci.* 5, 241–249. doi: 10.1038/nrn1347

Mao, T., Kusefoglu, D., Hooks, B. M., Huber, D., Petreanu, L., and Svoboda, K. (2011). Long-range neuronal circuits underlying the interaction between sensory and motor cortex. *Neuron* 72, 111–123. doi: 10.1016/j.neuron.2011.07.029

Matyas, F., Sreenivasan, V., Marbach, F., Wacongne, C., Barsy, B., Mateo, C., et al. (2010). Motor control by sensory cortex. *Science* 330, 1240–1243. doi: 10.1126/science.1195797

McAfee, S. S., Liu, Y., Dhamala, M., and Heck, D. H. (2018). Thalamocortical transmission of visual information in mice involves synchronized spiking aligned with high gamma oscillations. *Front. Neurosci.* 12:837. doi: 10.3389/fnins.2018.00837

Mesulam, M. M. (1998). From sensation to cognition. *Brain* 121(Pt 6), 1013–1052.

Miao, C., Cao, Q., Moser, M. B., and Moser, E. I. (2017). Parvalbumin and somatostatin interneurons control different space-coding networks in the medial entorhinal cortex. *Cell* 171, 507–521 e17. doi: 10.1016/j.cell.2017.08.050

Mitchell, A. S. (2015). The mediodorsal thalamus as a higher order thalamic relay nucleus important for learning and decision-making. *Neurosci. Biobehav. Rev.* 54, 76–88. doi: 10.1016/j.neubiorev.2015.03.001

Nakajima, M., and Halassa, M. M. (2017). Thalamic control of functional cortical connectivity. *Curr. Opin. Neurobiol.* 44, 127–131. doi: 10.1016/j.conb.2017.04.001

Palmigiano, A., Geisel, T., Wolf, F., and Battaglia, D. (2017). Flexible information routing by transient synchrony. *Nat. Neurosci.* 20, 1014–1022. doi: 10.1038/nn.4569

Pisano, T. J., Dhanerawala, Z. M., Kislin, M., Bakshinskaya, D., Engel, E. A., Hansen, E. J., et al. (2021). Homologous organization of cerebellar pathways to sensory, motor, and associative forebrain. *Cell Rep.* 36:109721. doi: 10.1016/j.celrep.2021.109721

Popa, D., Spolidoro, M., Proville, R. D., Guyon, N., Belliveau, L., and Lena, C. (2013). Functional role of the cerebellum in gamma-band synchronization of the sensory and motor cortices. *J. Neurosci.* 33, 6552–6556. doi: 10.1523/JNEUROSCI.5521-12.2013

Proville, R. D., Spolidoro, M., Guyon, N., Dugue, G. P., Selimi, F., Isope, P., et al. (2014). Cerebellum involvement in cortical sensorimotor circuits for the control of voluntary movements. *Nat. Neurosci.* 17, 1233–1239. doi: 10.1038/nn.3773

Ray, J. P., and Price, J. L. (1993). The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys. *J. Comp. Neurol.* 337, 1–31.

Saadon-Grosman, N., Angeli, P. A., DiNicola, L. M., and Buckner, R. L. (2022). A third somatomotor representation in the human cerebellum. *J. Neurophysiol.* 128, 1051–1073. doi: 10.1152/jn.00165.2022

Schmahmann, J. D. (2004). Disorders of the cerebellum: Ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J. Neuropsychiatry Clin. Neurosci.* 16, 367–378.

Schmitt, L. I., Wimmer, R. D., Nakajima, M., Happ, M., Mofakham, S., and Halassa, M. M. (2017). Thalamic amplification of cortical connectivity sustains attentional control. *Nature* 545, ,219–223. doi: 10.1038/nature22073

Siegel, M., Donner, T. H., Oostenveld, R., Fries, P., and Engel, A. K. (2008). Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. *Neuron* 60, 709–719. doi: 10.1016/j.neuron.2008.09.010

Sigurdsson, T., and Duvarci, S. (2016). Hippocampal-prefrontal interactions in cognition, behavior and psychiatric disease. *Front. Syst. Neurosci.* 9:190. doi: 10.3389/fnsys.2015.00190

Vaadia, E., Haalman, I., Abeles, M., Bergman, H., Prut, Y., Slovin, H., et al. (1995). Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature* 373, 515–518.

Van der Werf, Y. D., Witter, M. P., and Groenewegen, H. J. (2002). The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res. Brain Res. Rev.* 39, 107–140. doi: 10.1016/s0165-0173(02)00181-9

Varela, C., Kumar, S., Yang, J. Y., and Wilson, M. A. (2014). Anatomical substrates for direct interactions between hippocampus, medial prefrontal cortex, and the thalamic nucleus reuniens. *Brain Struct. Funct.* 219, 911–929. doi: 10.1007/s00429-013-0543-5

Vertes, R. P., Hoover, W. B., Szigeti-Buck, K., and Leranth, C. (2007). Nucleus reuniens of the midline thalamus: Link between the medial prefrontal cortex and the hippocampus. *Brain Res. Bull.* 71, 601–609. doi: 10.1016/j.brainresbull.2006.12.002

Watson, T. C., Jones, M. W., and Apps, R. (2009). Electrophysiological mapping of novel prefrontal - cerebellar pathways. *Front. Integr. Neurosci.* 3:18. doi: 10.3389/neuro.07.018.2009

Wiestler, T., McGonigle, D. J., and Diedrichsen, J. (2011). Integration of sensory and motor representations of single fingers in the human cerebellum. *J. Neurophysiol.* 105, 3042–3053. doi: 10.1152/jn.00106.2011

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Prefrontal modulation of anxiety through a lens of noradrenergic signaling

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Anxiety disorders are the most common class of mental illness in the U.S., affecting 40 million individuals annually. Anxiety is an adaptive response to a stressful or unpredictable life event. Though evolutionarily thought to aid in survival, excess intensity or duration of anxiogenic response can lead to a plethora of adverse symptoms and cognitive dysfunction. A wealth of data has implicated the medial prefrontal cortex (mPFC) in the regulation of anxiety. Norepinephrine (NE) is a crucial neuromodulator of arousal and vigilance believed to be responsible for many of the symptoms of anxiety disorders. NE is synthesized in the locus coeruleus (LC), which sends major noradrenergic inputs to the mPFC. Given the unique properties of LC-mPFC connections and the heterogeneous subpopulation of prefrontal neurons known to be involved in regulating anxiety-like behaviors, NE likely modulates PFC function in a cell-type and circuit-specific manner. In working memory and stress response, NE follows an inverted-U model, where an overly high or low release of NE is associated with sub-optimal neural functioning. In contrast, based on current literature review of the individual contributions of NE and the PFC in anxiety disorders, we propose a model of NE level- and adrenergic receptor-dependent, circuit-specific NE-PFC modulation of anxiety disorders. Further, the advent of new techniques to measure NE in the PFC with unprecedented spatial and temporal resolution will significantly help us understand how NE modulates PFC function in anxiety disorders.

KEYWORDS

prefrontal cortex, locus coeruleus, anxiety, norepinephrine, noradrenaline, noradrenergic receptors, stress

Introduction

Anxiety is defined as the anticipation of future threat (American Psychiatric Association [APA], 2013). This physiological and psychological response is thought to be a normal, healthy, adaptive response to aid in survival in an ever-changing world. However, persistent, disruptive, and exacerbated anxiety can become debilitating through threat-generalization to non-threatening situations, producing a constant state of heightened arousal. Pathological anxiety disorders are separated into three main categories: obsessive-compulsive and related disorders, trauma- and stressor-related disorders, and generalized anxiety disorders (American Psychiatric Association [APA], 2013). Although these disorders vary in their etiology, in all cases, the resulting cognitive and behavioral deficits significantly impair normal functioning. Not only do disorders of this nature affect an individual's performance

at school/work, relationships, and self-esteem, but they also lead to significant economic and personal burdens (Bereza et al., 2009; Mondin et al., 2013; Pagotto et al., 2015). Anxiety disorders have a lifetime prevalence of 28% (Kessler et al., 2005), affecting about 40 million individuals in the United States of America and 970 million worldwide. Despite the commonality of these disorders, generalized anxiety disorder (GAD) is one of the least successfully treated psychiatric disorders (Li et al., 2020), and progress toward anxiolytic drug discovery has been slow (Griebel and Holmes, 2013). The treatment gaps in GAD and other anxiety disorders result from our limited understanding of the biological mechanisms by which anxiety symptoms emerge or how these mechanisms are altered by current treatments (Li et al., 2020).

It is increasingly recognized that cognitive deficits underlie various symptoms associated with stress-related psychiatric illnesses, such as anxiety (Beck, 2005; Moran, 2016). A frontal brain structure heavily involved in cognitive functioning is the prefrontal cortex (PFC). This brain region exerts top-down control over behavior, thought, and emotion (Datta and Arnsten, 2019). Lesions of the PFC produce symptoms such as poor judgment, increased distractibility and hyperactivity, poor attentional regulation, and disorganized behavior (Arnsten, 1998), similar to the symptoms seen in anxiety disorders. This suggests the PFC may be implicated in the pathophysiology of anxiety (Kenwood et al., 2022).

One neurotransmitter that is thought to play an extensive role in both anxiety and modulation of PFC function is norepinephrine (NE). The locus coeruleus (LC), a brainstem structure, provides the primary source of NE to the mammalian neocortex (Chandler et al., 2014b; Poe et al., 2020; Breton-Provencher et al., 2021; Ross and Van Bockstaele, 2021; see **Figures 1**, **2**). Cortical projections from the LC are heterogeneous, with distinct biochemical and electrophysiological properties (Chandler and Waterhouse, 2012; Chandler et al., 2014a; Morris et al., 2020). Further, these minimally divergent projection neurons coordinate their molecular phenotypes and physiological profiles to the operation of their specific terminal fields, governing varying levels of NE release. For example, the LC projects to the PFC with much denser NE varicosities compared to other cortical regions such as sensory and motor cortices (Agster et al., 2013). This unique arrangement makes sense in terms of behavioral significance, since the LC exhibits more robust modulatory actions (such as greater NE release) in prefrontal decision-making circuits compared to circuits related to motor movement.

Recent research has indicated that both NE and the PFC are extensively involved in anxiety etiology through distinctly different cell-type, microcircuit-, and macrocircuit-level modulation (Goddard et al., 2010). However, how NE modulation in the PFC coordinates action to optimize PFC function for appropriate attention, cognition, and behavior, and how this may go awry in pathological anxiety states remains unclear. This review summarizes current rodent, primate, and human literature regarding the neurobiology of LC-NE-PFC regulation. Further, we will bridge the work between what is known about LC-NE modulation in pathological anxiety and what is known about prefrontal regulation of pathological anxiety. We hope to shed light on the many remaining unknowns, which may be important for improving the therapeutic arsenal for the management of anxiety disorders.

LC-NE system modulates PFC neural activity

As introduced above, the PFC receives uniquely dense innervation from the LC, surpassing the degree of NE varicosities in other crucial brain sensory regions, including, motor, and thalamic regions (Agster et al., 2013; **Figures 1**, **2**). It is proposed that activation of the LC and subsequent NE release terminates the brain's resting state and commences a brain-state adjustment to orchestrate attention (Corbetta et al., 2008; Sestieri et al., 2011; Tang et al., 2012; Buckner, 2013), facilitate task-relevant behaviors, and help optimize task performance (Aston-Jones and Cohen, 2005). Investigators found that both within and between trials, LC neuron depolarization occurs before forebrain neural activity and is related to cognition (Bouret and Sara, 2005). LC-released NE has a robust effect on the functional integrity of the PFC. As LC-NE neuronal firing rate is associated with the attentional state, it has long been appreciated that NE significantly affects various attentional processes governed by the PFC. NE modulates cortical function during vigilance, attention, arousal, and stress (Aston-Jones et al., 1991; Berridge et al., 1993; Berridge and Waterhouse, 2003; Morilak et al., 2005). Specifically, noradrenergic signaling in the PFC is essential for cognitive changes associated with each of these states (Aston-Jones et al., 2000) and plays a modulatory role in the higher order functioning required to adapt to the demands of a changing or stressful environment (Lapiz and Morilak, 2006; Bondi et al., 2010; Arnsten, 2015).

Though differential innervation of the mPFC subregions (Chandler et al., 2013; Cerpa et al., 2019) and functional disassociations in these subregions (Cerpa et al., 2019) is recognized, the distinct modulatory effects of NE on the ACC, PL and IL prefrontal subregions remain barely studied. Nevertheless, some reported data indicate potential differential modulatory effects of NE on the PFC in a subregion-specific manner. For example, a recent study investigating changes in the norepinephrine transporter (NET) and dopamine-beta-hydroxylase (DBH) density in functionally distinct subregions of the PFC, including IL, PL, ACC, and OFC in adolescent rats found that NET, but not DBH, changed across adolescence in

Abbreviations: adBNST, anterodorsal bed nucleus stria terminalis; ADHD, attention deficit hyperactivity disorder; aPVT, anterior paraventricular thalamus; avBNST, anteroventral BNST; AR, adrenergic receptor; BLA, basolateral amygdala; BMA, basomedial amygdala; BNST, bed nucleus stria terminalis; cAMP, cyclic AMP (adenosine monophosphate); CeA, central amygdala; CeM, centromedial amygdala; cIC, caudal insular cortex; COM, commissural; CPn, corticopontine; DA, dopamine; DBH, dopamine beta hydroxylase; dlLS, dorsolateral lateral septum; dlPFC, dorsolateral prefrontal cortex; dmLS, dorsomedial lateral septum; dmS, dorsomedial striatum; DREADDS, designer receptors exclusively activated by designer drugs; EPM, elevated plus maze; EZM, elevated zero maze; GAD, generalized anxiety disorder; gIC, gustatory insular cortex; GRAB-NE, G-protein-coupled receptor activation based NE sensor; IL, infralimbic; LC, locus coeruleus; LS, lateral septum; MDD, major depressive disorder; NE, norepinephrine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; OCD, obsessive compulsive disorder; OFT, open field test; ovBNST, oval bed nucleus stria terminalis; PFC, prefrontal cortex; pIC, primary interoceptive posterior insular cortex; PL, prelimbic; pPVT, posterior paraventricular thalamus; PTSD, post-traumatic stress disorder; PVT, paraventricular thalamus; raIC, rostral agranular insular cortex; SAD, social anxiety disorder; vmPFC, ventromedial prefrontal cortex; vlLS, ventrolateral lateral septum.

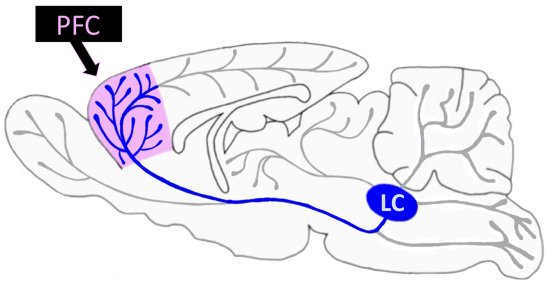

FIGURE 1
Rodent locus coeruleus (LC) projections are widespread but especially dense in the prefrontal cortex (PFC). The LC projects widely across the rodent brain (gray) including the PFC (pink); LC-PFC projections are particularly dense (blue) compared to other LC projections.

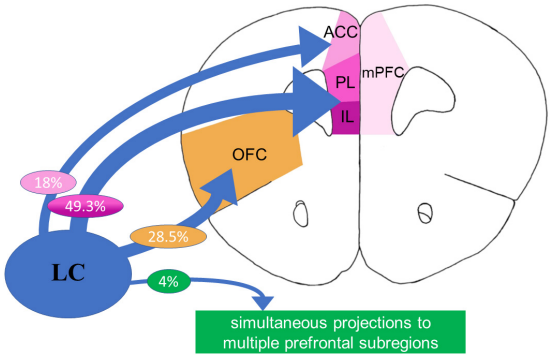

FIGURE 2
The rodent prefrontal cortex (PFC) receives dense projections from the locus coeruleus (LC). Subregions of the rat medial prefrontal cortex (mPFC) receive dense innervation from the LC, with significantly higher amount of norepinephrine (NE) varicosities (Agster et al., 2013) and high percentage of LC projections to the prelimbic (PL)/infralimbic (IL) regions compared to other cortical regions, and relatively low (4%) overlap (Chandler et al., 2014a).

a regionally selective manner. The PL and the OFC showed higher levels of NET at early adolescence (Bradshaw et al., 2016). Additionally, infusion of methylphenidate, an NET inhibitor, into the ACC and IL, but not PL and OFC, inhibited social play (Achterberg et al., 2015), indicating NE-mediated region-specific inhibitory effects (Achterberg et al., 2015). In addition, the mPFC output to subcortical brain areas is known to control different cognitive, social, and emotional processing. Beyond these studies, however, it remains unknown whether and how NE may play unique modulatory roles in distinct subregions and cell types of the PFC. Also, despite the known effects of NE on general PFC-dependent cognition and attention and its interactions with stress, the spatiotemporal dynamic of adrenergic modulation of PFC-dependent behavior remains elusive (Breton-Provencher and Sur, 2019; Breton-Provencher et al., 2021, 2022). Thus, more research is needed to understand the differential and subregion-specific PFC-NE mechanisms associated with anxiety-like behaviors. We will first examine what is known about NE modulation at the molecular level in the PFC, how this affects behaviors, and what remains to be explored.

Laminar and synaptic distribution of adrenergic receptors

Norepinephrine modulates neural activity through various types of adrenergic receptors (ARs, **Box 1**). All subdivisions of the PFC contain cells expressing one or more variations of α- or β-adrenergic receptors and subtypes. The various AR receptors have been identified in both excitatory and inhibitory PFC neurons across numerous cortical layers pre- and post-synaptically (**Tables 1**, **2**).

Behavioral implications of adrenergic receptors

The focus of NE-related neuroscience research in recent decades has centered on understanding how activation or inhibition of these adrenergic receptors may affect different behaviors and their clinical implications in the treatment of various neurological disorders. The functionality of neuromodulators, including NE, follow an inverted-U model (**Figures 3**, **4**; Arnsten, 2011; Cools and Arnsten, 2022). Under normal conditions, NE provides essential regulation of the PFC to keep neurons in an "awakened" state where they can effectively process and exchange information with one another. When conditions vary from "normal," *i.e.*, hypo- or hyper-arousal, NE-prefrontal dynamics also change. This dose-specific model demonstrates that during the moderate release of NE, PFC functioning is strengthened and sculpted to optimize function based on environmental demands; this results in alert phenotypes with optimal working memory, cognition, and attentional control. Conversely, in situations where NE release is either too sparse or too intense, a hindrance to PFC functioning occurs, and behavioral impairments arise (Arnsten, 2009, 2011; Chandler et al., 2014b; Xing et al., 2016; Northoff and Tumati, 2019; Ross and Van Bockstaele, 2021). For example, too little NE results in drowsiness and hypo-vigilance; contrastingly, too much NE elicits symptoms such as hyperarousal and anxiety. Furthermore, the varied release of NE into the PFC can cause differential receptor activation and consequent control of decision-making, arousal, and attention. Thus, the inverted-U model provides a basis for understanding how varying amounts of NE release influences prefrontal top-down control over other brain regions. Given the association between anxiety and excessive NE release, here we focus more on each adrenergic receptor subtype and its role in hyperarousal; hypoarousal, the other end of the inverted-U, is also briefly discussed (**Figure 4**).

Hyperarousal: NE overload

α1 adrenergic receptors

Excessive NE release, as would occur during an environmental stressor, activates lower affinity α1 adrenergic receptors (Arnsten et al., 1998; Arnsten, 2009; Datta et al., 2019). Bulk activation of these receptors depletes functional connectivity to more regulatory parts of the brain involved in executive function (such as the PFC), while enhancing connections to brain

TABLE 1A Laminar and cellular distribution of α-adrenergic receptors (AR) in the medial prefrontal cortex (mPFC).

A) Laminar distribution of different α -adrenergic receptors subtypes in medial prefrontal cortex (mPFC) layers I–VI.					
	mPFC layer				
α -AR receptor subtype	I	II/III	V	VI	References
α1A	–	☑	☑	☑☑	Marek and Aghajanian, 1999; Santana and Artigas, 2017; Santana et al., 2013
α1B	–	☑	☑	☑	Marek and Aghajanian, 1999; Santana and Artigas, 2017; Santana et al., 2013
α1D	–	☑☑	☑	–	Marek and Aghajanian, 1999; Santana and Artigas, 2017; Santana et al., 2013
α2A	☑	☑	☑	☑	Goldman-Rakic et al., 1990; Ramos and Arnsten, 2007
α2B	Below the threshold for detection				Aoki et al., 1998a
α2C	Below the threshold for detection				Aoki et al., 1998a

B) Presence of α -adrenergic receptor subtypes on excitatory and inhibitory neurons in the medial prefrontal cortex (mPFC).					
	Type of mPFC neuron		Synaptic location		
α -AR receptor subtype	Glutamatergic (excitatory)	GABAergic (inhibitory)	Pre-synaptic	Post-synaptic	References
α1A	☑	☑	☑☑	☑	Berridge, 2008; Mitrano et al., 2012; Santana et al., 2013; Santana and Artigas, 2017
α1B	☑	☑	?	?	Achterberg et al., 2015; Bradshaw et al., 2016
α1D	☑	☑ (sparsely)	?	?	Achterberg et al., 2015; Bradshaw et al., 2016
α2A	?	?	☑	☑	Berridge and Waterhouse, 2003; Brocos-Mosquera et al., 2021
α2B	?	?	?	?	–
α2C	?	?	?	?	–

BOX 1 Noradrenergic receptor overview.

Noradrenergic responsivity is mediated by three adrenergic receptors (ARs) in the brain: α1, α2, and β adrenergic receptors. Each family of these different G-protein-coupled receptors plays a distinct, often opposing, role in the brain based on their intrinsic signaling pathways.

α1 receptors (consisting of three sub-types: α1A, α1B, and α1D) display anatomic and functional differences throughout the PFC depending on the receptor subtype. α1 receptors signal via the Gq-protein coupled receptor cascade, where they are coupled to the PKC signaling pathway. PKC signaling is mediated through activation of phospholipase CàDAG pathway, generating DAG and IP3. IP3 stimulates the release of intracellular Ca2+. Previous research has shown post-synaptic α1 receptor activation in the PFC may disengage optimal prefrontal functioning, as shown through impaired working-memory performance.

α2 receptors (consisting of three sub-types: α2A, α2B, and α2D) signal through the Gi-protein coupled receptor cascade. Of the three subtypes, α2A is overwhelmingly predominant in the PFC. Following activation of α2 receptors, cAMP production is inhibited, which in turn, inhibits PKA and prevents phosphorylation of downstream proteins. In addition, inhibition of cAMP production reduces cAMPmediated opening of K+ channels and inhibits HCN channels. Closure of HCN channels on PFC dendritic spines suppresses isolated excitatory inputs and enhances responses to coherent bursts of synaptic activity, resulting in increased synaptic efficacy between communicating neurons. Additional activation of α2A receptors colocalized with HCN channels participate in signal enhancement and consequent improvements in the network "signal-to-noise" ratio through Gi-mediated inhibition of cAMP. Previous research has shown post-synaptic α2 receptor activation in the PFC may engage prefrontal functioning, as shown through enhanced working-memory performance. Contrastingly, presynaptic α2 noradrenergic receptors serve as autoreceptors and participate in a noradrenergic negative feedback mechanism to promote the closure of Ca2+ channels on NE axons, eventually inhibiting NE release in the synapse.

β receptors (consisting of three sub-types: β1, β2, and β3) signal through the Gs-protein coupled receptor cascade. Following activation of β receptors, adenylyl cyclase initiates a cAMP-dependent protein kinase A (PKA) activation, resulting in the phosphorylation of Ca2+ channels and an increase in Ca2+ influx, thus, exciting pre-synaptic neurons and enhancing NE release in the synapse. Both pre- and post-synaptic β-ARs in layer V/VI mPFC pyramidal neurons enhance excitatory neurotransmission, though effects of these receptors, especially post-synaptically, have yet to be specifically studied in other distinct mPFC layers.

regions involved in emotional processing. This impairs higher-order functional abilities of the PFC, such as working memory and attention, and shifts the brain from a state of top-down control (PFC-mediated, thoughtful control) to bottom-up control (salience-driven, impulsive control that is mediated by subcortical structures). Specifically, α1-AR activation releases Ca^{2+} from intracellular stores through the PLC-PKC pathway (Ramos and Arnsten, 2007). Once this system is activated and the animal

TABLE 2A Laminar and cellular distribution of β-adrenergic receptors in the medial prefrontal cortex (mPFC).

A) Laminar distribution of of different β -adrenergic receptor subtypes in medial prefrontal cortex (mPFC) layers I–VI.					
	mPFC layer				
β -AR receptor subtype	I	II/III	V	VI	References
β1	–	☑☑	☑	☑	Liu et al., 2014
β2	–	☑	☑	☑	Goldman-Rakic et al., 1990; Zhou et al., 2013
β3	?	?	?	?	–

B) Presence of β -adrenergic receptor subtypes on excitatory and inhibitory neurons in the medial prefrontal cortex (mPFC).					
	Type of mPFC neuron		Synaptic location		
β -AR receptor subtype	Glutamatergic (excitatory)	GABAergic (inhibitory)	Pre-synaptic	Post-synaptic	References
β1	☑	☑	☑	☑	Aoki et al., 1998b; Ji et al., 2008; Torkaman-Boutorabi et al., 2014
β2	☑	☑	☑☑	☑	Aoki et al., 1998b; Ji et al., 2008; Zhou et al., 2013
β3	?	?	?	?	–

is aroused, it is difficult to deactivate this system, as it engages physiological processes that are designed to directly aid in the survival of an organism (Moran, 2016). Resulting arousal acts in a positive feedback loop, as NE neurons change their firing rate by arousal state (Arnsten, 2009). Thus, as α1 receptors are activated in the PFC, arousal state increases, excessive NE release is prolonged, and α1 receptors continue to be activated. Activation of α1 receptors is accompanied by intermediate levels of both tonic and phasic firing in the LC (Atzori et al., 2016).

Activation of prefrontal α1-ARs via phenylephrine, an α1 agonist, resulted in impaired working memory performance in spatial alternation tasks in rats. This effect was rescued through administration of the α1 antagonist, urapidil (Arnsten et al., 1999; Birnbaum et al., 1999). Pharmacological studies utilize α1 receptor blockers, such as prazosin, to treat hyper-arousal related symptoms of post-traumatic stress disorder (PTSD) (Arnsten, 2007). In addition, the neuroleptic α1 blocker, clozapine, prevented stress-induced impairments of cognitive functioning in rodents and non-human primates (Arnsten, 1998), further connecting the overactivation of these receptors to hyperarousal. The anxiogenic effects of α1-AR activation and anxiolytic effects of α1-AR blockade support the idea that activation of these receptors promote hyperarousal states that may lead to prefrontal dysfunction.

α2 adrenergic receptors

The α2-AR agonist guanfacine enhances prefrontal cortical functions in rats, monkeys, and human beings and ameliorates prefrontal cortical deficits in patients with ADHD (Franowicz et al., 2002; Carr et al., 2007; Wang et al., 2007). Blockade of α2 receptors in the primate PFC erodes delay-related firing and instigates a variety of symptoms of ADHD, including limited impulse control and impaired working memory, leading to increased distractibility (Arnsten, 2007, 2009; Gamo et al., 2010; Ross and Van Bockstaele, 2021). Over-induced NE release facilitates the engagement of α1 receptors and reduces the beneficial cognitive control provided by α2-AR activation (Arnsten, 2000, 2009). It is likely that under conditions of hyperarousal and excessive release of NE, α2 receptors completely lose their beneficiary effect on prefrontal function and are overpowered by the activation of α1 and β receptors.

Psychostimulants such as amphetamine and methylphenidate are given in low doses to enhance the release and prevent the reuptake of NE in the PFC (Berridge et al., 2006). These drugs given in small doses emphasize the fine line of NE between beneficial α2 stimulation and detrimental α2 receptor inactivation (Arnsten, 2007).

β adrenergic receptors

Excessive NE release engages β-ARs. This activation is associated with fight-or-flight response, life-or-death decision-making, high limbic activation, and likely impairment of PFC functioning. Massive engagement of cortical and subcortical β-ARs results in deficits in working memory and favors impulsive and autonomic sympathetic responses (Bouret and Sara, 2005; Hains and Arnsten, 2008). Hyperarousal and high β-AR engagement are accompanied by maximum levels of LC tonic firing and low levels of phasic firing (Atzori et al., 2016). Though intermediate levels of LC tonic firing can be helpful for normal attentional functioning, high tonic firing has been associated with anxious states (Morris et al., 2020), as well as distress and neurodegeneration (Atzori et al., 2016). Supporting this claim, β agonists induced anxiogenic effects in rodents (Hecht et al., 2014). Further, β activation impairs fear extinction (Atzori et al., 2016) and remote footshock-induced memory (Fan et al., 2022), which may lead to a more dramatic and persistent anxiogenic response upon bulk activation. Though research surrounding specific β-AR subtype modulation in the PFC is sparse, a recent study demonstrated β2 optogenetic activation in the mPFC resulted anxiogenic responses in the OFT and EZM. These effects were attenuated through miRNA

knockout of β2 mPFC pyramidal cell receptors (Lei et al., 2022).

The use of β blockers rescues attenuation dopaminergic modulatory effects following acute restraint stress (Chang and Grace, 2013). Specifically, administration of propranolol, a β-AR antagonist, restored DA function through reversal of stress-induced attenuation of VTA dopamine neuron population activity. Moreover, β antagonism has ben shown to prevent the development of anxiety-like behaviors in mice (Gorman and Dunn, 1993) and humans (Jefferson, 1974) through modulation of anxiety-related somatic responses (Hayes and Schulz, 1987). In several other studies, administering β blockers decreased the biochemical and behavioral effects of social stress (Wohleb et al., 2011), restraint stress (Tamburella et al., 2010), and shock-probe defensive burying response (Bondi et al., 2007). In addition, administration of the β1 antagonist, betaxolol, improved working memory in both rats and monkeys, suggesting blockage of these receptors improves prefrontal cognitive functioning (Ramos et al., 2005). The anxiolytic effects of the β blockers support the notion that these receptors likely contribute to hyperarousal following excessive NE release.

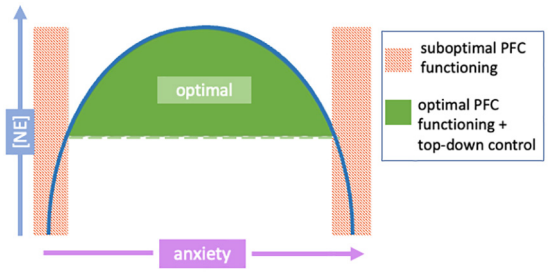

FIGURE 3
The relationship between norepinephrine (NE) levels and anxiety follows an inverted-U shaped correlation. The relationship of NE release and anxiety levels follows an inverted-U shape. Green areas indicate moderate and manageable arousal/anxiety levels as a result of moderate NE release; this area of a "happy medium" allows continued optimal prefrontal cortex (PFC) functioning and top-down control (and thus, normal behavior). Red shaded areas show areas of either hyper- or hypo-NE release, causing the PFC to be taken "offline" causing loss of necessary regulatory control over other brain regions (impaired PFC-dependent functions). Modified from Arnsten (2011).

Hypoarousal: insufficient NE

α1 adrenergic receptors

Generally, α1 receptors activate neurons to promote wakefulness and sustain neuronal activity. Insufficient stimulation of these receptors through inadequate NE release is less likely to be detrimental to cognition, as in the case of overstimulation, but likely induces inactivity and fatigue (Atzori et al., 2016). Additionally, given the lower binding affinity of α1 receptors compared to α2-ARs (Ramos and Arnsten, 2007), it is possible that very low levels of NE do not engage α1-ARs to cause detrimental behavioral phenotypes.

α2 adrenergic receptors

Since α2-ARs play a crucial role in optimal PFC functioning, insufficient activation of α2 receptors primarily impacts cognition and attention. Constant hypoactivation of α2 receptors may lead to impaired prefrontal, subcortical, and motor functioning, representing a depressive state. In human postmortem studies of patients diagnosed with major depressive disorder (MDD), increased α2-agonist ligand binding was observed at α2-adrenegic autoreceptors on NE neuronal cell bodies (García-Sevilla et al., 1999; Hamon and Blier, 2013). Consistently, postmortem analyses of the PFC of MDD-diagnosed suicide victims showed increases in mRNA levels of presynaptic inhibitory α2 autoreceptors (Escribá et al., 2004). Moreover, low stimulation of postsynaptic prefrontal α2 receptors induces symptoms such as cognitive impairment, inattention, and drowsiness (Blier and Briley, 2011). These findings suggest that insufficient levels of noradrenergic neurotransmission may contribute to depression etiology.

β adrenergic receptors

Insufficient activation of β-ARs, given their role in anxiogenesis, may not be as detrimental to prefrontal functioning as hypoactivation of other adrenergic receptors. Interestingly, down-regulation of beta adrenergic expression has been observed with antidepressant treatment (Stahl, 1992). Further, given that β-ARs have the lowest binding affinity of all noradrenergic receptor subtypes (Ramos and Arnsten, 2007), it is possible that lack of engagement of these receptors does not induce problematic or observable phenotypes.

Prefrontal circuit-level top-down modulation of anxiety

The execution of anxiety-related behaviors involves detection of environmental stimuli through sensory systems, assignment of emotional value to these cues via subcortical structures, and execution of behavior based on this information via cortical modulation. The PFC is thought to coordinate situational evaluation and corresponding behavioral outcomes through its extensive connections with other regions of the brain, including the amygdala, bed nucleus stria terminalis (BNST), insula, striatum, lateral septum, and the paraventricular thalamic nucleus (PVT), among others in underlying anxiety circuits (Calhoon and Tye, 2015; Mack et al., 2022; **Figure 5**). Elucidating distinct neural circuit dynamics involved in PFC control of maladaptive behaviors in pathological anxiety can provide insight into the neural pathology underlying dysfunction and may provide an avenue for future circuit-based treatments. Circuit-level modulation is often conserved in translation from mouse to human (Calhoon and Tye, 2015; Poe et al., 2020; Anastasiades and Carter, 2021), allowing for experimentation with animal models that offer clinical applications within this sector of modern neuroscience.

Given what is known about the impact of varying levels of NE on prefrontal function, it is likely that these modulatory effects alter the activity of PFC projection neurons regulating downstream anxiety-related brain regions. To fully understand how NE

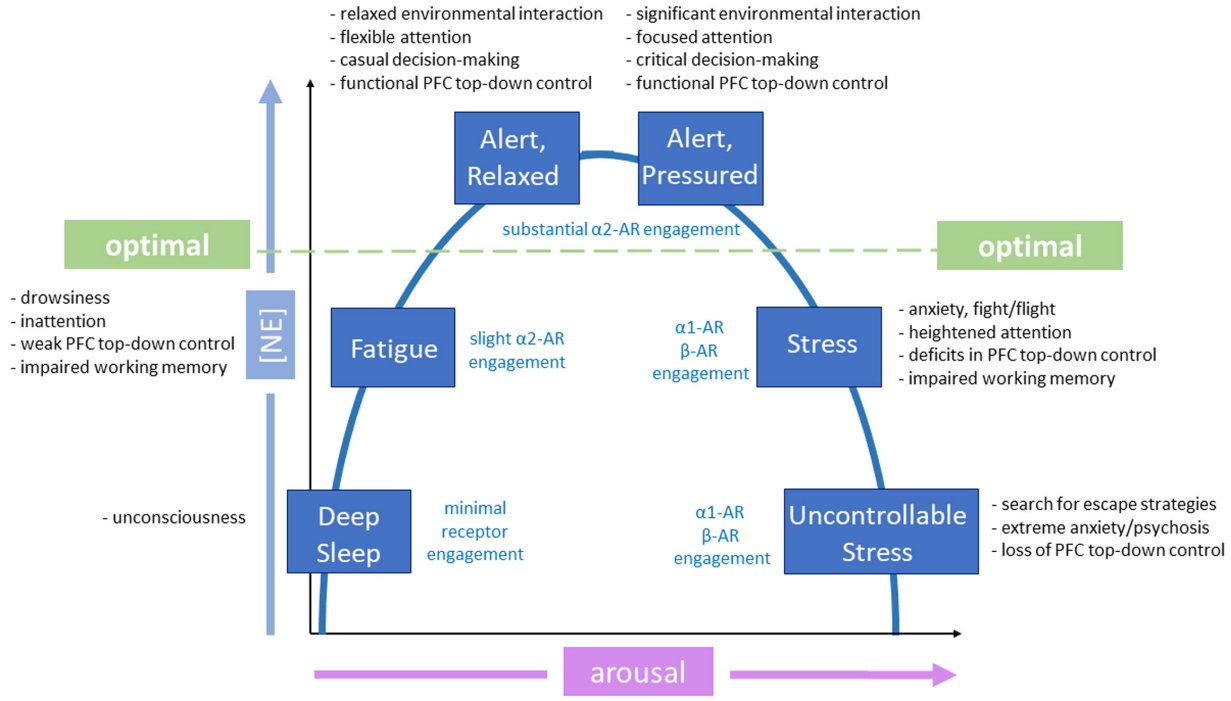

FIGURE 4
Inverted-U functionality of different adrenergic receptors in behaviors. Inverted-U model of norepinephrine (NE) modulation relates to activation of various levels and types of adrenergic receptors and phenotypes. Different adrenergic receptors are activated depending on level of arousal. The green dotted line indicates the threshold for optimal prefrontal functioning, influenced by substantial α2-adrenergic receptor (AR) engagement. Phenotypic manifestations associated with each state and level of NE release are also provided. Modified from Cools and Arnsten (2022).

modulates top-down prefrontal control, a better understanding of NE modulation of distinct PFC connections is necessary. Though very little is known about NE actions on unique PFC circuits, understanding the important prefrontal circuits involved in anxiolytic responses provides a direction for targeted investigation of how NE specifically modulates these pathways and affects consequent anxiety-related behaviors. In this section, we emphasize what is currently known about PFC, pathological anxiety and avoidance behavior through distinct PFC top-down connections to anxiety-relevant brain regions. This provides a basis for our later proposed model that integrates NE into the prefrontal top-down modulation of anxiety.

PFC-amygdala

The amygdala is one of the most highly studied brain regions regarding mood and anxiety disorders, and has long been investigated for its direct role in regulating sustained anxiety symptoms (Tye et al., 2011; Felix-Ortiz et al., 2013, 2016; Allsop et al., 2014; Felix-Ortiz and Tye, 2014; Calhoon and Tye, 2015). This brain region plays a significant role in emotional processing, cognitive evaluation of emotional stimuli, and emotional learning through its intricate connections to cortical and subcortical regions (Janak and Tye, 2015; Giovanniello et al., 2020). The amygdala is made up of several subnuclei [basolateral amygdala (BLA), central amygdala (CeA), centromedial amygdala (CeM), and basomedial amygdala (BMA), among others] (Marek et al., 2019), whose contribution to anxiety differs depending on the subregion (Treit et al., 1993; Möller et al., 1997; Moreira et al., 2007). The PFC sends projections to various subregions of the amygdala, including the BLA and CeA (Coley et al., 2021). Activation of the entire PFC produced a reduction in amygdala activity, demonstrating the inhibitory effect of PFC projections to the amygdala (Quirk et al., 2003). Moreover, specific effects of prefrontal regulation of the amygdala often vary by PFC subregion.

Both the prelimbic (PL) and infralimbic (IL) subregions of the rodent PFC project to BLA and CeA subregions. In a study by Adhikari et al. (2015), activation of the IL projections to the BMA resulted in reduced anxiety-like behaviors and physiological responses. In contrast to the anxiolytic effects of IL inputs to the amygdala, connections from the PL subregion are thought to drive fear expression (Pendyam et al., 2013; Marek et al., 2019) and promote anxiety (Kim et al., 2011). Haikonen et al. (2022) recently combined viral tracing and electrophysiological techniques to examine the effects of maternal separation (MS) on mPFC-to-BLA connectivity and function in young (P14-21) rats. Prolonged MS as an early-life stressor in young rodents is thought to induce emotional and behavioral abnormalities in adulthood, including increased anxiety-like behavior (Kestering-Ferreira et al., 2021). Interestingly, mice that underwent this MS-induced anxiogenic protocol demonstrated increased prefrontal inputs to BLA GABAergic interneurons and a transient increase in the strength of feed-forward inhibition in the BLA during development. The enhanced GABAergic inhibition raises the induction threshold of long-term potentiation and associates with lower functional synchronization within prefrontal-amygdala

networks *in vivo*. These changes are sex-dependent, with the parameters detected in male but not female rats, who were also resistant to MS-dependent changes in anxiety-like behaviors (Haikonen et al., 2022).

In human studies of clinical anxiety disorders, consistent hyperactivation of the amygdala was observed (Etkin and Wager, 2007; Boehme et al., 2014). In fact, in early human connectivity analyses, subjects with more anxious temperaments had reduced vmPFC-amygdala coupling when presented with aversive stimuli (Pezawas et al., 2005). Interestingly, though varying from mouse studies, the dlPFC (dorsolateral PFC, analogous to rodent PL) exerted a significant inhibitory influence on the right amygdala that was absent in patients with GAD (Dong et al., 2019). Further, in patients with SAD (social anxiety disorder), decreased activity in PFC was also observed (Martin et al., 2010), which may explain some of the cognitive deficit-related symptoms observed in anxiety disorders. It is posited that overactivation of the amygdala observed in anxiety disorders is driven by the loss of prefrontal top-down control. This claim is supported by a recent study that found that stronger vmPFC-amygdala connectivity predicted lower anxiety levels (Kim and Whalen, 2009; Kim et al., 2011). Further, strength of dlPFC-amygdala connections were also correlated with anxiety levels, with the least anxious individuals having the most robust connections (Etkin et al., 2009). Given this evidence, it is likely that the loss of PFC-regulated top-down control is implicated in amygdala-mediated anxiogenic responses.

Hypoactivation of the PFC may lead to hyper-responsivity of the amygdala to even non-threatening environmental cues, triggering full-scale responses often observed in PTSD (Whalen et al., 1998), panic disorder (Kent and Rauch, 2003), and other anxiety disorders. This idea is displayed in mouse models, as mice with limited prefrontal-amygdala interaction displayed significant threat-generalization (Charney et al., 2017). Altogether, the evidence summarized here supports an association between PFC-amygdala circuitry and anxiety. Despite this, it remains unknown whether and how NE may modulate PFC projections to the amygdala under both normal and pathological conditions. While it has been shown that NE release in the BLA promotes anxiety-like behavior (McCall et al., 2017), it remains unclear how NE release in the PFC may act on BLA-projecting neurons. Given the inverse relationship between PFC-amygdala connectivity and anxiety, it is plausible that excessive NE release disrupts functionality of this circuit through loss of prefrontal top-down control.

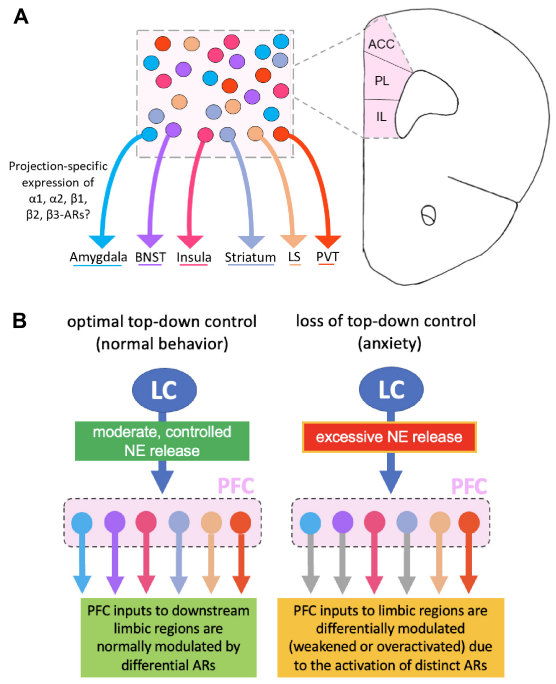

FIGURE 5
Norepinephrine (NE) modulation of distinct prefrontal cortical neurons that project to different anxiety-related subcortical regions. **(A)** The prefrontal cortex (PFC) sends dense projections to numerous brain regions implicated in anxiety, yet there is currently no research on which NE receptor subtypes exist on these output pathways. **(B)** Left panel: Potential circuit-based mechanisms by which optimal locus coeruleus (LC)-mediated NE release in the PFC modulates different PFC output circuits through activation of differential adrenergic receptors (ARs). Right panel: Excessive NE release weakens or over activates PFC outputs to the downstream limbic regions, depending on projection-specific activation of distinct AR subtypes. This in turn results in a shift of dynamic balance among the different circuitries, leading to a loss of prefrontal top-down control and the production of an anxiety-like phenotype.

PFC-BNST

Though the bed nucleus stria terminalis (BNST) is a relatively small brain region, it can be divided into 18 heterogeneous subregions (Robinson et al., 2019). These subregions are seemingly distinct and, at times, opposing in functionality (Jennings et al., 2013; Kim et al., 2013). Previous rodent studies have demonstrated direct input from the PFC to the BNST (Dong et al., 2001; Vertes, 2004; Radley and Sawchenko, 2011; Radley et al., 2013; Glangetas et al., 2017; Johnson et al., 2019) that is particularly dense in IL-avBNST circuits but is also present between the PL and avBNST regions (Johnson et al., 2019). Rodent studies investigating vmPFC-BNST and ACC-BNST (anterior cingulate cortex-BNST) connections in anxiety-like behaviors found that animals exposed to shock demonstrated decreased connectivity in both circuits (Alvarez et al., 2011). This finding supports a relationship between anxiety-like behaviors and loss of PFC top-down modulation of the BNST in rodents.

Moreover, silencing of PL inputs to the avBNST with optogenetics resulted in anxiogenic behavioral phenotypes, including increased immobility and elevated hormonal stress responses during shock-probe burying and tail suspension tests (Radley et al., 2009; Johnson et al., 2019). These results suggest a functional role of PL inputs to the avBNST in reducing anxiety-like behavior. Contrastingly, in a backward conditioning paradigm, IL inputs to the BNST are activated by unpredictable threats (Goode et al., 2019). This may have translational applications to anxiety- and other stress-related disorders, where threats are often inexplicit and unpredictable.

Evidence of prefrontal innervations to the BNST also exist in humans (Dong et al., 2001; Vertes, 2004; Motzkin et al., 2015). Though not PFC-BNST circuit specific, meta-analyses of

neuroimaging studies have demonstrated heightened activation of the BNST while subjects awaited aversive cues (Clauss et al., 2015). Further, a correlation between level of BNST activation and arousal during exposure to unpredictable shocks was observed (Alvarez et al., 2011). In patients with PTSD, heightened sensitivity to stimuli, a hallmark of anxiety disorders, is associated with increased BNST activation. Moreover, increased BNST activity was observed in patients with GAD when compared to healthy controls (Yassa et al., 2012). Thus, there are several lines of evidence that support BNST-based modulation of hypervigilance and hyperarousal. It is possible that in the presence of a stressful or aversive event, BNST activation modulates a sustained, or continuous, anxious state. This heightened state may be exaggerated in anxious individuals (Yassa et al., 2012), resulting in some of the physical and emotional symptoms exhibited in anxiety disorders.

Given what is known about the anatomical and functional heterogeneity of PFC subregions, varying efferent connections from different cortical subregions to the BNST likely control different aspects of anxiety-like behavior (Jennings et al., 2013; Kim et al., 2013). Though similar anxiety-inducing experiments have not been conducted in humans due to ethical and technical limitations, considering the homology that exists between the rodent and human brain, similar anxiety-specific changes in PFC-BNST circuitry are likely present. The studies discussed above provide a robust connection between PFC-BNST modulation and anxiety disorders, but the downstream circuitry, cell-type specificity, and subregion modulation of these symptoms remain elusive. However, increased activity of the BNST and decreases in PFC-BNST connection during anxiety-like behavior supports the notion that anxiety may be due to loss of PFC top-down control to the BNST.

PFC-insula

The insula plays an essential role in emotional experience and subjective feelings (Calder et al., 2000; Borg et al., 2013), making it an essential node in the anxiety network. Given its extensive connections with the amygdala and PFC (Paulus, 2008; Simmons et al., 2008; Engel et al., 2009; Freese and Amaral, 2009), the insula has been consistently implicated in the etiology of anxiety disorders (Damsa et al., 2009). This brain structure is divided into rostral agranular insular cortex (raIC); gustory insular cortex (gIC); primary interoceptive posterior insular cortex (pIC), and caudal insular cortex (cIC) (Bruce et al., 2012). Chemogenetic experiments have revealed insular subregions have distinct and often opposing roles in anxiety response. For example, rostral regions play an anxiogenic role (as raIC inactivation increased exploratory behavior and activation decreased these behaviors), whereas caudal regions produce anxiolytic responses in rodents (cIC inactivation decreased exploration and cIC activation promoted exploratory behavior, indicative of decreased anxiety). Conversely, activation of raIC and gIC induced opposite anxiogenic effects, confirming prior results (Bruce et al., 2012).

In a human study by van Tol et al. (2012), subjects were given a word-encoding task (where subjects were presented with positive, negative, or neutral words) and found that negative words had greater insular activation in patients with anxiety disorders compared to healthy controls. Moreover, healthy patients with greater trait anxiety levels had proportional increases in insular activation (Stein et al., 2007), showing anxiety-like symptoms recruit activation of the insula. In healthy subjects, increased levels of trait anxiety consequently resulted in increased insular activation (Engel et al., 2009). Similarly, the degree of insular (right middle insula) activation in women diagnosed with PTSD was greater than in trauma-exposed controls (Lanius et al., 2007; Lindauer et al., 2008; Strigo et al., 2010). This pattern of heightened insular activation in patients with PSTD was further observed when subjects were exposed to emotional, trauma-unrelated stimuli (Simmons et al., 2008; Fonzo et al., 2010). Patients with anxiety disorders may constantly entertain exaggerated interoceptive cues generated by the overactivated insula, which could increase anxiety symptoms and lead to further elevation of insular activity (Stein et al., 2007).

Hyperactivation of various brain regions in anxiety disorders is thought to be attributed to loss of top-down control via vPFC hypoactivation (Bruce et al., 2012). Though PFC-IC circuit-specific research is limited, hypoactivation of the PFC is related to emotional control in patients with PTSD (Etkin and Wager, 2007). Further, decreased ACC volumes were positively correlated to the presence of PTSD symptoms (Kasai et al., 2008). This evidence combined with increased insular activity in these disorders supports the idea that the relationship between increased insular activation and anxiety is due to a loss of PFC top-down control to the insula. With simultaneous increased insular activation and loss of top-down control from the PFC, this circuit may serve in the development or exacerbation of anxiety disorders.

PFC-striatum

The striatum is a complex brain region that contributes to a plethora of behavioral processing implicated in anxiety disorders, including attention, motivation, and learning (Lago et al., 2017). Prior studies investigating the role of the striatum in anxiety disorders often focus on the ventral striatum for its role in processing affect (Cardinal et al., 2002; Christakou et al., 2004; Schott et al., 2008) but the dorsomedial (dmS) striatum has been and found to influence other aspects involved in anxiety disorders, including decision making (Balleine et al., 2007), avoidance behavior (Aupperle and Paulus, 2010; Aupperle et al., 2015; LeBlanc et al., 2020), and action initiation (Porter et al., 2015). Interestingly, deep brain stimulation of the striatum in rodents (Rodriguez-Romaguera et al., 2012) and humans (Rauch et al., 2006; Denys et al., 2010) has shown that activation of this brain region results in a reduction in anxiety-related symptoms.

In rodents, an especially relevant input to the dmS is the dorsomedial PFC (Sesack et al., 1989; Gabbott et al., 2005). The role of this dmPFC-dmS circuit has previously been demonstrated in decision-making under conflict, a trait that is often disrupted in anxiety disorders (Friedman et al., 2015). A recent study reported that greater activity in dmPFC-dmS projection neurons was observed during open arm occupancy compared to that of the closed arms in the elevated plus maze (EPM); this effect was not observed in other dmPFC circuits, such as the dmPFC-amygdalar projection neurons. Further, stimulation of the

dmPFC-dmS pathway increased open arm exploration, showing an increased drive to approach and decreased anxiety-like behavior (Loewke et al., 2020). Inhibition of this circuit decreased open-arm exploration, illustrating the involvement of this pathway in anxiety-related avoidance. These findings provide evidence supporting the control of dmPFC-dmS circuitry in regulating anxiety-like behavior in the EPM and elevated zero maze (EZM) (Loewke et al., 2020). Moreover, these results support the model of prefrontal top-down control over defensive action, such as avoidance. Investigators have posed that corticostriatal circuitry may integrate previous learning contingencies and the behavioral state of the organism to integrate signals and select subsequent appropriate behavioral responses. This hypothesis is supported by the cortical processing of aversive experience; it is reasonable to conclude that this circuit plays a key role in the generation of defensive response via prefrontal-striatal projection neurons (Kirouac, 2021).

Ventral and dorsomedial regions of the striatum receive prominent PFC afferents (Cisler and Koster, 2010; Liljeholm and O'Doherty, 2012; Calhoon and Tye, 2015; Howland et al., 2022). The ventral striatum is known to be involved in learning and motivation (Dayan and Balleine, 2002; O'Doherty et al., 2004; Cauda et al., 2011; Porter et al., 2015). Motivation is often thought of in the context of addiction (Martin et al., 2002; Chambers et al., 2003), but can be included in anxiety research when reframed to the context of a motivation to avoid danger, or risk avoidance (Lago et al., 2017). This is particularly relevant as individuals diagnosed with anxiety disorders tend to possess abnormally high risk-avoidance levels, which could be attributed to ventral striatal dysfunction (Lago et al., 2017). Regarding circuit-level connectivity, the ventral striatum, which includes the nucleus accumbens (NAc) shell and core, receives input from orbitofrontal and anterior cingulate cortices in humans (Heimer et al., 2007; Ernst and Fudge, 2009; Bolstad et al., 2013; Porter et al., 2015). The ventral striatum, especially NAc, receives dense excitatory afferents from the PFC. NAc volume appears to be a predictor of anxiety symptoms following treatment (Burkhouse et al., 2020), while NAc deep brain stimulation decreases ratings of depression and anxiety (Bewernick et al., 2010). Many noradrenergic dopamine-beta-hydroxylase immunoreactive (DBH-ir) fibers were found in the shell but few were in the core regions (Berridge et al., 1997). A further study indicated that the primary source of NE afferents to the shell of NAc is from the A2 region, with lesser contribution from the A1 and LC (Delfs et al., 1998). Thus, LC-mediated NE release may influence NAc activity through PFC projection neurons. However, how PFC-NAc pathway is modulated by NE and which receptor subtypes are involved in the regulation of anxiety-like behavior remain to be determined.

PFC-PVT

The paraventricular thalamus (PVT) is a midline thalamic structure that integrates information from the motor, limbic, and cortical circuits in the brain (Sesack et al., 1989; Vertes, 2004; Gao et al., 2020, 2023; Iglesias and Flagel, 2021; Penzo and Gao, 2021). The PVT is often separated anatomically and functionally into two subregions: the anterior PVT (aPVT) and posterior PVT (pPVT) (Li and Kirouac, 2012; Kirouac, 2015). Robust sources of input to this brain region include the IL and PL cortices (Li and Kirouac, 2012; Kirouac, 2015), as indicated through retrograde (Krout et al., 2002; Otake et al., 2002) and anterograde (Hurley et al., 1991; Canteras and Swanson, 1992; Vertes, 2004) studies in rodents. The PVT has been known to be a key node in the emotional processing network (Barson et al., 2020) and mediates behavioral responses to stress.

The aPVT receives information from the IL concerning motivational state and arousal. The pPVT receives input from both PL and IL subregions of the PFC, which is thought to communicate information about salient emotional stimuli (Otis et al., 2017, 2019).

Due to the known involvement of the PVT and the PFC in fear, anxiety, and arousal, this circuit may work to modulate behavioral responses to aversive and/or threatening stimuli, though more work is needed to confirm this hypothesis. Although gaps in knowledge surrounding PFC-PVT circuitry do exist, the dense connections between these regions and the behaviors they are known to regulate suggest a likely top-down influence of the PFC on the PVT. While NE signaling in the PVT has been shown to influence cellular responses to stress (Beas et al., 2018), an interesting avenue of future research will be determining how NE release in the PFC alters activity between the PFC and the PVT, and how this may relate to stress and pathological anxiety.

PFC-lateral septum

The lateral septum (LS) is a forebrain region implicated in various behaviors, including feeding, rewards, sociability, and fear. Alongside these functions, the LS has long been involved in the control of stress responses and anxiety (Sheehan et al., 2004). This brain region was once described as a homogenous structure, but has now been recognized as a heterogeneous region with different subregions, cell types, and microcircuits (Risold and Swanson, 1997). The LS can be characterized into four major subregions, dorsolateral septum (dlLS), dorsomedial septum (dmLS), ventrolateral septum (vlLS), and ventromedial septum (vmLS), each exhibiting differential effects on anxiety based on their unique afferent and efferent connections (Rizzi-Wise and Wang, 2021). For example, the dorsal LS is implicated in promoting anxiety (Thomas et al., 2013), while the activation of ventral LS regions reduces anxiety (Parfitt et al., 2017) and fear (Parfitt et al., 2017; Besnard et al., 2020). Phenotypes that arise from vLS activation suggest this region plays a role in suppressing negative affect (Rizzi-Wise and Wang, 2021), thus blunting the psychological severity of stressors (Sheehan et al., 2004). On the other hand, lesions to the LS produce "septal rage" or over-reactivity to stimuli and excessive fear response (Albert and Chew, 1980). Similarly, inhibition of individual LS neurons increases anxiety (Sheehan et al., 2004).

There have been significantly fewer studies investigating PFC inputs to the LS. The IL subregion of the PFC sends dense projections to the intermediate parts of the LS, moderate inputs to the dorsal LS, and sparse inputs to the ventral LS

(Hurley et al., 1991; Canteras and Swanson, 1992; Vertes, 2004). One of the only studies investigating PFC modulation of the LS found that optogenetic activation of PFC terminals in the LS had overall anxiogenic effects, as shown by increased open arm avoidance and decreased open arm entry probability in the EPM, as well as increased freezing and decreased time spent in the center of the arena in the open field test (OFT) (Chen et al., 2021). Further, opto- and chemo-genetic inhibition of the IL-LSe pathway produces anxiolytic effects, as observed through decreased open arm avoidance, increased probability of open arm entry, and increased center occupancy in the OFT (Chen et al., 2021). These findings identify the LS as a key target of IL to enhance anxiety-related behavioral responses, suggesting a direct, local IL-LS synaptic connection to modulate anxiety and fear (Chen et al., 2021). However, this finding seems inconsistent with the idea of top-down prefrontal control of the proper behavioral response. Further studies in a IL-LS subcircuit- and cell-type-specific manner would provide novel insight into the role of IL-LS pathway in anxiety-like behaviors (Besnard and Leroy, 2022).

A model of NE modulation of PFC top-down control

Despite the well-known sensitivity of the PFC to changes in the LC-NE system (Arnsten, 1998), it remains almost completely unexplored how NE release differentially influences each of the PFC circuits mentioned above. Especially, if these distinct PFC projections express different adrenergic receptors and whether they are differentially modulated by LC activity and its released NE in the PFC (**Figure 5**). Nonetheless, some evidence suggests NE regulates distinct PFC populations. For example, adrenergic modulation shifts the dynamic properties of corticopontine (CPn) but not commissural (COM) neurons and increases the excitability of CPn neurons significantly more than COM neurons (Dembrow et al., 2010), indicating subcircuit-specific neuromodulation in the PFC. These findings describe some of the functional consequences of selective neuromodulation on behavioral states during goal-directed behavior (Dembrow and Johnston, 2014). Evidence of differential effects of NE signaling on varying subcircuit-specific PFC modulation, though limited, inspires the idea that other prefrontal circuits are uniquely modulated by NE in the PFC. Combining our knowledge of PFC anxiety-related circuits with the molecular and behavioral framework of general NE modulation in the PFC, we propose a model of adrenergic influence on prefrontal top-down control of anxiety (**Figure 5**).

In this model, we posit that controlled NE release in the PFC maintains optimal functioning of the PFC, eliciting control over other more emotionally-related limbic regions involved in anxiety (eg., amygdala, BNST, insula, striatum, PVT). We pose that this prefrontal top-down control integrates limbic responses with conscious planning and decision-making to elicit appropriate behavioral responses (**Figure 5**). Conversely, conditions of excessive NE release, evoked by unpredictable environmental threats or other perceived psychological stressors (such as those observed in anxiety disorders), may either weaken or overactivate PFC projections to these anxiety-related brain regions. Given that excessive stimulation of ARs inhibits cognitive functioning (Arnsten, 1998) and may take the PFC "offline," it is likely that the loss of top-down control over some or all of these aforementioned brain regions would shift brain states to a mode of subcortical modulation and thus play a vital role in the generation of anxiety (**Figure 5**).

However, this model has yet to be tested directly, and understanding exactly which PFC circuits are impacted by excessive NE release is of great interest from a preclinical and clinical perspective. Altogether, there is a need for more research to elucidate the impact of NE on specific PFC circuits known to be involved in pathological anxiety.

It is also noteworthy to consider the reciprocal connections between the PFC and each or some of these brain regions, and how these regions may individually impact optimal prefrontal functioning in the context of NE signaling. While it remains unknown which AR receptors are expressed on specific PFC output populations, it is also unclear whether afferent inputs to the PFC from other anxiety-related brain regions (*e.g.*, ventral hippocampus) also express AR receptors, which could further contribute to substantial modulation of PFC activity following NE release. Although PFC projection pathways have been the focus of this review, the influence of NE on distinct afferent inputs proves to be a critical area of research in circuit- and systems-based neuroscience. More work is needed to understand whether and how PFC inputs and outputs are uniquely engaged by NE to regulate anxiety-like behaviors.

Finally, it should be noted that given the reciprocal descending pathways from the PFC to the LC, any dynamic activity changes in the mPFC could also have a feedback effect on the LC neuronal activity. However, there are limited studies investigating prefrontal-LC projections, making the speculation of how these projections may affect anxiety-like behavior challenging. Nevertheless, it was reported that electrical stimulation of the PFC in anesthetized rats activated the LC through NMDA and non-NMDA mechanisms (Jodo and Aston-Jones, 1997). Given the PFC's role in attention via NE modulation (Arnsten, 1998, 2011; Berridge and Waterhouse, 2003 Morris et al., 2020), presumably it is possible that low level's of NE in the PFC can induce activation of the LC, which increases NE release to an optimal level to regulate sustained attention and decision-making. In contrast, a high level of NE release in the PFC, as would occur during stress or anxiety-evoking situations, can disengage optimal prefrontal functioning. Therefore, it is unlikely these prefrontal projections to the LC provide negative-feedback signals to provide top-down control to the LC to inhibit NE release during anxiety-like behavior. Even so, more research is needed on the neurochemical and behavioral effects of this descending pathway on anxiety-like behaviors.

Future directions

Preclinical experiments suggest that all NE receptor subtypes participate in anxiety-like processes. Given the extensive use of pharmacological agents that target NE receptors to treat pathological anxiety and the clear relationship between PFC dysfunction in the clinical population, revealing the intricacies of

BOX 2 Outstanding questions.

1. NE is known to modulate decision making and cognitive functions in the PFC, but the circuit-level mechanisms have been unexplored. Revealing which specific cell types and circuitry are affected by NE release in the PFC is an important and interesting avenue of future research
2. Sex differences are known to play a role in NE signaling and receptor expression in the PFC and related circuitry. Whether and how these sex differences contribute to the susceptibility or etiology of pathological anxiety still remains unknown.
3. PFC-NE plays a role in the functionality of the PFC and its ability to provide top-down control, yet the precise projection neurons and interneurons involved remains elusive.
4. The presence of α1 and α2 receptors have been identified in both excitatory and GABAergic neurons in the PFC. However, it is unknown if these receptors are colocalized on the same cells or if cells are constricted to receptor subtype specificity. Moreover, which adrenergic receptor subtypes are expressed on various PFC projection neurons, especially those efferent pathways known to be involved in the modulation of anxiety.
5. It is still unknown whether and how the development of pathological anxiety disorders alters NE release, adrenergic receptor expression, and/or sensitivity in PFC neurons.

NE receptor signaling in modulation of PFC circuit-level control of anxiety is crucial.

Overall, evidence supports a decisive role for NE and distinct PFC circuits in driving anxiety-related behaviors. Significant progress has been made in the last two decades in investigating the LC-NE system's direct influence on anxiety and other aversive behaviors. Despite these advances, more work is needed to bridge the gap between NE signaling and PFC circuit function in anxiety by revealing the precise circuit-level effects of NE release in the PFC. Although the field has yet to directly investigate NE-PFC influences on anxiety etiology, asking questions from a combinatorial standpoint of molecular signaling in conjunction with known circuit-based regulation of behavior, as in our proposed model, is now possible due to recent technological advances. For instance, particularly in rodents, new tools have provided extraordinary temporal and spatial resolution to investigate causal functions of neural circuits and have already yielded impressive results identifying discrete PFC circuits mediating specific anxious behaviors, including approach-avoidance, social deficits, and fear. Our model, though speculatory, can begin to be directly tested using tools such as the GRAB-NE biosensor to detect endogenous NE release in the brain, offering an unprecedented opportunity to uncover the temporal dynamics of NE signaling in the PFC and its resulting effects on behavior (Feng et al., 2019). These dynamics can be fine-tuned even further using the Cre-Lox system to restrict NE biosensor expression to specific PFC circuits and excitatory versus inhibitory PFC cell types. In addition, increasingly advanced computational data analysis, such as deep learning to analyze micro-behaviors, may reveal additional anxiety-like behaviors in rodents that were previously overlooked by manual scoring. Moreover, retrograde tracing studies to visualize exactly where NE-modulated PFC-projection neurons are located, in conjunction with fluorescent *in situ* hybridization (FISH) for specific NE receptor subtypes will further pry into the unknown details of NE receptor expression on distinct PFC-circuits. With vigorous investigation using these new tools, we can begin to address our proposed model and many other outstanding questions that remain (see **Box 2**–Outstanding questions). Implementing a combination of these new and improved techniques is needed to truly uncover the precise dynamics of the LC-NE-PFC's role in anxiety, which is an exciting destination in the future of neuroscience research.

In addition, though sex-differences in anxiety etiology is not discussed in this review, this should not be overlooked. The US National Institute of Mental Health reports that the lifetime prevalence of anxiety disorders is two to three times higher in women than in men (Yonkers et al., 2003; Grant et al., 2005; Kessler et al., 2006, 2009, 2012; Tolin and Foa, 2006; Leach et al., 2008) and women demonstrate distinctly lower treatment efficacy (Donner and Lowry, 2013). Whether and how sex hormones converge with NE signaling in the PFC to guide behavior, and how this may potentially mediate sex differences in pathological anxiety is another intriguing and important line of future research. Despite some recent progress, there is still a substantial delay in the conceptual idea that the field must study both males and females to effectively investigate and treat disorders across sexes. A future of inclusive data collection generates hope for filling the gap in knowledge involving the female brain and developing improved, comprehensive treatments for anxiety and other psychiatric disorders.

It is interesting to speculate that a particular neural circuit dysfunction could be casually involved in multiple psychiatric diseases, including anxiety. Further, given the substantial rate of co-morbidity and shared symptomology among various mental illnesses, the identification of distinct neurobiological mechanisms underlying these diseases is one of the most pressing needs and invigorating avenues of research into psychiatric disorders. Treating psychiatric disorders that disrupt these complex, intertwined neural systems may require a broad, circuit-level approach. A shift in how we consider the underpinnings of anxiety—such that the brain works in a circuit-dependent manner, where changes (including neuromodulatory influences) in each subregion affect the next—promises to remodel how anxiety disorders are treated.

Current technological advances for neuroscience experiments, particularly in rodents, have provided exceptional temporal and spatial resolution to investigate causal functions of neural circuits mediating specific anxious behaviors, including approach-avoidance, social deficits, and fear. Combinatorial approaches with increasingly advanced computational data analysis, such as deep learning to analyze micro-behaviors, will directly aid researchers in answering these critical questions. In particular, the recent advent of biosensors to detect endogenous NE release in the brain offers an unprecedented opportunity to uncover the temporal dynamics of NE signaling in the PFC and its resulting effects on the behavior. In particular, using the Cre-Lox system to restrict NE biosensor expression to specific PFC circuits and cell types, we can begin to address some of the outstanding questions that remain (**Box 2**). Implementing a combination of these new and improved techniques is needed to truly uncover the precise dynamics of the LC-NE-PFC's role in anxiety, which is an exciting destination in the future of neuroscience research.

Author contributions

NB, NM, and W-JG wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Achterberg, E., van Kerkhof, L., Damsteegt, R., Trezza, V., and Vanderschuren, L. (2015). Methylphenidate and atomoxetine inhibit social play behavior through prefrontal and subcortical limbic mechanisms in rats. *J. Neurosci.* 35, 161–169. doi: 10.1523/JNEUROSCI.2945-14.2015

Adhikari, A., Lerner, T., Finkelstein, J., Pak, S., Jennings, J., Davidson, T., et al. (2015). Basomedial amygdala mediates top-down control of anxiety and fear. *Nature* 527, 179–185. doi: 10.1038/nature15698

Agster, K., Mejias-Aponte, C., Clark, B., and Waterhouse, B. (2013). Evidence for a regional specificity in the density and distribution of noradrenergic varicosities in rat cortex. *J. Comp. Neurol.* 521, 2195–2197. doi: 10.1002/cne.23270

Albert, D., and Chew, G. (1980). The septal forebrain and the inhibitory modulation of attack and defense in the rat. A review. *Behav. Neural Biol.* 30, 357–388. doi: 10.1016/s0163-1047(80)91247-9

Allsop, S., Vander Weele, C., Wichmann, R., and Tye, K. (2014). Optogenetic insights on the relationship between anxiety-related behaviors and social deficits. *Front. Behav. Neurosci.* 8:241. doi: 10.3389/fnbeh.2014.00241

Alvarez, R., Chen, G., Bodurka, J., Kaplan, R., and Grillon, C. (2011). Phasic and sustained fear in humans elicits distinct patterns of brain activity. *Neuroimage* 55, 389–400.

American Psychiatric Association [APA] (2013). *Diagnostic and statistical manual of mental disorders*, 5th Edn. Washington, DC: American Psychiatric Association Publishing.

Anastasiades, P., and Carter, A. (2021). Circuit organization of the rodent medial prefrontal cortex. *Trends Neurosci.* 44, 550–563. doi: 10.1016/j.tins.2021.03.006

Aoki, C., Venkatesan, C., Go, C., Forman, R., and Kurose, H. (1998a). Cellular and subcellular sites for noradrenergic action in the monkey dorsolateral prefrontal cortex as revealed by the immunocytochemical localization of noradrenergic receptors and axons. *Cereb. Cortex* 8, 269–277. doi: 10.1093/cercor/8.3.269

Aoki, C., Venkatesan, C., and Kurose, H. (1998b). Noradrenergic modulation of the prefrontal cortex as revealed by electron microscopic immunocytochemistry. *Adv. Pharmacol.* 42, 777–780. doi: 10.1016/s1054-3589(08)60862-5

Arnsten, A. (1998). Catecholamine modulation of prefrontal cortical cognitive function. *Trends Cogn. Sci.* 2, 436–447. doi: 10.1016/s1364-6613(98)01240-6

Arnsten, A. (2000). Through the looking glass: Differential noradenergic modulation of prefrontal cortical function. *Neural Plast.* 7, 133–146. doi: 10.1155/NP.2000.133

Arnsten, A. (2007). Catecholamine and second messenger influences on prefrontal cortical networks of "representational knowledge": A rational bridge between genetics and the symptoms of mental illness. *Cereb. Cortex* 17(Suppl. 1), i6–i15. doi: 10.1093/cercor/bhm033

Arnsten, A. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nat. Rev. Neurosci.* 10, 410–422. doi: 10.1038/nrn2648

Arnsten, A. (2011). Catecholamine influences on dorsolateral prefrontal cortical networks. *Biol. Psychiatry* 69, e89–e99. doi: 10.1016/j.biopsych.2011.01.027

Arnsten, A. (2015). Stress weakens prefrontal networks: Molecular insults to higher cognition. *Nat. Neurosci.* 18, 1376–1385. doi: 10.1038/nn.4087

Arnsten, A., Mathew, R., Ubriani, R., Taylor, J., and Li, B. (1999). Alpha-1 noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. *Biol. Psychiatry* 45, 26–31. doi: 10.1016/s0006-3223(98)00296-0

Arnsten, A., Steere, J., Jentsch, D., and Li, B. (1998). Noradrenergic influences on prefrontal cortical cognitive function: Opposing actions at postjunctional alpha 1 versus alpha 2-adrenergic receptors. *Adv. Pharmacol.* 42, 764–767. doi: 10.1016/s1054-3589(08)60859-5

Aston-Jones, G., Chiang, C., and Alexinsky, T. (1991). Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance. *Prog. Brain Res.* 88, 501–520. doi: 10.1016/s0079-6123(08)63830-3

Aston-Jones, G., and Cohen, J. (2005). Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *J. Comp. Neurol.* 493, 99–110. doi: 10.1002/cne.20723

Aston-Jones, G., Rajkowski, J., and Cohen, J. (2000). Locus coeruleus and regulation of behavioral flexibility and attention. *Prog. Brain Res.* 126, 165–182. doi: 10.1016/S0079-6123(00)26013-5

Atzori, M., Cuevas-Olguin, R., Esquivel-Rendon, E., Garcia-Oscos, F., Salgado-Delgado, R., Saderi, N., et al. (2016). Locus ceruleus norepinephrine release: A central regulator of CNS spatio-temporal activation? *Front. Synaptic Neurosci.* 8:25. doi: 10.3389/fnsyn.2016.00025

Aupperle, R., Melrose, A., Francisco, A., Paulus, M., and Stein, M. (2015). Neural substrates of approach-avoidance conflict decision-making. *Hum. Brain Mapp.* 36, 449–462. doi: 10.1002/hbm.22639

Aupperle, R., and Paulus, M. (2010). Neural systems underlying approach and avoidance in anxiety disorders. *Dialogues Clin. Neurosci.* 12, 517–531. doi: 10.31887/DCNS.2010.12.4/raupperle

Balleine, B., Delgado, M., and Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. *J. Neurosci.* 27, 8161–8165. doi: 10.1523/JNEUROSCI.1554-07.2007

Barson, J., Mack, N., and Gao, W. (2020). The paraventricular nucleus of the thalamus is an important node in the emotional processing network. *Front. Behav. Neurosci.* 14:598469. doi: 10.3389/fnbeh.2020.598469

Beas, B., Wright, B., Skirzewski, M., Leng, Y., Hyun, J., Koita, O., et al. (2018). The locus coeruleus drives disinhibition in the midline thalamus via a dopaminergic mechanism. *Nat. Neurosci.* 21, 963–973. doi: 10.1038/s41593-018-0167-4

Beck, A. (2005). The current state of cognitive therapy: A 40-year retrospective. *Arch. Gen. Psychiatry* 62, 953–959. doi: 10.1001/archpsyc.62.9.953

Bereza, B., Machado, M., and Einarson, T. (2009). Systematic review and quality assessment of economic evaluations and quality-of-life studies related to generalized anxiety disorder. *Clin. Ther.* 31, 1279–1308. doi: 10.1016/j.clinthera.2009.06.004

Berridge, C. (2008). Noradrenergic modulation of arousal. *Brain Res. Rev.* 58, 1–17. doi: 10.1016/j.brainresrev.2007.10.013

Berridge, C., Devilbiss, D., Andrzejewski, M., Arnsten, A., Kelley, A., Schmeichel, B., et al. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biol. Psychiatry* 60, 1111–1120. doi: 10.1016/j.biopsych.2006.04.022

Berridge, C., Page, M., Valentino, R., and Foote, S. (1993). Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. *Neuroscience* 55, 381–393. doi: 10.1016/0306-4522(93)90507-c

Berridge, C., Stratford, T., Foote, S., and Kelley, A. (1997). Distribution of dopamine beta-hydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens. *Synapse* 27, 230–241.

Berridge, C., and Waterhouse, B. (2003). The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Res. Brain Res. Rev.* 42, 33–84. doi: 10.1016/s0165-0173(03)00143-7

Besnard, A., and Leroy, F. (2022). Top-down regulation of motivated behaviors via lateral septum sub-circuits. *Mol. Psychiatry* 27, 3119–3128. doi: 10.1038/s41380-022-01599-3

Besnard, A., Miller, S., and Sahay, A. (2020). Distinct dorsal and ventral hippocampal CA3 outputs govern contextual fear discrimination. *Cell Rep.* 30, 2360–2373.e5. doi: 10.1016/j.celrep.2020.01.055

Bewernick, B., Hurlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., et al. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biol. Psychiatry* 67, 110–116. doi: 10.1016/j.biopsych.2009.09.013

Birnbaum, S., Gobeske, K., Auerbach, J., Taylor, J., and Arnsten, A. F. (1999). A role for norepinephrine in stress-induced cognitive deficits: Alpha-1-adrenoceptor mediation in the prefrontal cortex. *Biol. Psychiatry* 46, 1266–1274. doi: 10.1016/s0006-3223(99)00138-9

Blier, P., and Briley, M. (2011). The noradrenergic symptom cluster: Clinical expression and neuropharmacology. *Neuropsychiatr. Dis. Treat.* 7(Suppl. 1), 15–20. doi: 10.2147/NDT.S19613

Boehme, S., Ritter, V., Tefikow, S., Stangier, U., Strauss, B., Miltner, W., et al. (2014). Brain activation during anticipatory anxiety in social anxiety disorder. *Soc. Cogn. Affect. Neurosci.* 9, 1413–1418. doi: 10.1093/scan/nst129

Bolstad, I., Andreassen, O., Reckless, G., Sigvartsen, N., Server, A., and Jensen, J. (2013). Aversive event anticipation affects connectivity between the ventral striatum and the orbitofrontal cortex in an fMRI avoidance task. *PLoS One* 8:e68494. doi: 10.1371/journal.pone.0068494

Bondi, C., Barrera, G., Lapiz, M., Bedard, T., Mahan, A., and Morilak, D. (2007). Noradrenergic facilitation of shock-probe defensive burying in lateral septum of rats, and modulation by chronic treatment with desipramine. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 31, 482–495. doi: 10.1016/j.pnpbp.2006.11.015

Bondi, C., Jett, J., and Morilak, D. (2010). Beneficial effects of desipramine on cognitive function of chronically stressed rats are mediated by alpha1-adrenergic receptors in medial prefrontal cortex. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 913–923. doi: 10.1016/j.pnpbp.2010.04.016

Borg, C., Bedoin, N., Peyron, R., Bogey, S., Laurent, B., and Thomas-Antérion, C. (2013). Impaired emotional processing in a patient with a left posterior insula-SII lesion. *Neurocase* 19, 592–603. doi: 10.1080/13554794.2012.713491

Bouret, S., and Sara, S. (2005). Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci.* 28, 574–582. doi: 10.1016/j.tins.2005.09.002

Bradshaw, S., Agster, K., Waterhouse, B., and McGaughy, J. (2016). Age-related changes in prefrontal norepinephrine transporter density: The basis for improved cognitive flexibility after low doses of atomoxetine in adolescent rats. *Brain Res.* 1641(Pt B), 245–257. doi: 10.1016/j.brainres.2016.01.001

Breton-Provencher, V., Drummond, G., Feng, J., Li, Y., and Sur, M. (2022). Spatiotemporal dynamics of noradrenaline during learned behaviour. *Nature* 606, 732–738. doi: 10.1038/s41586-022-04782-2

Breton-Provencher, V., Drummond, G., and Sur, M. (2021). Locus coeruleus norepinephrine in learned behavior: Anatomical modularity and spatiotemporal integration in targets. *Front. Neural Circuits* 15:638007. doi: 10.3389/fncir.2021.638007

Breton-Provencher, V., and Sur, M. (2019). Active control of arousal by a locus coeruleus GABAergic circuit. *Nat. Neurosci.* 22, 218–228. doi: 10.1038/s41593-018-0305-z

Brocos-Mosquera, I., Gabilondo, A., Diez-Alarcia, R., Muguruza, C., Erdozain, A., Meana, J., et al. (2021). α2A- and α2C-adrenoceptor expression and functionality in postmortem prefrontal cortex of schizophrenia subjects. *Eur. Neuropsychopharmacol.* 52, 3–11. doi: 10.1016/j.euroneuro.2021.05.012

Bruce, S., Buchholz, K., Brown, W., Yan, L., Durbin, A., and Sheline, Y. (2012). Altered emotional interference processing in the amygdala and insula in women with post-traumatic stress disorder. *Neuroimage Clin.* 2, 43–49. doi: 10.1016/j.nicl.2012.11.003

Buckner, R. (2013). The brain's default network: Origins and implications for the study of psychosis. *Dialogues Clin. Neurosci.* 15, 351–358. doi: 10.31887/DCNS.2013.15.3/rbuckner

Burkhouse, K., Jagan Jimmy, Defelice, N., Klumpp, H., Ajilore, O., Hosseini, B., et al. (2020). Nucleus accumbens volume as a predictor of anxiety symptom improvement following CBT and SSRI treatment in two independent samples. *Neuropsychopharmacology* 45, 561–569. doi: 10.1038/s41386-019-0575-5

Calder, A., Keane, J., Manes, F., Antoun, N., and Young, A. (2000). Impaired recognition and experience of disgust following brain injury. *Nat. Neurosci.* 3, 1077–1078. doi: 10.1038/80586

Calhoon, G., and Tye, K. (2015). Resolving the neural circuits of anxiety. *Nat. Neurosci.* 18, 1394–1404. doi: 10.1038/nn.4101

Canteras, N., and Swanson, L. (1992). Projections of the ventral subiculum to the amygdala, septum, and hypothalamus: A PHAL anterograde tract-tracing study in the rat. *J. Comp. Neurol.* 324, 180–194. doi: 10.1002/cne.903240204

Cardinal, R., Parkinson, J., Hall, J., and Everitt, B. (2002). Emotion and motivation: The role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci. Biobehav. Rev.* 26, 321–352. doi: 10.1016/s0149-7634(02)00007-6

Carr, D., Andrews, G., Glen, W., and Lavin, A. (2007). alpha2-Noradrenergic receptors activation enhances excitability and synaptic integration in rat prefrontal cortex pyramidal neurons via inhibition of HCN currents. *J. Physiol.* 584(Pt 2), 437–450. doi: 10.1113/jphysiol.2007.141671

Cauda, F., Cavanna, A., D'agata, F., Sacco, K., Duca, S., and Geminiani, G. (2011). Functional connectivity and coactivation of the nucleus accumbens: A combined functional connectivity and structure-based meta-analysis. *J. Cogn. Neurosci.* 23, 2864–2877. doi: 10.1162/jocn.2011.21624

Cerpa, J., Marchand, A., and Coutureau, E. (2019). Distinct regional patterns in noradrenergic innervation of the rat prefrontal cortex. *J. Chem. Neuroanat.* 96, 102–109. doi: 10.1016/j.jchemneu.2019.01.002

Chambers, R., Taylor, J., and Potenza, M. (2003). Developmental neurocircuitry of motivation in adolescence: A critical period of addiction vulnerability. *Am. J. Psychiatry* 160, 1041–1052. doi: 10.1176/appi.ajp.160.6.1041

Chandler, D., Gao, W., and Waterhouse, B. (2014a). Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proc. Natl. Acad. Sci. U.S.A.* 111, 6816–6821. doi: 10.1073/pnas.1320827111

Chandler, D., Lamperski, C., and Waterhouse, B. (2013). Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. *Brain Res.* 1522, 38–58. doi: 10.1016/j.brainres.2013.04.057

Chandler, D., and Waterhouse, B. (2012). Evidence for broad versus segregated projections from cholinergic and noradrenergic nuclei to functionally and anatomically discrete subregions of prefrontal cortex. *Front. Behav. Neurosci.* 6:20. doi: 10.3389/fnbeh.2012.00020

Chandler, D., Waterhouse, B., and Gao, W. (2014b). New perspectives on catecholaminergic regulation of executive circuits: Evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. *Front. Neural Circuits* 8:53. doi: 10.3389/fncir.2014.00053

Chang, C., and Grace, A. (2013). Amygdala β-noradrenergic receptors modulate delayed downregulation of dopamine activity following restraint. *J. Neurosci.* 33, 1441–1450. doi: 10.1523/JNEUROSCI.2420-12.2013

Charney, D. S., Nestler, E. J., Sklar, P., and Buxbaum, J. D. (2017). *Charney and Nestler's neurobiology of mental illness*, 5th Edn. Oxford: Oxford University Press.

Chen, Y., Wu, J., Hu, N., Zhuang, J., Li, W., Zhang, S., et al. (2021). Distinct projections from the infralimbic cortex exert opposing effects in modulating anxiety and fear. *J. Clin. Invest.* 131:e145692. doi: 10.1172/JCI145692

Christakou, A., Robbins, T., and Everitt, B. (2004). Prefrontal cortical-ventral striatal interactions involved in affective modulation of attentional performance: Implications for corticostriatal circuit function. *J. Neurosci.* 24, 773–780. doi: 10.1523/JNEUROSCI.0949-03.2004

Cisler, J., and Koster, E. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin. Psychol. Rev.* 30, 203–216. doi: 10.1016/j.cpr.2009.11.003

Clauss, J., Avery, S., and Blackford, J. (2015). The nature of individual differences in inhibited temperament and risk for psychiatric disease: A review and meta-analysis. *Prog. Neurobiol.* 127–128, 23–45. doi: 10.1016/j.pneurobio.2015.03.001

Coley, A., Padilla-Coreano, N., Patel, R., and Tye, K. (2021). Valence processing in the PFC: Reconciling circuit-level and systems-level views. *Int. Rev. Neurobiol.* 158, 171–212. doi: 10.1016/bs.irn.2020.12.002

Cools, R., and Arnsten, A. (2022). Neuromodulation of prefrontal cortex cognitive function in primates: The powerful roles of monoamines and acetylcholine. *Neuropsychopharmacology* 47, 309–328. doi: 10.1038/s41386-021-01100-8

Corbetta, M., Patel, G., and Shulman, G. (2008). The reorienting system of the human brain: From environment to theory of mind. *Neuron* 58, 306–324. doi: 10.1016/j.neuron.2008.04.017

Damsa, C., Kosel, M., and Moussally, J. (2009). Current status of brain imaging in anxiety disorders. *Curr. Opin. Psychiatry* 22, 96–110. doi: 10.1097/YCO.0b013e328319bd10

Datta, D., and Arnsten, A. (2019). Loss of prefrontal cortical higher cognition with uncontrollable stress: Molecular mechanisms, changes with age, and relevance to treatment. *Brain Sci.* 9:113. doi: 10.3390/brainsci9050113

Datta, D., Yang, S., Galvin, V., Solder, J., Luo, F., Morozov, Y., et al. (2019). Noradrenergic α1-adrenoceptor actions in the primate dorsolateral prefrontal cortex. *J. Neurosci.* 39, 2722–2734. doi: 10.1523/JNEUROSCI.2472-18.2019

Dayan, P., and Balleine, B. (2002). Reward, motivation, and reinforcement learning. *Neuron* 36, 285–298. doi: 10.1016/s0896-6273(02)00963-7

Delfs, J., Zhu, Y., Druhan, J., and Aston-Jones, G. (1998). Origin of noradrenergic afferents to the shell subregion of the nucleus accumbens: Anterograde and retrograde tract-tracing studies in the rat. *Brain Res.* 806, 127–140. doi: 10.1016/s0006-8993(98)00672-6

Dembrow, N., Chitwood, R., and Johnston, D. (2010). Projection-specific neuromodulation of medial prefrontal cortex neurons. *J. Neurosci.* 30, 16922–16937. doi: 10.1523/JNEUROSCI.3644-10.2010

Dembrow, N., and Johnston, D. (2014). Subcircuit-specific neuromodulation in the prefrontal cortex. *Front. Neural Circuits* 8:54. doi: 10.3389/fncir.2014.00054

Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., et al. (2010). Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 67, 1061–1068. doi: 10.1001/archgenpsychiatry.2010.122

Dong, H., Petrovich, G., and Swanson, L. (2001). Topography of projections from amygdala to bed nuclei of the stria terminalis. *Brain Res. Brain Res. Rev.* 38, 192–246. doi: 10.1016/s0165-0173(01)00079-0

Dong, M., Xia, L., Lu, M., Li, C., Xu, K., and Zhang, L. (2019). A failed top-down control from the prefrontal cortex to the amygdala in generalized anxiety disorder: Evidence from resting-state fMRI with granger causality analysis. *Neurosci. Lett.* 707:134314. doi: 10.1016/j.neulet.2019.134314

Donner, N., and Lowry, C. (2013). Sex differences in anxiety and emotional behavior. *Pflugers Arch.* 465, 601–626. doi: 10.1007/s00424-013-1271-7

Engel, K., Bandelow, B., Gruber, O., and Wedekind, D. (2009). Neuroimaging in anxiety disorders. *J. Neural Transm* 116, 703–716. doi: 10.1007/s00702-008-0077-9

Ernst, M., and Fudge, J. (2009). A developmental neurobiological model of motivated behavior: Anatomy, connectivity and ontogeny of the triadic nodes. *Neurosci. Biobehav. Rev.* 33, 367–382. doi: 10.1016/j.neubiorev.2008.10.009

Escribá, P., Ozaita, A., and García-Sevilla, J. (2004). Increased mRNA expression of alpha2A-adrenoceptors, serotonin receptors and mu-opioid receptors in the brains of suicide victims. *Neuropsychopharmacology* 29, 1512–1521. doi: 10.1038/sj.npp.1300459

Etkin, A., Prater, K., Schatzberg, A., Menon, V., and Greicius, M. (2009). Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. *Arch. Gen. Psychiatry* 66, 1361–1372. doi: 10.1001/archgenpsychiatry.2009.104

Etkin, A., and Wager, T. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am. J. Psychiatry* 164, 1476–1488. doi: 10.1176/appi.ajp.2007.07030504

Fan, X., Song, J., Ma, C., Lv, Y., Wang, F., Ma, L., et al. (2022). Noradrenergic signaling mediates cortical early tagging and storage of remote memory. *Nat. Commun.* 13:7623. doi: 10.1038/s41467-022-35342-x

Felix-Ortiz, A., Beyeler, A., Seo, C., Leppla, C., Wildes, C., and Tye, K. (2013). BLA to vHPC inputs modulate anxiety-related behaviors. *Neuron* 79, 658–664. doi: 10.1016/j.neuron.2013.06.016

Felix-Ortiz, A., Burgos-Robles, A., Bhagat, N., Leppla, C., and Tye, K. (2016). Bidirectional modulation of anxiety-related and social behaviors by amygdala projections to the medial prefrontal cortex. *Neuroscience* 321, 197–209. doi: 10.1016/j.neuroscience.2015.07.041

Felix-Ortiz, A., and Tye, K. (2014). Amygdala inputs to the ventral hippocampus bidirectionally modulate social behavior. *J. Neurosci.* 34, 586–595. doi: 10.1523/JNEUROSCI.4257-13.2014

Feng, J., Zhang, C., Lischinsky, J., Jing, M., Zhou, J., Wang, H., et al. (2019). A genetically encoded fluorescent sensor for rapid and specific in vivo detection of norepinephrine. *Neuron* 102, 745–761.e8. doi: 10.1016/j.neuron.2019.02.037

Fonzo, G., Simmons, A., Thorp, S., Norman, S., Paulus, M., and Stein, M. (2010). Exaggerated and disconnected insular-amygdalar blood oxygenation level-dependent response to threat-related emotional faces in women with intimate-partner violence posttraumatic stress disorder. *Biol. Psychiatry* 68, 433–441. doi: 10.1016/j.biopsych.2010.04.028

Franowicz, J., Kessler, L., Borja, C., Kobilka, B., Limbird, L., and Arnsten, A. (2002). Mutation of the alpha2A-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine. *J. Neurosci.* 22, 8771–8777. doi: 10.1523/JNEUROSCI.22-19-08771.2002

Freese, J. L., and Amaral, D. G. (2009). "Neuroanatomy of the primate amygdala," in *The human amygdala*, eds P. J. Whalen and E. A. Phelps (New York, NY: The Guilford Press), 3–42.

Friedman, A., Homma, D., Gibb, L., Amemori, K., Rubin, S., Hood, A., et al. (2015). A corticostriatal path targeting striosomes controls decision-making under conflict. *Cell* 161, 1320–1333. doi: 10.1016/j.cell.2015.04.049

Gabbott, P., Warner, T., Jays, P., Salway, P., and Busby, S. (2005). Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. *J. Comp. Neurol.* 492, 145–177. doi: 10.1002/cne.20738

Gamo, N., Wang, M., and Arnsten, A. (2010). Methylphenidate and atomoxetine enhance prefrontal function through α2-adrenergic and dopamine D1 receptors. *J. Am. Acad. Child Adolesc. Psychiatry* 49, 1011–1023. doi: 10.1016/j.jaac.2010.06.015

Gao, C., Gohel, C., Leng, Y., Ma, J., Goldman, D., Levine, A., et al. (2023). Molecular and spatial profiling of the paraventricular nucleus of the thalamus. *eLife* 12:e81818. doi: 10.7554/eLife.81818

Gao, C., Leng, Y., Ma, J., Rooke, V., Rodriguez-Gonzalez, S., Ramakrishnan, C., et al. (2020). Two genetically, anatomically and functionally distinct cell types segregate across anteroposterior axis of paraventricular thalamus. *Nat. Neurosci.* 23, 217–228. doi: 10.1038/s41593-019-0572-3

García-Sevilla, J., Escribá, P., Ozaita, A., La Harpe, R., Walzer, C., Eytan, A., et al. (1999). Up-regulation of immunolabeled alpha2A-adrenoceptors, Gi coupling proteins, and regulatory receptor kinases in the prefrontal cortex of depressed suicides. *J. Neurochem.* 72, 282–291. doi: 10.1046/j.1471-4159.1999.0720282.x

Giovanniello, J., Yu, K., Furlan, A., Nachtrab, G., Sharma, R., Chen, X., et al. (2020). A central amygdala-globus pallidus circuit conveys unconditioned stimulus-related information and controls fear learning. *J. Neurosci.* 40, 9043–9054. doi: 10.1523/JNEUROSCI.2090-20.2020

Glangetas, C., Massi, L., Fois, G., Jalabert, M., Girard, D., Diana, M., et al. (2017). NMDA-receptor-dependent plasticity in the bed nucleus of the stria terminalis triggers long-term anxiolysis. *Nat. Commun.* 8:14456. doi: 10.1038/ncomms14456

Goddard, A., Ball, S., Martinez, J., Robinson, M., Yang, C., Russell, J., et al. (2010). Current perspectives of the roles of the central norepinephrine system in anxiety and depression. *Depress Anxiety* 27, 339–350. doi: 10.1002/da.20642

Goldman-Rakic, P., Lidow, M., and Gallager, D. (1990). Overlap of dopaminergic, adrenergic, and serotoninergic receptors and complementarity of their subtypes in primate prefrontal cortex. *J. Neurosci.* 10, 2125–2138. doi: 10.1523/JNEUROSCI.10-07-02125.1990

Goode, T., Ressler, R., Acca, G., Miles, O., and Maren, S. (2019). Bed nucleus of the stria terminalis regulates fear to unpredictable threat signals. *eLife* 8:e46525. doi: 10.7554/eLife.46525

Gorman, A., and Dunn, A. (1993). Beta-adrenergic receptors are involved in stress-related behavioral changes. *Pharmacol. Biochem. Behav.* 45, 1–7. doi: 10.1016/0091-3057(93)90078-8

Grant, B., Hasin, D., Stinson, F., Dawson, D., June Ruan, W., Goldstein, R., et al. (2005). Prevalence, correlates, co-morbidity, and comparative disability of DSM-IV generalized anxiety disorder in the USA: Results from the national epidemiologic survey on alcohol and related conditions. *Psychol. Med.* 35, 1747–1759. doi: 10.1017/S0033291705006069

Griebel, G., and Holmes, A. (2013). 50 years of hurdles and hope in anxiolytic drug discovery. *Nat. Rev. Drug. Discov.* 12, 667–687. doi: 10.1038/nrd4075

Haikonen, J., Englund, J., Amarilla, S., Kharybina, Z., Shintyapina, A., Kegler, K., et al. (2022). Aberrant cortical projections to amygdala GABAergic neurons contribute to developmental circuit dysfunction following early life stress. *iScience* 26:105724. doi: 10.1016/j.isci.2022.105724

Hains, A., and Arnsten, A. (2008). Molecular mechanisms of stress-induced prefrontal cortical impairment: Implications for mental illness. *Learn. Mem.* 15, 551–564. doi: 10.1101/lm.921708

Hamon, M., and Blier, P. (2013). Monoamine neurocircuitry in depression and strategies for new treatments. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 45, 54–63. doi: 10.1016/j.pnpbp.2013.04.009

Hayes, P., and Schulz, S. (1987). Beta-blockers in anxiety disorders. *J. Affect. Disord.* 13, 119–130. doi: 10.1016/0165-0327(87)90017-6

Hecht, P., Will, M., Schachtman, T., Welby, L., and Beversdorf, D. (2014). Beta-adrenergic antagonist effects on a novel cognitive flexibility task in rodents. *Behav. Brain Res.* 260, 148–154. doi: 10.1016/j.bbr.2013.11.041

Heimer, L., Van Hoesen, G., Trimble, M., and Zahm, D. (2007). *Anatomy of neuropsychiatry*, 1st Edn. Cambridge, MA: Academic Press.

Howland, J., Ito, R., Lapish, C., and Villaruel, F. (2022). The rodent medial prefrontal cortex and associated circuits in orchestrating adaptive behavior under variable demands. *Neurosci. Biobehav. Rev.* 135:104569. doi: 10.1016/j.neubiorev.2022.104569

Hurley, K., Herbert, H., Moga, M., and Saper, C. (1991). Efferent projections of the infralimbic cortex of the rat. *J. Comp. Neurol.* 308, 249–276. doi: 10.1002/cne.903080210

Iglesias, A., and Flagel, S. (2021). The paraventricular thalamus as a critical node of motivated behavior via the hypothalamic-thalamic-striatal circuit. *Front. Integr. Neurosci.* 15:706713. doi: 10.3389/fnint.2021.706713

Janak, P., and Tye, K. (2015). From circuits to behaviour in the amygdala. *Nature* 517, 284–292. doi: 10.1038/nature14188

Jefferson, J. (1974). Beta-adrenergic receptor blocking drugs in psychiatry. *Arch. Gen. Psychiatry* 31, 681–691. doi: 10.1001/archpsyc.1974.01760170071012

Jennings, J., Sparta, D., Stamatakis, A., Ung, R., Pleil, K., Kash, T., et al. (2013). Distinct extended amygdala circuits for divergent motivational states. *Nature* 496, 224–228. doi: 10.1038/nature12041

Ji, X., Cao, X., Zhang, C., Feng, Z., Zhang, X., Ma, L., et al. (2008). Pre- and postsynaptic beta-adrenergic activation enhances excitatory synaptic transmission in layer V/VI pyramidal neurons of the medial prefrontal cortex of rats. *Cereb. Cortex* 18, 1506–1520. doi: 10.1093/cercor/bhm177

Jodo, E., and Aston-Jones, G. (1997). Activation of locus coeruleus by prefrontal cortex is mediated by excitatory amino acid inputs. *Brain Res.* 768, 327–332. doi: 10.1016/s0006-8993(97)00703-8

Johnson, S., Emmons, E., Lingg, R., Anderson, R., Romig-Martin, S., LaLumiere, R., et al. (2019). Prefrontal-bed nucleus circuit modulation of a passive coping response set. *J. Neurosci.* 39, 1405–1419. doi: 10.1523/JNEUROSCI.1421-18.2018

Kasai, K., Yamasue, H., Gilbertson, M., Shenton, M., Rauch, S., and Pitman, R. (2008). Evidence for acquired pregenual anterior cingulate gray matter loss from a twin study of combat-related posttraumatic stress disorder. *Biol. Psychiatry* 63, 550–556. doi: 10.1016/j.biopsych.2007.06.022

Kent, J., and Rauch, S. (2003). Neurocircuitry of anxiety disorders. *Curr Psychiatry Rep.* 5, 266–273. doi: 10.1007/s11920-003-0055-8

Kenwood, M., Kalin, N., and Barbas, H. (2022). The prefrontal cortex, pathological anxiety, and anxiety disorders. *Neuropsychopharmacology* 47, 260–275. doi: 10.1038/s41386-021-01109-z

Kessler, R., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., et al. (2009). The global burden of mental disorders: An update from the WHO world mental health (WMH) surveys. *Epidemiol. Psichiatr. Soc.* 18, 23–33. doi: 10.1017/s1121189x00001421

Kessler, R., Berglund, P., Demler, O., Jin, R., Merikangas, K., and Walters, E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 62, 593–602. doi: 10.1001/archpsyc.62.6.593

Kessler, R., Chiu, W., Jin, R., Ruscio, A., Shear, K., and Walters, E. (2006). The epidemiology of panic attacks, panic disorder, and agoraphobia in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 63, 415–424. doi: 10.1001/archpsyc.63.4.415

Kessler, R., Petukhova, M., Sampson, N., Zaslavsky, A., and Wittchen, H. - (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int. J. Methods Psychiatr. Res.* 21, 169–184. doi: 10.1002/mpr.1359

Kestering-Ferreira, E., Tractenberg, S., Lumertz, F., Orso, R., Creutzberg, K., Wearick-Silva, L., et al. (2021). Long-term effects of maternal separation on anxiety-like behavior and neuroendocrine parameters in adult Balb/c mice. *Chronic Stress* 5:24705470211067181. doi: 10.1177/24705470211067181

Kim, M., Loucks, R., Palmer, A., Brown, A., Solomon, K., Marchante, A., et al. (2011). The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behav. Brain Res.* 223, 403–410. doi: 10.1016/j.bbr.2011.04.025

Kim, M., and Whalen, P. (2009). The structural integrity of an amygdala-prefrontal pathway predicts trait anxiety. *J. Neurosci.* 29, 11614–11618. doi: 10.1523/JNEUROSCI.2335-09.2009

Kim, S., Adhikari, A., Lee, S., Marshel, J., Kim, C., Mallory, C., et al. (2013). Diverging neural pathways assemble a behavioural state from separable features in anxiety. *Nature* 496, 219–223. doi: 10.1038/nature12018

Kirouac, G. (2015). Placing the paraventricular nucleus of the thalamus within the brain circuits that control behavior. *Neurosci. Biobehav. Rev.* 56, 315–329. doi: 10.1016/j.neubiorev.2015.08.005

Kirouac, G. (2021). The paraventricular nucleus of the thalamus as an integrating and relay node in the brain anxiety network. *Front. Behav. Neurosci.* 15:627633. doi: 10.3389/fnbeh.2021.627633

Krout, K., Belzer, R., and Loewy, A. (2002). Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *J. Comp. Neurol.* 448, 53–101. doi: 10.1002/cne.10236

Lago, T., Davis, A., Grillon, C., and Ernst, M. (2017). Striatum on the anxiety map: Small detours into adolescence. *Brain Res.* 1654(Pt B), 177–184. doi: 10.1016/j.brainres.2016.06.006

Lanius, R., Frewen, P., Girotti, M., Neufeld, R., Stevens, T., and Densmore, M. (2007). Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: A functional MRI investigation. *Psychiatry Res.* 155, 45–56. doi: 10.1016/j.pscychresns.2006.11.006

Lapiz, M., and Morilak, D. (2006). Noradrenergic modulation of cognitive function in rat medial prefrontal cortex as measured by attentional set shifting capability. *Neuroscience* 137, 1039–1049. doi: 10.1016/j.neuroscience.2005.09.031

Leach, L., Christensen, H., Mackinnon, A., Windsor, T., and Butterworth, P. (2008). Gender differences in depression and anxiety across the adult lifespan: The role of psychosocial mediators. *Soc. Psychiatry Psychiatr. Epidemiol.* 43, 983–998. doi: 10.1007/s00127-008-0388-z

LeBlanc, K., London, T., Szczot, I., Bocarsly, M., Friend, D., Nguyen, K., et al. (2020). Striatopallidal neurons control avoidance behavior in exploratory tasks. *Mol. Psychiatry* 25, 491–505. doi: 10.1038/s41380-018-0051-3

Lei, Z., Lam, Y., Li, C., Fu, Z., Ramkrishnan, A., Liu, S., et al. (2022). β2-adrenoceptors in the medial prefrontal cortex excitatory neurons regulate anxiety-like behavior in mice. *Int. J. Mol. Sci.* 23:5578. doi: 10.3390/ijms23105578

Li, J., Zhong, Y., Ma, Z., Wu, Y., Pang, M., Wang, C., et al. (2020). Emotion reactivity-related brain network analysis in generalized anxiety disorder: A task fMRI study. *BMC Psychiatry* 20:429. doi: 10.1186/s12888-020-02831-6

Li, S., and Kirouac, G. (2012). Sources of inputs to the anterior and posterior aspects of the paraventricular nucleus of the thalamus. *Brain Struct. Funct.* 217, 257–273. doi: 10.1007/s00429-011-0360-7

Liljeholm, M., and O'Doherty, J. (2012). Contributions of the striatum to learning, motivation, and performance: An associative account. *Trends Cogn. Sci.* 16, 467–475. doi: 10.1016/j.tics.2012.07.007

Lindauer, R., Booij, J., Habraken, J., van Meijel, E., Uylings, H., Olff, M., et al. (2008). Effects of psychotherapy on regional cerebral blood flow during trauma imagery in patients with post-traumatic stress disorder: A randomized clinical trial. *Psychol. Med.* 38, 543–554. doi: 10.1017/S0033291707001432

Liu, Y., Liang, X., Ren, W., and Li, B. (2014). Expression of β1- and β2-adrenoceptors in different subtypes of interneurons in the medial prefrontal cortex of mice. *Neuroscience* 257, 149–157. doi: 10.1016/j.neuroscience.2013.10.078

Loewke, A. C., Minerva, A. R., Nelson, A. B., Kreitzer, A. C., and Gunaydin, L. A. (2020). Fronto-striatal projections regulate approach-avoidance conflict. *bioRxiv [Preprint]* doi: 10.1101/2020.03.05.979708

Mack, N., Deng, S., Yang, S., Shu, Y., and Gao, W. (2022). Prefrontal cortical control of anxiety: Recent advances. *Neuroscientist* doi: 10.1177/10738584211069071 [Epub ahead of print].

Marek, G., and Aghajanian, G. (1999). 5-HT2A receptor or alpha1-adrenoceptor activation induces excitatory postsynaptic currents in layer V pyramidal cells of the medial prefrontal cortex. *Eur. J. Pharmacol.* 367, 197–206. doi: 10.1016/s0014-2999(98)00945-5

Marek, R., Sun, Y., and Sah, P. (2019). Neural circuits for a top-down control of fear and extinction. *Psychopharmacology* 236, 313–320. doi: 10.1007/s00213-018-5033-2

Martin, C., Kelly, T., Rayens, M., Brogli, B., Brenzel, A., Smith, W., et al. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* 41, 1495–1502. doi: 10.1097/00004583-200212000-00022

Martin, E., Ressler, K., Binder, E., and Nemeroff, C. (2010). The neurobiology of anxiety disorders: Brain imaging, genetics, and psychoneuroendocrinology. *Clin. Lab. Med.* 30, 865–891. doi: 10.1016/j.cll.2010.07.006

McCall, J., Siuda, E., Bhatti, D., Lawson, L., McElligott, Z., Stuber, G., et al. (2017). Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. *eLife* 6:e18247. doi: 10.7554/eLife.18247

Mitrano, D., Schroeder, J., Smith, Y., Cortright, J., Bubula, N., Vezina, P., et al. (2012). α-1 Adrenergic receptors are localized on presynaptic elements in the nucleus accumbens and regulate mesolimbic dopamine transmission. *Neuropsychopharmacology* 37, 2161–2172. doi: 10.1038/npp.2012.68

Möller, C., Wiklund, L., Sommer, W., Thorsell, A., and Heilig, M. (1997). Decreased experimental anxiety and voluntary ethanol consumption in rats following central but not basolateral amygdala lesions. *Brain Res.* 760, 94–101. doi: 10.1016/s0006-8993(97)00308-9

Mondin, T., Konradt, C., Cardoso Tde, A., Quevedo Lde, A., Jansen, K., Mattos, L., et al. (2013). Anxiety disorders in young people: A population-based study. *Braz. J. Psychiatry* 35, 347–352. doi: 10.1590/1516-4446-2013-1155

Moran, T. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. *Psychol. Bull.* 142, 831–864. doi: 10.1037/bul0000051

Moreira, C., Masson, S., Carvalho, M., and Brandão, M. (2007). Exploratory behaviour of rats in the elevated plus-maze is differentially sensitive to inactivation of the basolateral and central amygdaloid nuclei. *Brain Res. Bull.* 71, 466–474. doi: 10.1016/j.brainresbull.2006.10.004

Morilak, D., Barrera, G., Echevarria, D., Garcia, A., Hernandez, A., Ma, S., et al. (2005). Role of brain norepinephrine in the behavioral response to stress. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 29, 1214–1224. doi: 10.1016/j.pnpbp.2005.08.007

Morris, L., McCall, J., Charney, D., and Murrough, J. (2020). The role of the locus coeruleus in the generation of pathological anxiety. *Brain Neurosci. Adv.* 4:2398212820930321. doi: 10.1177/2398212820930321

Motzkin, J., Philippi, C., Oler, J., Kalin, N., Baskaya, M., and Koenigs, M. (2015). Ventromedial prefrontal cortex damage alters resting blood flow to the bed nucleus of stria terminalis. *Cortex* 64, 281–288. doi: 10.1016/j.cortex.2014.11.013

Northoff, G., and Tumati, S. (2019). "Average is good, extremes are bad" - Non-linear inverted U-shaped relationship between neural mechanisms and functionality of mental features. *Neurosci. Biobehav. Rev.* 104, 11–25. doi: 10.1016/j.neubiorev.2019.06.030

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., and Dolan, R. (2004). Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304, 452–454. doi: 10.1126/science.1094285

Otake, K., Kin, K., and Nakamura, Y. (2002). Fos expression in afferents to the rat midline thalamus following immobilization stress. *Neurosci. Res.* 43, 269–282. doi: 10.1016/s0168-0102(02)00042-1

Otis, J., Namboodiri, V., Matan, A., Voets, E., Mohorn, E., Kosyk, O., et al. (2017). Prefrontal cortex output circuits guide reward seeking through divergent cue encoding. *Nature* 543, 103–107. doi: 10.1038/nature21376

Otis, J., Zhu, M., Namboodiri, V., Cook, C., Kosyk, O., Matan, A., et al. (2019). Paraventricular thalamus projection neurons integrate cortical and hypothalamic signals for cue-reward processing. *Neuron* 103, 423–431.e4.

Pagotto, L., Mendlowicz, M., Coutinho, E., Figueira, I., Luz, M., Araujo, A., et al. (2015). The impact of posttraumatic symptoms and comorbid mental disorders on the health-related quality of life in treatment-seeking PTSD patients. *Compr. Psychiatry* 58, 68–73. doi: 10.1016/j.comppsych.2015.01.002

Parfitt, G., Nguyen, R., Bang, J., Aqrabawi, A., Tran, M., Seo, D., et al. (2017). Bidirectional control of anxiety-related behaviors in mice: Role of inputs arising from the ventral hippocampus to the lateral septum and medial prefrontal cortex. *Neuropsychopharmacology* 42, 1715–1728. doi: 10.1038/npp.2017.56

Paulus, M. (2008). The role of neuroimaging for the diagnosis and treatment of anxiety disorders. *Depress Anxiety* 25, 348–356. doi: 10.1002/da.20499

Pendyam, S., Bravo-Rivera, C., Burgos-Robles, A., Sotres-Bayon, F., Quirk, G., and Nair, S. (2013). Fear signaling in the prelimbic-amygdala circuit: A computational modeling and recording study. *J. Neurophysiol.* 110, 844–861. doi: 10.1152/jn.00961.2012

Penzo, M., and Gao, C. (2021). The paraventricular nucleus of the thalamus: An integrative node underlying homeostatic behavior. *Trends Neurosci.* 44, 538–549. doi: 10.1016/j.tins.2021.03.001

Pezawas, L., Meyer-Lindenberg, A., Drabant, E., Verchinski, B., Munoz, K., Kolachana, B., et al. (2005). 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: A genetic susceptibility mechanism for depression. *Nat. Neurosci.* 8, 828–834. doi: 10.1038/nn1463

Poe, G., Foote, S., Eschenko, O., Johansen, J., Bouret, S., Aston-Jones, G., et al. (2020). Locus coeruleus: A new look at the blue spot. *Nat. Rev. Neurosci.* 21, 644–659. doi: 10.1038/s41583-020-0360-9

Porter, J., Roy, A., Benson, B., Carlisi, C., Collins, P., Leibenluft, E., et al. (2015). Age-related changes in the intrinsic functional connectivity of the human ventral vs. dorsal striatum from childhood to middle age. *Dev. Cogn. Neurosci.* 11, 83–95. doi: 10.1016/j.dcn.2014.08.011

Quirk, G., Likhtik, E., Pelletier, J., and Paré, D. (2003). Stimulation of medial prefrontal cortex decreases the responsiveness of central amygdala output neurons. *J. Neurosci.* 23, 8800–8807. doi: 10.1523/JNEUROSCI.23-25-08800.2003

Radley, J., Anderson, R., Hamilton, B., Alcock, J., and Romig-Martin, S. (2013). Chronic stress-induced alterations of dendritic spine subtypes predict functional decrements in an hypothalamo-pituitary-adrenal-inhibitory prefrontal circuit. *J. Neurosci.* 33, 14379–14391. doi: 10.1523/JNEUROSCI.0287-13.2013

Radley, J., Gosselink, K., and Sawchenko, P. (2009). A discrete GABAergic relay mediates medial prefrontal cortical inhibition of the neuroendocrine stress response. *J. Neurosci.* 29, 7330–7340. doi: 10.1523/JNEUROSCI.5924-08.2009

Radley, J., and Sawchenko, P. E. (2011). A common substrate for prefrontal and hippocampal inhibition of the neuroendocrine stress response. *J. Neurosci.* 31, 9683–9695. doi: 10.1523/JNEUROSCI.6040-10.2011

Ramos, B., and Arnsten, A. (2007). Adrenergic pharmacology and cognition: Focus on the prefrontal cortex. *Pharmacol. Ther.* 113, 523–536. doi: 10.1016/j.pharmthera.2006.11.006

Ramos, B., Colgan, L., Nou, E., Ovadia, S., Wilson, S., and Arnsten, A. (2005). The beta-1 adrenergic antagonist, betaxolol, improves working memory performance in rats and monkeys. *Biol. Psychiatry* 58, 894–900. doi: 10.1016/j.biopsych.2005.05.022

Rauch, S., Dougherty, D., Malone, D., Rezai, A., Friehs, G., Fischman, A., et al. (2006). A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. *J. Neurosurg.* 104, 558–565. doi: 10.3171/jns.2006.104.4.558

Risold, P., and Swanson, L. (1997). Chemoarchitecture of the rat lateral septal nucleus. *Brain Res. Brain Res. Rev.* 24, 91–113. doi: 10.1016/s0165-0173(97)00008-8

Rizzi-Wise, C., and Wang, D. (2021). Putting together pieces of the lateral septum: Multifaceted functions and its neural pathways. *eNeuro* 8:ENEURO.0315-21.2021. doi: 10.1523/ENEURO.0315-21.2021

Robinson, O., Pike, A., Cornwell, B., and Grillon, C. (2019). The translational neural circuitry of anxiety. *J. Neurol. Neurosurg. Psychiatry* 90, 1353–1360. doi: 10.1136/jnnp-2019-321400

Rodriguez-Romaguera, J., Do Monte, F., and Quirk, G. (2012). Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. *Proc. Natl. Acad. Sci. U.S.A.* 109, 8764–8769. doi: 10.1073/pnas.1200782109

Ross, J., and Van Bockstaele, E. (2021). The locus coeruleus- norepinephrine system in stress and arousal: Unraveling historical, current, and future perspectives. *Front. Psychiatry* 11:601519. doi: 10.3389/fpsyt.2020.601519

Santana, N., and Artigas, F. (2017). Laminar and cellular distribution of monoamine receptors in rat medial prefrontal cortex. *Front. Neuroanat.* 11:87. doi: 10.3389/fnana.2017.00087

Santana, N., Mengod, G., and Artigas, F. (2013). Expression of α(1)-adrenergic receptors in rat prefrontal cortex: Cellular co-localization with 5-HT(2A) receptors. *Int. J. Neuropsychopharmacol.* 16, 1139–1151. doi: 10.1017/S1461145712001083

Schott, B., Minuzzi, L., Krebs, R., Elmenhorst, D., Lang, M., Winz, O., et al. (2008). Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. *J. Neurosci.* 28, 14311–14319. doi: 10.1523/JNEUROSCI.2058-08.2008

Sesack, S., Deutch, A., Roth, R., and Bunney, B. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. *J. Comp. Neurol.* 290, 213–242. doi: 10.1002/cne.902900205

Sestieri, C., Corbetta, M., Romani, G., and Shulman, G. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: Functional and topographic analyses. *J. Neurosci.* 31, 4407–4420. doi: 10.1523/JNEUROSCI.3335-10.2011

Sheehan, T., Chambers, R., and Russell, D. (2004). Regulation of affect by the lateral septum: Implications for neuropsychiatry. *Brain Res. Brain Res. Rev.* 46, 71–117. doi: 10.1016/j.brainresrev.2004.04.009

Simmons, A., Paulus, M., Thorp, S., Matthews, S., Norman, S., and Stein, M. (2008). Functional activation and neural networks in women with posttraumatic stress disorder related to intimate partner violence. *Biol. Psychiatry* 64, 681–690. doi: 10.1016/j.biopsych.2008.05.027

Stahl, S. (1992). Neuroendocrine markers of serotonin responsivity in depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 16, 655–659. doi: 10.1016/0278-5846(92)90022-7

Stein, M., Simmons, A., Feinstein, J., and Paulus, M. (2007). Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. *Am. J. Psychiatry* 164, 318–327. doi: 10.1176/ajp.2007.164.2.318

Strigo, I., Matthews, S., and Simmons, A. (2010). Right anterior insula hypoactivity during anticipation of homeostatic shifts in major depressive disorder. *Psychosom. Med.* 72, 316–323. doi: 10.1097/PSY.0b013e3181d07873

Tamburella, A., Micale, V., Leggio, G., and Drago, F. (2010). The beta3 adrenoceptor agonist, amibegron (SR58611A) counteracts stress-induced behavioral and neurochemical changes. *Eur. Neuropsychopharmacol.* 20, 704–713. doi: 10.1016/j.euroneuro.2010.04.006

Tang, Y., Rothbart, M., and Posner, M. (2012). Neural correlates of establishing, maintaining, and switching brain states. *Trends Cogn. Sci.* 16, 330–337. doi: 10.1016/j.tics.2012.05.001

Thomas, E., Burock, D., Knudsen, K., Deterding, E., and Yadin, E. (2013). Single unit activity in the lateral septum and central nucleus of the amygdala in the elevated plus-maze: A model of exposure therapy? *Neurosci. Lett.* 548, 269–274. doi: 10.1016/j.neulet.2013.05.078

Tolin, D., and Foa, E. (2006). Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychol. Bull.* 132, 959–992. doi: 10.1037/0033-2909.132.6.959

Torkaman-Boutorabi, A., Hashemi-Hezaveh, S., Sheidadoust, H., and Zarrindast, M. (2014). The possible role of medial prefrontal cortex beta-1-adrenoceptors in morphine-induced amnesia. *Pharmacology* 93, 272–277. doi: 10.1159/000362282

Treit, D., Pesold, C., and Rotzinger, S. (1993). Dissociating the anti-fear effects of septal and amygdaloid lesions using two pharmacologically validated models of rat anxiety. *Behav. Neurosci.* 107, 770–785. doi: 10.1037//0735-7044.107.5.770

Tye, K., Prakash, R., Kim, S., Fenno, L., Grosenick, L., Zarabi, H., et al. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature* 471, 358–362. doi: 10.1038/nature09820

van Tol, M., Demenescu, L., van der Wee, N., Kortekaas, R., Marjan, M. A., Boer, J., et al. (2012). Functional magnetic resonance imaging correlates of emotional word encoding and recognition in depression and anxiety disorders. *Biol. Psychiatry* 71, 593–602. doi: 10.1016/j.biopsych.2011.11.016

Vertes, R. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse* 51, 32–58. doi: 10.1002/syn.10279

Wang, M., Ramos, B., Paspalas, C., Shu, Y., Simen, A., Duque, A., et al. (2007). Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell* 129, 397–410. doi: 10.1016/j.cell.2007.03.015

Whalen, P., Bush, G., McNally, R., Wilhelm, S., McInerney, S., Jenike, M., et al. (1998). The emotional counting Stroop paradigm: A functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol. Psychiatry* 44, 1219–1228. doi: 10.1016/s0006-3223(98)00251-0

Wohleb, E., Hanke, M., Corona, A., Powell, N., Stiner, L., Bailey, M., et al. (2011). β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. *J. Neurosci.* 31, 6277–6288. doi:10.1523/JNEUROSCI.0450-11.2011

Xing, B., Li, Y., and Gao, W. (2016). Norepinephrine versus dopamine and their interaction in modulating synaptic function in the prefrontal cortex. *Brain Res.* 1641(Pt B), 217–233. doi: 10.1016/j.brainres.2016.01.005

Yassa, M., Hazlett, R., Stark, C., and Hoehn-Saric, R. (2012). Functional MRI of the amygdala and bed nucleus of the stria terminalis during conditions of uncertainty in generalized anxiety disorder. *J. Psychiatr. Res.* 46, 1045–1052. doi: 10.1016/j.jpsychires.2012.04.013

Yonkers, K., Bruce, S., Dyck, I., and Keller, M. (2003). Chronicity, relapse, and illness–course of panic disorder, social phobia, and generalized anxiety disorder: Findings in men and women from 8 years of follow-up. *Depress Anxiety* 17, 173–179. doi: 10.1002/da.10106

Zhou, H., Sun, Y., Cai, W., He, X., Yi, F., Li, B., et al. (2013). Activation of β2-adrenoceptor enhances synaptic potentiation and behavioral memory via cAMP-PKA signaling in the medial prefrontal cortex of rats. *Learn. Mem.* 20, 274–284. doi: 10.1101/lm.030411.113

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The influence of action on perception spans different effectors

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Perception and action are fundamental processes that characterize our life and our possibility to modify the world around us. Several pieces of evidence have shown an intimate and reciprocal interaction between perception and action, leading us to believe that these processes rely on a common set of representations. The present review focuses on one particular aspect of this interaction: the influence of action on perception from a motor effector perspective during two phases, action planning and the phase following execution of the action. The movements performed by eyes, hands, and legs have a different impact on object and space perception; studies that use different approaches and paradigms have formed an interesting general picture that demonstrates the existence of an action effect on perception, before as well as after its execution. Although the mechanisms of this effect are still being debated, different studies have demonstrated that most of the time this effect pragmatically shapes and primes perception of relevant features of the object or environment which calls for action; at other times it improves our perception through motor experience and learning. Finally, a future perspective is provided, in which we suggest that these mechanisms can be exploited to increase trust in artificial intelligence systems that are able to interact with humans.

KEYWORDS

object properties, reaching, grasping, eye movements, walking

Introduction

At the basis of a successful behavior there is the interplay between perception and action. Typically, perception informs the action mechanism regarding the features of the environment and this mechanism is responsible for changes in the environment. If, on the one hand, it is doubtless that perception influences the action, the influence of action on perception cannot be taken for granted to the same extent. Starting from such a consideration, this review aims to examine the influence of action on visual perception of different properties of objects (i.e., size, orientation, and location) focusing on the actions performed by different motor effectors such as the eye, the hand, and the leg. Since two phases can be distinguished when looking at the influence of action on perception, namely planning and execution, in the following sections we provide a separate overview of some of the studies that explore the effect of action planning on the perception of the object/stimulus, and of those that examine action execution and its effect on perception.

The effect of action planning on perception

As perceivers, we receive, on a daily basis, a wide variety of information concerning the features of the surrounding environment. As active players, we constantly explore this environment based on the sensory processing of those stimuli related to our goals/intentions and subsequent actions. For example, everyday tasks such as grasping a cup or the handle of a frying pan are highly precise actions that we perform automatically; however, these involve a complex sensorimotor approach, many aspects of which are still unknown.

An action, an intended and targeted movement, is distinguished by several sequential sections that organize its processing and work in close coordination with perception (Hommel et al., 2016). Within this processing (assessment of environmental information, location in three-dimensional space, and selection, integration, and initiation of the action), action planning represents a fundamental component (Hommel et al., 2016; Mattar and Lengyel, 2022).

Action planning is specified as a process which considers the execution of actions based on the environment and expected outcomes (Sutton and Barto, 1998; Mattar and Lengyel, 2022). Action planning could be referred to as the period between the decision phase and the initial impulse phase. During the action planning phase, the player generates an action goal (based on the temporal and spatial properties of the environment) which is then transferred to the motor system to achieve that specific purpose. That is, first the information is organized and subsequently integrated into a plan. This particularity provides plasticity and favors the adaptation to possible changes to the input information and goals (Mattar and Lengyel, 2022). For example, when grasping an object, it can be observed how the hand adjusts to the intrinsic properties of that object (Jeannerod, 1981), which hints at the relevance of action planning in the interaction between the environment and the final goal. In fact, input information is processed in parallel by pathways acting in a shared action-perception framework (Prinz, 1990; Hommel et al., 2001), within which planning itself has been observed to influence (Hommel et al., 2001, 2016; Witt, 2018).

Notwithstanding the considerable scientific literature on how planning contributes to cognitive processes, the current findings merely give us a glimpse of the long road ahead. Here, in the following sections, we outline the most important behavioral studies regarding the impact of action planning on perception.

The eye domain

Our visual system captures primordial information which guides our actions. Once the visual environment and objects of interest are defined, the visuo-spatial information is then transferred in order to plan, execute, and control those goal-directed actions (Hayhoe, 2017). The impact of vision on motor actions has always been a topic of great scientific interest (Prablanc et al., 1979; Desmurget et al., 1998; Land, 2006, 2009). Several decades ago, groundbreaking studies were already describing how vision improves goal-directed movement accuracy (Woodworth, 1899; Bernstein, 1967). Since then, subsequent studies have sought to investigate how vision influences planning, execution, and control of movements.

Visual information greatly contributes to the action planning phase. During planning, the presence of visual feedback regarding the limb is paramount. For example, motor actions are more accurate when visual feedback is provided during action planning, regardless of whether the limb is visible or not during the action (Prablanc et al., 1979; Conti and Beaubaton, 1980; Pelisson et al., 1986; Velay and Beaubaton, 1986; Elliott et al., 1991, 2014; Rossetti et al., 1994; Desmurget et al., 1995, 1997; Coello and Grealy, 1997; Bagesteiro et al., 2006; Bourdin et al., 2006; Sarlegna and Sainburg, 2009).

Indeed, vision plays a key role in action planning since movements are apparently planned as vectors based on the extrinsic coordinates of the visual environment (Morasso, 1981; Flanagan and Rao, 1995; Wolpert et al., 1995; Sarlegna and Sainburg, 2009). Once visual information has been extracted, planning should consider those properties that will shape further actions. An example may be that of driving a car and approaching an intersection. Our visual system extracts information regarding the location and movement of other cars, pedestrians, and traffic signals at the intersection. Based on the extrinsic coordinates of the visual environment, during action planning we determine the appropriate vectors for our movements, such as accelerating, braking, or turning, that allow us to navigate the intersection safely and efficiently.

In a common framework, two stages within action planning have been suggested: the primary stage, in which vision is fundamental to determine the visuo-spatial attributes (target, limbs, and environment), and the secondary stage, in which the primary input is transformed into motor commands to generate the action (Sarlegna and Sainburg, 2009). Therefore, in a normal context, during action planning, vision provides the relevant information which facilitates the success of an action.

Acquiring visuo-spatial information would not be possible without eye movements. If a target falls in the peripheral visual field, eye movements assist in conveying the exact location of the target. Suppose we want to reach for an object. Considering the retinal spatial resolution, when a target of interest to be reached is identified, the region of highest retinal resolution should be focused on that target (Liversedge and Findlay, 2000; Land, 2006). To this end, before the reaching action begins, the eyes perform a saccadic movement toward the object and then fixate it constantly until it is reached by the hand. Within this brief scenario, the relevance of eye movements, which continuously support the coupling of vision and action, can be appreciated (Land, 2006, 2009; Hayhoe, 2017; de Brouwer et al., 2021).

Research into the interaction between the visual and motor systems has shown how the eyes constantly support and guide our actions in multiple dynamic tasks (Angel et al., 1970; Biguer et al., 1982; Pelisson et al., 1986; Land, 1992; Land et al., 1999; Neggers and Bekkering, 1999, 2000, 2001, 2002; Johansson et al., 2001; Patla and Vickers, 2003). For example, Land et al. (1999) demonstrated that eye movements are directed to those objects

involved in our daily actions. In Neggers and Bekkering (1999, 2000, 2001, 2002) studies, a mechanism of gaze anchoring during hand actions was elegantly demonstrated. They observed that during reaching movements observers did not make saccadic movements toward another target until the hand had arrived at the target of interest. Similar findings were reported by Johansson et al. (2001). They instructed participants to reach and grasp a bar which they subsequently had to move while avoiding obstacles and finally attach to a switch. They reported that gaze fixation was focused on those points that were critical to the action. That is, eye movements continuously guided the action to grasp, navigate, and attach the object (Johansson et al., 2001). In other studies, it was shown that fixation patterns differ when an object is grasped or viewed passively (Vishwanath and Kowler, 2003; Brouwer et al., 2009). Both studies showed that during visualization, fixation patterns were focused on the object's center of gravity, whereas during grasping, fixation was affected by the contact zone of the index and thumb digits. Interestingly, Brouwer et al. (2009) observed that saccadic reaction times were slower in the grasping task as compared to the visualization task. This outcome reflects that the onset of eye movement was dependent on action planning, i.e., in those conditions in which the eye and hand participated in the same process.

The eye reaction time latencies relative to the action have already been reported in several studies (Bekkering et al., 1994, 1995; Lünenburger et al., 2000; Pelz et al., 2001; Hayhoe et al., 2003). Bekkering et al. (1994) measured eye and hand motor response latencies using single- and dual-task methodologies. Like Brouwer et al. (2009), and as can be appreciated in Figure 1, saccade reaction time latencies were highest in the dual approach, i.e., when both the eye and hand simultaneously moved toward the visual target. Hand latencies were similar in both the single and dual tasks (Bekkering et al., 1994). Conversely, in another study, lower saccadic reaction time latencies were reported when the eye and hand moved simultaneously toward a common target (Lünenburger et al., 2000). Perhaps the type of planned action (pointing, reaching, grasping, etc.) is decisive within this interference effect. Longer processing times may be required according to the type of action planned, and, thus, eye reaction times could be affected differently (Brouwer et al., 2009). These findings demonstrate that these motor systems (eye-limb) are not independent from each other, and that they share synergistic processes when targeted to the same goal.

Recent studies have revealed how eye movements support selection and action planning toward a goal. Particularly, exploration of the eye-limb relationship in naturalistic tasks has revealed how eye movements provide continuous information from the visual environment, generating a context of intrinsic properties and spatial coordinates during action planning to effectively guide future movements (Zelinsky et al., 1997; Land et al., 1999; Pelz et al., 2001; Brouwer et al., 2009). In tasks involving jar-opening or hand-washing it has been observed that reaching actions are preceded by anticipatory fixations toward the target of interest (Pelz et al., 2001; Hayhoe et al., 2003). These fixations occur during action planning and help the observer to obtain decisive spatial information to assist in the future action (Hayhoe et al., 2003). Other activities, such as walking or driving over difficult and tortuous surfaces, have shown how visuo-spatial information derived from eye movements is primordial during action planning

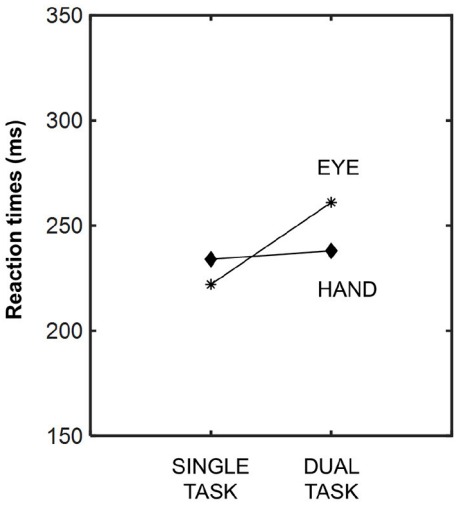

FIGURE 1
Averaged latencies of eye and hand responses, measured in milliseconds, under both experimental conditions: single- and dual-task. Modified from Bekkering et al. (1994).

(Land and Lee, 1994; Patla and Vickers, 2003; Land, 2006). For example, while walking, gaze fixation anticipates action by 0.8–1.1 s on average (Patla and Vickers, 2003; Land, 2006). This suggests that during planning, the visual system acts as an anticipatory system, in a feedforward manner, for the execution of the action.

Although previous studies focused on the role of the eyes as support in the planning of actions performed by other motor effectors, multiple studies have extensively examined the impact of eye motor planning on visual perception within the oculomotor system. These investigations have shown that spatial perception is enhanced at the location where the eye movement is intended to go, shortly before its execution (Hoffman and Subramaniam, 1995; Deubel and Schneider, 1996; Neggers et al., 2007). For example, research has shown that saccade target selection is influenced by object recognition (Deubel and Schneider, 1996), and that visual attention can influence the planning and execution of saccadic eye movements (Hoffman and Subramaniam, 1995). Additionally, a coupling between visuospatial attention and eye movements has been observed (Neggers et al., 2007), with attention often following the gaze. This coupling can be disrupted when transcranial magnetic stimulation is applied to the frontal eye fields, suggesting a causal relationship between attention and eye movements (Neggers et al., 2007). These outcomes may imply that the process of eye motor planning can have a significant impact on perception. Although the exact mechanisms underpinning this impact are not yet fully known, it is believed that the coordinated activity of multiple brain regions and systems, including the saccadic system, vestibular system, and attentional processes, is at play.

The hand domain

Over the past few decades, the scientific literature has provided compelling evidence as to how perception is biased by the planning of arm movements, such as reaching and grasping

(Musseler and Hommel, 1997; Prinz, 1997; Craighero et al., 1999; Wohlschläger, 2000; Hommel et al., 2001; Knoblich and Flach, 2001; Wühr and Müsseler, 2001; Hamilton et al., 2004; Kunde and Wuhr, 2004; Fagioli et al., 2007; Wykowska et al., 2009, 2011; Kirsch et al., 2012; Kirsch and Kunde, 2013; Kirsch, 2015). From the perceiver's point of view, it is intriguing to consider the fact that when planning a reaching or grasping movement toward an object, the perception of the object is somehow influenced. For example, when reaching for a cup of coffee, the perceiver's visual system considers the cup's location and orientation relative to the perceiver's body. The perceived properties of the cup may also be influenced by the planned action, as the perceiver's motor system may need to make adjustments based on these properties in order to successfully grasp the cup. This suggests that the motor system is not only involved in executing actions, but also in shaping perception based on the perceiver's intended actions. In fact, multiple perceptual aspects, such as orientation, size, luminance, location, motion, among many others, have been reported as target features that are directly influenced by action planning (Musseler and Hommel, 1997; Craighero et al., 1999; Wohlschläger, 2000; Zwickel et al., 2007; Lindemann and Bekkering, 2009; Kirsch et al., 2012). For example, studies by Kirsch have shown how planning itself interferes with distance perception and, therefore, with target spatial location (Kirsch et al., 2012; Kirsch and Kunde, 2013; Kirsch, 2015).

This action(planning)-perception interaction is dependent on whether the goal is related or not to the action. When there is a direct relationship between goal and action, perception is facilitated by the planning of the action, whereas when the two are independent, action planning interferes with perception (Hommel et al., 2016).

Several benchmark studies carried out in the 1990s and 2000s demonstrated various scenarios exhibiting facilitation and interference. Based on a set of five experiments, Musseler and Hommel (1997) reported the impact of action planning on the direction perception of a visual stimulus. Direction perception (right or left) was influenced by action planning concurrence (right or left button press). Specifically, identifying the direction of a right-pointing stimulus was more costly after planning a right button press (Musseler and Hommel, 1997). Given the common code (Hommel et al., 2001), action planning toward a concrete direction led to an interference scenario, i.e., the share-code weighting favored action over perception (Musseler and Hommel, 1997; Hommel et al., 2016).

Subsequent studies corroborated the interaction between perception and action planning processes. In Wohlschläger (2000) study, observers had to report the perceived motion direction of projected discs while turning a knob in a designated direction. Hand motion direction biased subjects' motion perception. Under a similar experimental approach to that of Craighero et al. (1999), Lindemann and Bekkering (2009) instructed volunteers to reach, grasp, and subsequently rotate an x-shaped manipulandum following the visual go signal's onset. Here, a tilted bar (-45° or +45°) served as the visual go signal. Volunteers detected the onset of the go signal faster in the congruent conditions, in which the go signal, and action planning presented the same direction (Lindemann and Bekkering, 2009). These findings imply that perception was facilitated in the direction in which the action had been previously planned. In contrast, like Musseler and Hommel (1997), Zwickel et al. (2007) reported action (planning)-perception coupling but in an interference scenario. In their study, reaction times were longer when movement deviations agreed with the action planning direction (Zwickel et al., 2007). Interference situations have also been reported by other authors (Schubö et al., 2001; Hamilton et al., 2004; Zwickel et al., 2010), indicating that the action (planning)-perception coupling is dependent on whether the perceived target is linked or not to the planned action.

Recent research has proven the relevance of the type of action planning in how perception is biased (Bekkering and Neggers, 2002; Fagioli et al., 2007; Symes et al., 2008; Wykowska et al., 2009, 2011; Gutteling et al., 2011). Bekkering and Neggers (2002) instructed observers to point at or grasp an object with a specific orientation and color. The authors found that while color errors were identical in both approaches, the number of orientation errors was lower in the grasping scenario (Bekkering and Neggers, 2002). Gutteling et al. (2011) asked participants to perform a grasping or pointing movement simultaneously with an orientation or luminance discrimination task (see Figure 2). Orientation sensitivity increased when planning a grasping action, as opposed to a pointing action. Size, location, and luminance have also been described as being perceptually dependent attributes of the type of action planning (Fagioli et al., 2007; Wykowska et al., 2009, 2011; Kirsch et al., 2012; Wykowska and Schubö, 2012; Kirsch and Kunde, 2013). Fagioli et al. (2007) revealed that planning a grasping action improved the ability to detect deviations in object size, while planning a reaching action facilitated the detection of location deviations. Studies by Wykowska et al. (2009) and Wykowska and Schubö (2012) corroborated the finding that planning to grasp improves size perception, while planning to reach enhances luminance perception.

All the above-mentioned scientific evidence seems to support the common coupling of action(planning)-perception. Planning an action primes those perceptual dimensions that can enhance one's own action (Hommel et al., 2001; Wykowska et al., 2009).

The majority of studies cited have shown that the motor system dynamically modulates the incoming perceptual information. However, these modulations have been observed when the perceptual information is intermixed with attentional and decisional mechanisms because they are strictly related to the motor response (i.e., Gutteling et al., 2011). Relevant literature was dedicated to understanding the temporal tuning of incoming perceptual information at very early cortical stages. To do this, different studies measured the contrast sensitivity of a brief visual stimulus that was not correlated with the action to be performed, and that was presented at different times during motor planning and execution. These studies used contrast sensitivity because it represents and reflects the activity of the primary visual cortex, since it has been demonstrated that the change of contrast visibility requires a modulation at this early cortical level (Boynton et al., 1999). Furthermore, it has recently been demonstrated that both sensory and motor processes are regulated by a rhythmic process that reflects the oscillations of neuronal excitability (Buzsáki and Draguhn, 2004; Thut et al., 2012). Combining all these

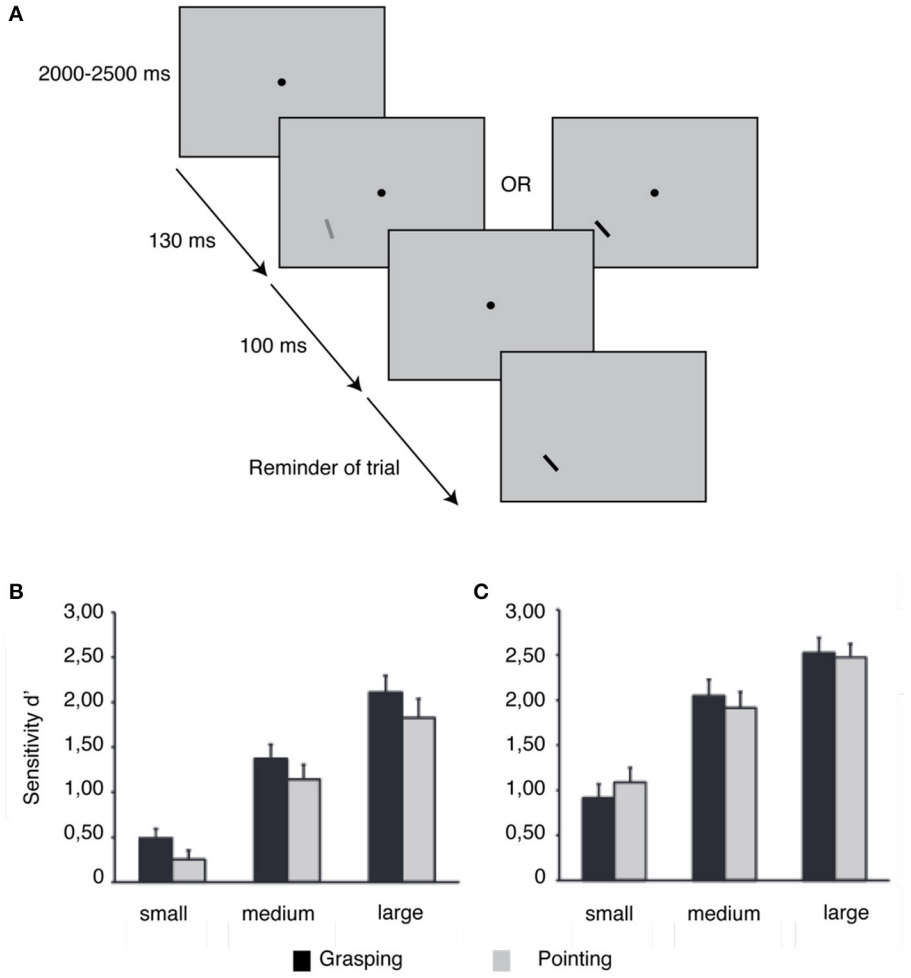

FIGURE 2
Effect of grasping and pointing planning on orientation and luminance detection. **(A)** Experimental approach. Experiments 1 and 2 used a similar stimulus display, which included a fixation spot and two bars. Participants were instructed to execute an action after a go-cue signaled by the appearance of the first bar. The second bar was either rotated slightly (Experiment 1) or differed in luminance (Experiment 2) from the first bar. **(B)** In Experiment 1, participants showed better orientation discrimination when planning a grasping action rather than when planning a pointing action. **(C)** Experiment 2 did not reveal any consistent change in luminance discrimination between grasping and pointing planning. Modified from Gutteling et al. (2011).

pieces of evidence, Tomassini et al. (2015) evaluated whether the rhythmic oscillations of visual contrast sensitivity were also present when synchronizing the perceptual information with the onset of a reaching and grasping movement. They found that the oscillations in contrast sensitivity emerged around 500 ms before movement onset, during action planning, even if perception was not related to the motor task (see Figure 3). These findings were extended in an electroencephalographic (EEG) study, in which the same group demonstrated that motor planning is combined with perceptual neural oscillations (Tomassini et al., 2017). The perceptual "action-locked" oscillations were also observed when the movements were performed with the eyes (Benedetto and Morrone, 2017; Benedetto et al., 2020). In this study, the results showed that saccadic preparation and visual contrast sensitivity oscillations are coupled, suggesting a functional alignment of the saccade onset with the visual suppression (Benedetto and Morrone, 2017).

The leg domain

The above-discussed research focuses on peripersonal space. However, it has been observed that the impact of action planning on perception can extend to the leg effector domain, resulting in facilitation effects on the perception of extrapersonal space. Several studies have shown that, when viewing objects in our extrapersonal space, we scale the perceived distance according to our intended motor action. For example, if we plan to walk a certain distance, we perceive the distance based on the amount of walking effort needed to traverse it, while, if we intend to throw a ball, the perceived distance is based on the amount of throwing effort required (Witt et al., 2004; Proffitt, 2006; Witt and Proffitt, 2008). The way we perceive our environment seems to be influenced by the specific actions we anticipate taking, with perception being adjusted based on an optimal cost-benefit principle (Proffitt, 2006). Recently, Fini et al. (2014, 2015a,b)

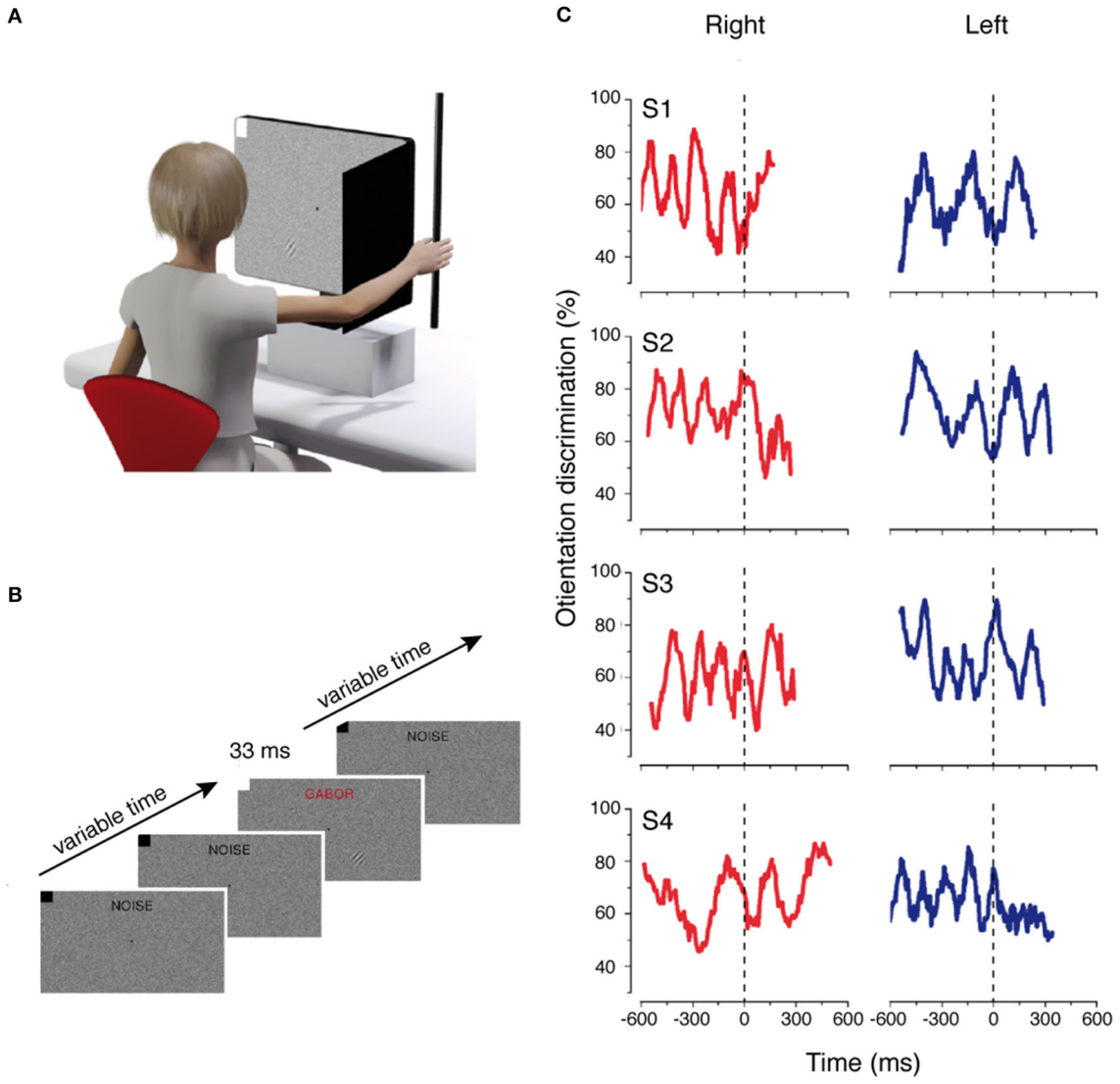

FIGURE 3
Rhythmic oscillations of contrast sensitivity synchronized with hand movements. **(A)** Experimental setup of the motor and visual tasks. **(B)** Example of trial sequence. Visual noise and fixation point were presented from the beginning of the trial to the end. At a random time from the start of the trial, a Gabor stimulus was displayed to the lower right or to the lower left of fixation. **(C)** Time course of the orientation discrimination responses for each participant aligned with the onset of the hand movement. Modified from Tomassini et al. (2015).

used a virtual paradigm to investigate the influence of anticipated actions on spatial perception. Participants were asked to judge the location of an object positioned at progressively increasing or decreasing distances from a reference frame. They noticed that participants perceived the target object to be closer to their own body when they intended to move toward it compared to when they had no intention of moving. This effect was not observed when the target object was compared to another static object (Fini et al., 2015a). Additionally, studies have demonstrated that when leg actions such as walking or running are primed, the portion of extrapersonal space judged as near in other-based coordinates is significantly expanded (Fini et al., 2017), together with an extension of peripersonal space during full-body actions such as walking compared to standing (Noel et al., 2015). These findings suggest that visual perception of the physical environment beyond our body is heavily influenced by our actions, intentions, and physical abilities. Apparently, the main way of exploring the extended environment seems to be through locomotion, as it is the only way to cover distances and access information from more distant locations in the extrapersonal space compared to near extrapersonal locations, where information can be extracted from different sources (di Marco et al., 2019).

The effect of action execution on perception

Human ability to perform actions impacts the visual perception of objects/targets. This represents the framework within which the influence of action execution on perception is typically explained.

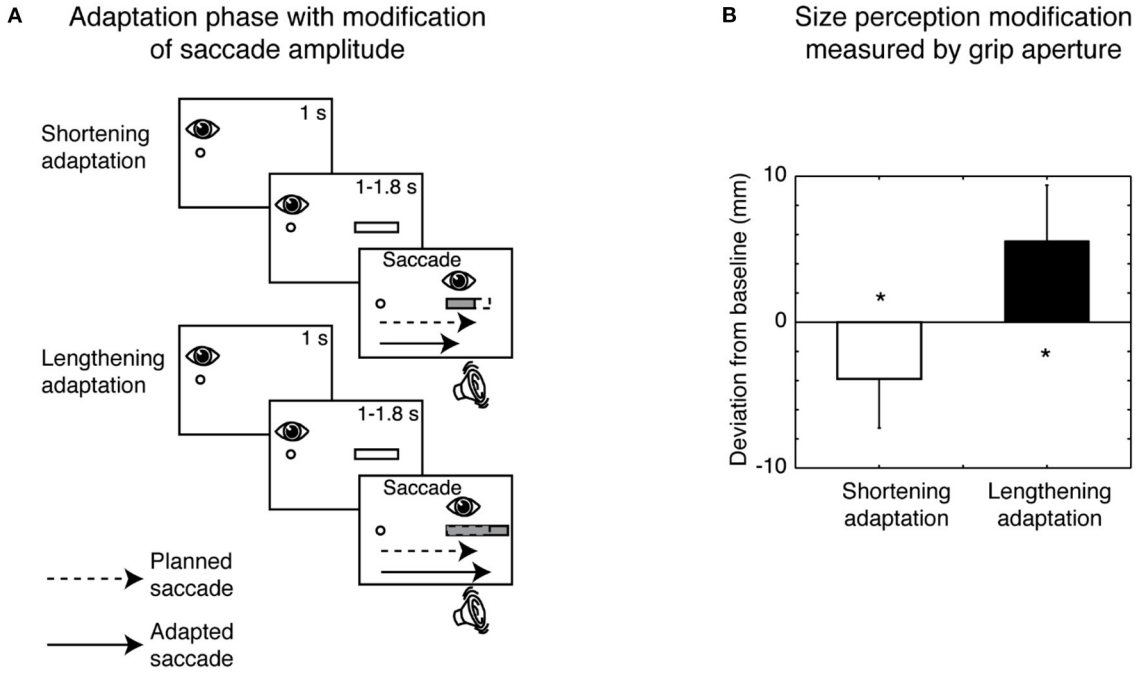

FIGURE 4
Size perception modification induced by saccadic adaptation. **(A)** Top row, Shortening adaptation condition. The fixation point was presented at the start of the trial. After 1 s, a bar appeared, but participants had to continue to focus on the fixation target. After a randomized time, an acoustic signal indicated the possibility of executing a saccade toward the bar. Then the bar was decreased in size by 30% of its length at the right border as soon as the saccade was detected. Bottom row, Lengthening adaptation phase. This condition was identical to the shortening adaptation condition, with the only difference being that the bar was increased in size by 30% during saccade execution. **(B)** Mean deviation of grip aperture from baseline in shortening adaptation (white column) and lengthening (black column) adaptation. The data were averaged across subjects and sizes. Error bars indicate SE. *$p < 0.05$, significant deviations from baseline (modified from Bosco et al., 2015).

The action-specific effects indicate all the effects generated from the ability to act on spatial perception (Proffitt, 2006, 2008). The first study suggesting that spatial perception was influenced by the ability to perform an action was carried out by Bhalla and Proffitt (1999). They showed that the perception of hill slant was influenced by the physiological potential. In fact, if the energetic costs required to climb them increased, the hills were estimated to be steeper. Following this work, several researchers have focused and expanded this concept beyond the physiological potential; however, these studies focus on other aspects of action. For example, softball players who were good at hitting the ball estimated it as being bigger compared to others (Witt and Proffitt, 2005; Gray, 2013). Similarly, archers who had a better shot than others estimated the target as bigger (Lee et al., 2012). Parkour athletes judged walls as lower compared to non-parkour athletes (Taylor et al., 2011), and good tennis players judged the net as being lower (Witt and Sugovic, 2010).

Another study examining a different branch of action-specific effects analyzed the affordance of the object, in other words, the possibility to act on or with an object (Gibson, 1979). Typically, the measurement of affordance perception is carried out by assessing the point at which an action is perceived as barely possible. For example, some studies have explored the width of a doorway that is perceived as being just possible to pass through, or the height of a step at which the affordance of stepping up is perceived (Warren, 1984; Mark, 1987; Warren and Whang, 1987). Other examples are studies in which people with broader shoulders perceived doorways to be smaller compared to people with narrower shoulders (Stefanucci and Geuss, 2009), or studies in which a target is presented beyond the distance of the arm's reach: the target is perceived as being closer when the participants use a reach-extending tool to reach the target and more distant when they reach without the tool (Witt et al., 2005; Witt and Proffitt, 2008; Witt, 2011; Davoli et al., 2012; Osiurak et al., 2012; Morgado et al., 2013). Given all these remarkable data, the next section focuses on the action-specific effects on perception as a function of the specific effector used, expanding the panorama to other investigation modes.

The eye domain

In the eye realm, the effect of saccade execution on perception has been investigated through saccadic adaptation and perisaccadic mislocalization mechanisms. Saccadic adaptation allows researchers to study how saccade amplitudes change according to changes in the post-saccadic target shift. This change can be either parallel or orthogonal to the main direction of the saccade. In other words, it is well established that saccade amplitudes adapt when a small target is horizontally shifted during saccade execution to another position in relation to

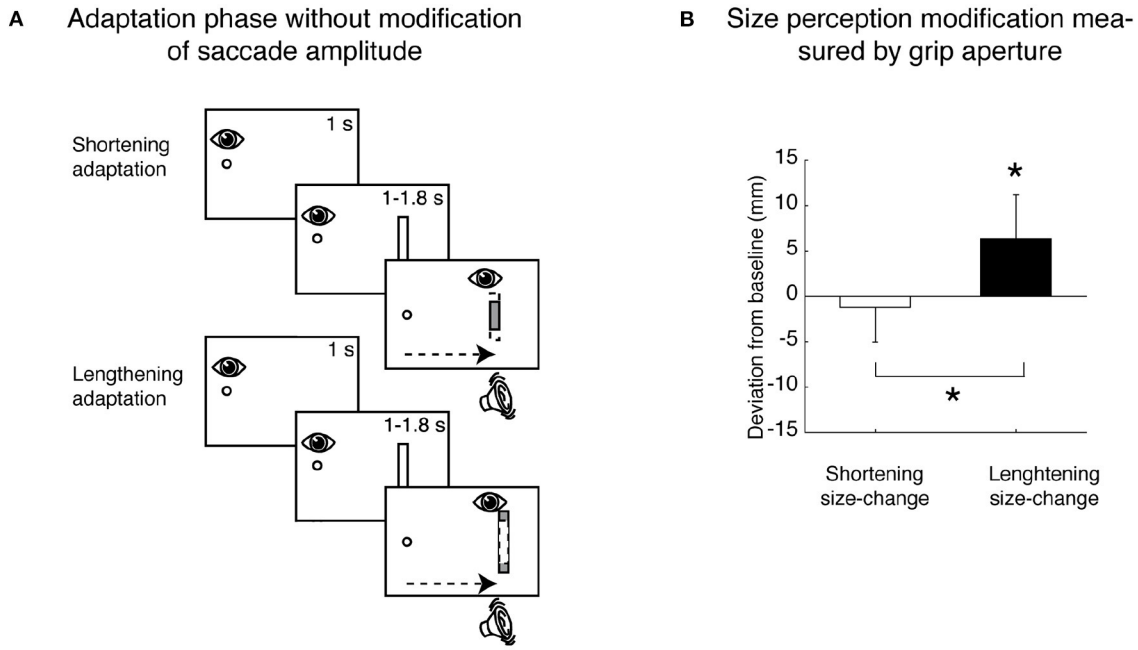

FIGURE 5
Size perception modification not induced by saccadic adaptation. **(A)** Top row, Shortening adaptation condition. The fixation point was presented at the start of the trial. After 1 s, a bar appeared, but participants had to continue to focus on the fixation target. After a randomized time, an acoustic signal indicated the possibility of executing a saccade toward the bar. Then the bar was symmetrically decreased in size by 30% of its length as soon as the saccade was detected. Bottom row, Lengthening adaptation. This was identical to the shortening adaptation, with the only difference being that the bar was symmetrically increased in size by 30% during the execution of the saccade. **(B)** Mean deviation of size perception (grip aperture) from baseline for the shortening (white column) and the lengthening (black column) adaptation trials. The data were averaged across participants and sizes. Details as in Figure 4 (modified from Bosco et al., 2020). $^{*}p < 0.05$, significance level.

the initial one (McLaughlin, 1967; Miller et al., 1981; Deubel, 1987; Watanabe et al., 2003; Hopp and Fuchs, 2004; Kojima et al., 2005; Ethier et al., 2008; Rahmouni and Madelain, 2019). Further studies investigated the possibility of the saccadic system sharing common coordinates with other domains. In fact, several researchers have demonstrated that the modification of motor variables induced by saccade adaptation leads to a concomitant modification of the perceived location of the target when the localization is executed by a pointing movement or by a perceptual report (Bahcall and Kowler, 1999; Awater et al., 2005; Bruno and Morrone, 2007; Collins et al., 2007; Zimmermann and Lappe, 2010; Garaas and Pomplun, 2011; Gremmler et al., 2014).

A particular application of the saccadic adaptation paradigm was developed using spatially extended targets that, during the saccade, systematically changed their horizontal size (Bosco et al., 2015), and in reading studies (McConkie et al., 1989; Lavergne et al., 2010). In particular, the manipulation used in Bosco et al. (2015) influenced the target visual perception. The modification of size perception occurred according to the direction of saccadic amplitude adaptation: if the saccade was adapted to a smaller amplitude, target size was perceived as being smaller; if the saccade adapted to a larger amplitude, target size was perceived as being larger (Bosco et al., 2015). The scheme of the adaptation phase paradigm and the consequent size perception modification measured by grip aperture of the hand is shown in Figure 4.

However, recent studies have shown that change in perception of visual features is present also without saccadic adaptation (Herwig and Schneider, 2014; Herwig et al., 2015, 2018; Valsecchi and Gegenfurtner, 2016; Paeye et al., 2018; Köller et al., 2020; Valsecchi et al., 2020). This phenomenon occurs with the following features: the perception of spatial frequency (Herwig and Schneider, 2014; Herwig et al., 2018), shape (Herwig et al., 2015; Paeye et al., 2018; Köller et al., 2020), and size (Valsecchi and Gegenfurtner, 2016; Bosco et al., 2020; Valsecchi et al., 2020). For example, Bosco et al. (2020) used a manipulation consisting in the systematic shortening and lengthening of a vertical bar during a horizontal saccade aimed to do not modify the saccade amplitude; by these conditions, they observed a significant difference in perceived size after the saccade execution (see Figure 5A for the scheme of saccadic adaptation paradigm in Bosco et al., 2020). This finding suggested that the modification of size perception does not rely on the modified saccadic amplitude induced by saccadic adaptation mechanisms (see Figure 5B, Bosco et al., 2020). In the study by Valsecchi et al. (2020), it was shown that saccadic adaptation and size recalibration share the same temporal development. However, size recalibration of the visual stimuli was also present in the opposite hemifield, but saccadic adaptation did not suggest that distinct mechanisms were involved. Although the modification of saccadic parameter induced by saccadic adaptation is not the causal mechanism for the modification of stimulus property perception, the shift of the target image from the periphery

to the fovea, typically performed by a saccade, remains the potential cause of the observed object perception modification.

A considerable body of literature has shown that the visual stimuli briefly presented just before the onset of a saccade, or during it, are mislocalized and perceived as being closer to the saccade target (Matin and Pearce, 1965; Honda, 1989; Schlag and Schlag-Rey, 1995; Ross et al., 1997). In other terms, this mislocalization consists in a shift of apparent position in the direction of the saccade (Honda, 1989, 1995; Schlag and Schlag-Rey, 1995; Cai et al., 1997; Lappe et al., 2000) and a compression of positions onto the target location of the saccade (Bischof and Kramer, 1968; Ross et al., 1997; Lappe et al., 2000). The shift is attributed to a mismatch between the actual eye position during the saccades and the predicted position originating from an internal corollary discharge (Duhamel et al., 1992; Nakamura and Colby, 2002; Kusunoki and Goldberg, 2003; Morrone et al., 2005).

Interestingly, the compression effect is primarily observed parallel to the saccade direction (Ross et al., 1997), and also in the orthogonal direction (Kaiser and Lappe, 2004; Zimmermann et al., 2014, 2015), suggesting that a linear translation of the internal coordinate system is a reductive explanation. Additionally, non-spatial features such as the shape and colors of perisaccadic stimuli have also been investigated to evaluate the effect of perisaccadic compression. Specifically, the discrimination of shape (Matsumiya and Uchikawa, 2001) and colors (Lappe et al., 2006; Wittenberg et al., 2008) of visual stimuli is preserved, but they are not perceived in separate positions. Although the mechanism of this effect is still an open question, the general view describes the perisaccadic mislocalization as being related to mechanisms aimed at maintaining visual stability (Matin and Pearce, 1965; Honda, 1989; Schlag and Schlag-Rey, 1995; Ross et al., 1997; Lappe et al., 2000; Pola, 2004; Binda and Morrone, 2018).

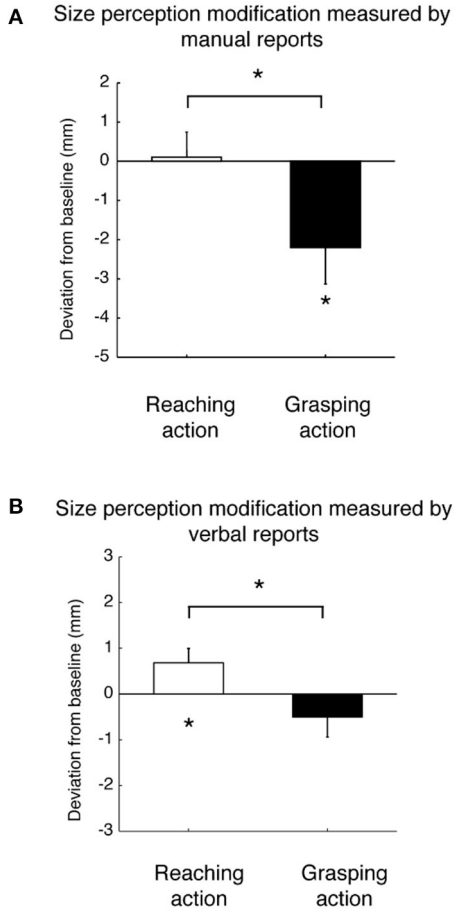

FIGURE 6
Size perception modification after reaching and grasping actions. **(A)** Mean deviation of perceptual responses by grip aperture for reaching (white column) and grasping (black column). **(B)** Mean deviation of verbal perceptual reports for reaching (white column) and grasping (black column). All data are averaged across participants and sizes. Error bars are standard errors of the mean. *$p < 0.05$, significance level (modified from Bosco et al., 2017).

The hand domain

The execution of different types of hand movements can generate perceptual modifications of object properties relevant for that type of action, such as the perception of size and weight. In 2017, Bosco et al. (2017) investigated the direct effect of reaching and grasping execution on the size perception of a visual target. They found that the change in size perception was larger after a grasping action than after a reaching action and all participants perceived objects to be smaller after the grasping compared to the reaching. These results were consistent in both manual and verbal reports, as is shown in Figure 6 (Bosco et al., 2017). Sanz Diez et al. (2022) evaluated size perception after a grasping movement performed toward a visual target that changed in size during the execution of the movement. Although the perceptual phase before and after grasping execution applied to the same target that, in these two moments of the task, was identical in size, they found that, after the grasping action, reports regarding perceptual size showed significant differences that depended on the type of size change that occurred during movement execution. In fact, as shown in Figure 7, observers reported a smaller size perception when the visual target was lengthened during the grasping execution and no perception modification when the visual target was shortened during the grasping execution (Sanz Diez et al., 2022). In both of the studies described above, the perceptual modification occurred according to the type of movement (i.e., reaching or grasping) and to the unpredictable changes of target size during the movement itself, suggesting that this modification can be considered to be a descriptive parameter of the previous motor action (Bosco et al., 2017; Sanz Diez et al., 2022).

An advantage of the effect of action execution on perception is represented by changes to the motor system obtained with skill learning. The formation and retrieval of sensorimotor memories acquired from previous hand-object interactions are fundamental for dexterous object manipulation learning (Westling and Johansson, 1984; Johansson and Westling, 1988). This allows the modulation of digit forces in a fashion that is anticipatory, i.e., before the lifting of the object (Gordon et al., 1993; Burstedt et al., 1999; Salimi et al., 2000). In a task requiring participants to lift an object while minimizing the roll caused by asymmetric mass

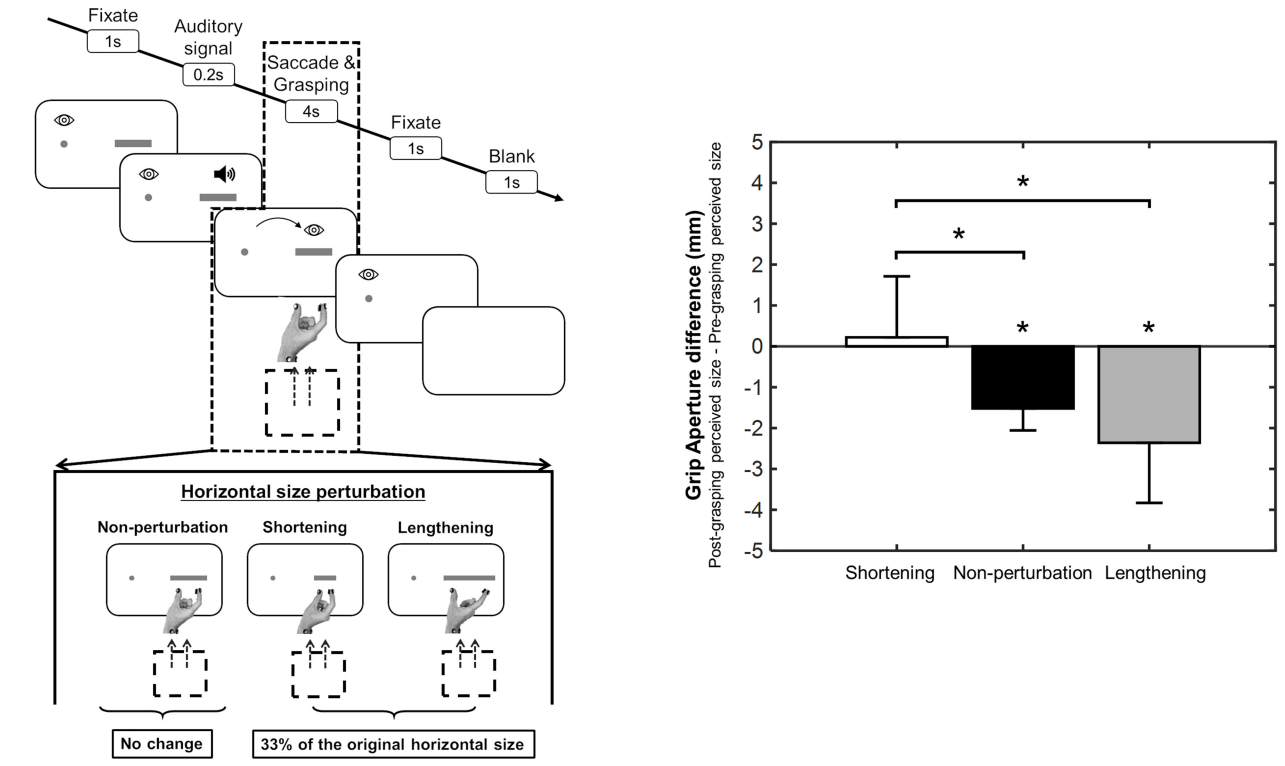

FIGURE 7
Size perception modification after size-perturbed grasping execution. **(A)** Experimental task sequence. **(B)** Mean Deviation values of grip aperture from the baseline averaged across size perturbation condition. Details as in Figure 5 (modified from Sanz Diez et al., 2022). $^{*}p < 0.05$, significance level.

distribution of an external torque, the implicit learning after action execution led to minimization of object roll by a re-arrangement of digit positions (Lukos et al., 2007, 2008) and a modulation of the force distribution exerted by the fingers (Salimi et al., 2000; Fu et al., 2010).

Within this perspective, it is also useful to describe the size-weight illusion (SWI), for the first time described by Charpentier (Charpentier, 1891). In fact, the SWI is visible when a subject lifts two objects of different size, but of equal weight, and reports the smaller object as being heavier. The SWI illusion is robust (Murray et al., 1999; Flanagan and Beltzner, 2000; Kawai, 2002a,b, 2003a,b; Grandy and Westwood, 2006; Dijker, 2008; Flanagan et al., 2008; Chouinard et al., 2009), and the effect is still present when the lifter knows that both objects are of the same weight (Flanagan and Beltzner, 2000). The SWI illusion has been thoroughly studied to understand the mechanism of signal integration for weight perception, and it is an example of how the sensorimotor system works in a Bayesian manner. According to this view, the nervous system combines prior knowledge regarding object properties learned by previous experience ("the prior") with current sensory information ("the likelihood"), to appropriately estimate object property ("the posterior") for action and perception functions (van Beers et al., 2002; Körding and Wolpert, 2006). In most cases, the combination of prior and likelihood generates correct perception and behavior, but perception can be misleading. In the case of SWI, for example, the prior is perceived higher than the likelihood, generating a perception that does not correspond with the actual physical properties of the object. However, the repetition of the lifting action recalibrates the perception of weight, and the force distribution is adjusted according to the real weight of the objects. Although there is still no consensus as to the process that gives rise to the SWI, an objective aspect is that the execution of the manipulation action on the objects has a pragmatic effect on weight and size perception.

The leg domain

Walking interaction leads to a perception-action recalibration, and it is typically investigated by the measurement of perceived size or perceived distance. This is because, according to the size-distance invariance hypothesis (Sedgwick, 1986), size and distance perception are strictly coupled. Brenner and van Damme (1999) found that perceived object size, shape, and distance are

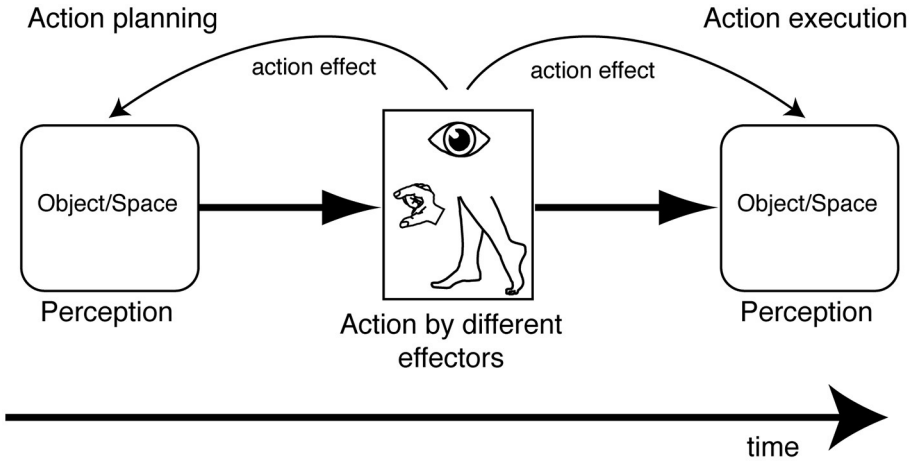

FIGURE 8
Summary of object/space perception modulation by action planning and action execution evoked by movement of different effectors.

largely independent. Although object size, shape, and distance estimations were similarly affected by changes in object distance perception, modifications in perceived shape caused by motion parallax did not affect perceived size or distance. This indicates their independence. Although the direct relationship between size and distance perception has been debated in this study, the judgements of distance and size have been shown to be tightly linked in other studies (Gogel et al., 1985; Hutchison and Loomis, 2006). Results showing an improvement in judgments of distances after the walking interaction were found by Waller & Richardson (Waller and Richardson, 2008). The same authors showed that distance judgments in a virtual environment were unaffected by interactions in which participants viewed only a simulation of visual walking (i.e., optic flow only). This suggested that a body-based movement is necessary. Furthermore, perceptual reports of distance increased in accuracy after participants performed a blind-walking task consisting in the receipt of visual or verbal feedback (Richardson and Waller, 2005; Mohler et al., 2006). The results showed the sufficiency of body-based interaction. Kelly et al. (2013) found that perceptual reports of object size improved after a walking interaction, because an increase in perceived distance was observed. The finding that perceptual reports regarding size improved after the interaction indicates that walking leads to a rescaling of space perception and not only to a simple recalibration of walked distance (Siegel et al., 2017). In open-loop blind walking tasks, calibration and recalibration of locomotion has been observed. In these tasks, an observer views a target on the ground and, after closing his/her eyes, he/she has to walk toward the target without seeing. In normal conditions, blind walking performance is quite accurate and reflects the perception of the target location (Rieser et al., 1990; Loomis and Philbeck, 2008). After manipulation of the rate of environmental optic flow in relation to the biomechanical rate of normal walking, observers undershot the target when the environmental flow was faster, and overshot the target when environmental flow was slower compared to the perception of normal walking speed (Rieser et al., 1995). Additionally, studies investigating the visual perception of egocentric distances showed that perceptual judgments (e.g., verbal reports) showed a systematic underestimation of egocentric distances (Foley, 1977; Li and Giudice, 2013), while blindfolded walking toward a remembered target location was executed more accurately (Loomis et al., 1992; Li and Giudice, 2013). Although the former suggests that a systematic compression of physical distance is visually perceived, visually directed walking is not affected by this perceptual distortion.

Conclusions and future perspectives

A multitude of works have been presented showing the effect of actions performed with the eyes, the hands, and the legs on visual perception of objects and space using different approaches and paradigms. The action influence is present before and after execution of the movement, suggesting that visual perception, when it is integrated with the action, is "ready to act" (before execution) and is transformed by action execution (see Figure 8 for a summary). In both cases, the perceptual responses, collected in different ways, are parameters that describe the subsequent or previous motor responses. This suggests a mechanism which exchanges information between the motor and perceptual system when we are in a specific visuomotor contingency. At a behavioral level, we can take advantage of these aspects because they can be used as action intention predictors when they occur during action planning and, interestingly, as a postdictive component that specifies the previous motor experience when they occur after action execution. In this latter case, the postdictive perceptual component also updates the information that is necessary for a potential subsequent action. The use of the action-based perceptual information can be helpful in all those artificial intelligent (AI) systems that are used with motor assistive devices. In fact, the use of perceptual information during action planning can be implemented with other parameters (e.g., neural signals) to extract action intentions that exploit the residual motor abilities of different effectors that are necessary to give perceptual responses by pressing a button, for example, or extending only certain fingers and not others. The use of perceptual information after action execution can be implemented in AI systems that are able to communicate with

humans, with the objective of creating a mutual learning exchange. In fact, the modification of perception following the execution of a particular movement may be used as a feedback signal, in order to correct a subsequent motor response and compensate for the error due to previous AI action decisions. This allows the system to improve the outcome of the action and, consequently, increases the user's trust in the AI system.

Author contributions

AB: conceptualization, visualization, writing original draft, and writing—review and editing. SDP: visualization and writing original draft. MF: writing—review and editing. PF: writing—review and editing and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

SDP is employed by Carl Zeiss Vision International GmbH.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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References

Angel, R. W., Alston, W., and Garland, H. (1970). Functional relations between the manual and oculomotor control systems. *Exp. Neurol.* 27, 248–257. doi: 10.1016/0014-4886(70)90218-9

Awater, H., Burr, D., Lappe, M., Morrone, M. C., and Goldberg, M. E. (2005). Effect of saccadic adaptation on localization of visual targets. *J. Neurophysiol.* 93, 3605–14. doi: 10.1152/jn.01013.2003

Bagesteiro, L. B., Sarlegna, F. R., and Sainburg, R. L. (2006). Differential influence of vision and proprioception on control of movement distance. *Exp. Brain Res.* 171, 358. doi: 10.1007/s00221-005-0272-y

Bahcall, D. O., and Kowler, E. (1999). Illusory shifts in visual direction accompany adaptation of saccadic eye movements. *Nature* 400, 864–6. doi: 10.1038/23693

Bekkering, H., Adam, J. J., van den Aarssen, A., Kingma, H., and Whiting, H. T. A. (1995). Interference between saccadic eye and goal-directed hand movements. *Exp. Brain. Res.* 106, 475–484. doi: 10.1007/BF00231070

Bekkering, H., Adam, Jos, J., Kingma, H., Huson, A., and Whiting, H. T. A. (1994). Reaction time latencies of eye and hand movements in single- and dual-task conditions. *Exp. Brain. Res.* 97, 12. doi: 10.1007/BF00241541

Bekkering, H., and Neggers, S. F. (2002). Visual search is modulated by action intentions. *Psychol. Sci.* 13, 370–374. doi: 10.1111/j.0956-7976.2002.00466.x

Benedetto, A., and Morrone, M. C. (2017). Saccadic suppression is embedded within extended oscillatory modulation of sensitivity. *J. Neurosci.* 37, 3661. doi: 10.1523/JNEUROSCI.2390-16.2016

Benedetto, A., Morrone, M. C., and Tomassini, A. (2020). The common rhythm of action and perception. *J. Cogn. Neurosci.* 32, 187–200. doi: 10.1162/jocn_a_01436

Bernstein, N. (1967). *The Co-Ordination and Regulation of Movements.* Oxford: Pergamon Press.

Bhalla, M., and Proffitt, D. R. (1999). Visual–motor recalibration in geographical slant perception. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 1076–1096. doi: 10.1037/0096-1523.25.4.1076

Biguer, B., Jeannerod, M., and Prablanc, C. (1982). The coordination of eye, head, and arm movements during reaching at a single visual target. *Exp. Brain. Res.* 46, 301–304. doi: 10.1007/BF00237188

Binda, P., and Morrone, M. C. (2018). Vision during saccadic eye movements. *Annu. Rev. Vis. Sci.* 4, 193–213. doi: 10.1146/annurev-vision-091517-034317

Bischof, N., and Kramer, E. (1968). Untersuchungen und berlegungen zur Richtungswahrnehmung bei willkrlichen sakkadischen Augenbewegungen. *Psychol. Forsch.* 32, 185–218. doi: 10.1007/BF00418660

Bosco, A., Daniele, F., and Fattori, P. (2017). Reaching and grasping actions and their context shape the perception of object size. *J. Vis.* 17, 10. doi: 10.1167/17.12.10

Bosco, A., Lappe, M., and Fattori, P. (2015). Adaptation of saccades and perceived size after trans-saccadic changes of object size. *J. Neurosci.* 35, 14448–14456. doi: 10.1523/JNEUROSCI.0129-15.2015

Bosco, A., Rifai, K., Wahl, S., Fattori, P., and Lappe, M. (2020). Trans-saccadic adaptation of perceived size independent of saccadic adaptation. *J. Vis.* 20, 19. doi: 10.1167/jov.20.7.19

Bourdin, C., Bringoux, L., Gauthier, G. M., and Vercher, J. L. (2006). Vision of the hand prior to movement onset allows full motor adaptation to a multi-force environment. *Brain. Res. Bull.* 71, 101–110. doi: 10.1016/j.brainresbull.2006.08.007

Boynton, G. M., Demb, J. B., Glover, G. H., and Heeger, D. J. (1999). Neuronal basis of contrast discrimination. *Vision Res.* 39, 257–269. doi: 10.1016/S0042-6989(98)00113-8

Brenner, E., and van Damme, W. J. M. (1999). Perceived distance, shape and size. *Vision Res.* 39, 975–986. doi: 10.1016/S0042-6989(98)00162-X

Brouwer, A.-M., Franz, V. H., and Gegenfurtner, K. R. (2009). Differences in fixations between grasping and viewing objects. *J. Vis.* 9, 1–24. doi: 10.1167/9.1.18

Bruno, A., and Morrone, M. C. (2007). Influence of saccadic adaptation on spatial localization: comparison of verbal and pointing reports. *J. Vis.* 7, 1–13. doi: 10.1167/7.5.16

Burstedt, M. K. O., Flanagan, J. R., and Johansson, R. S. (1999). Control of grasp stability in humans under different frictional conditions during multidigit manipulation. *J. Neurophysiol.* 82, 2393–2405. doi: 10.1152/jn.1999.82.5.2393

Buzsáki, G., and Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science* 304, 1926–1929. doi: 10.1126/science.1099745

Cai, R. H., Pouget, A., Schlag-Rey, M., and Schlag, J. (1997). Perceived geometrical relationships affected by eye-movement signals. *Nature* 386, 601–604. doi: 10.1038/386601a0

Charpentier, A. (1891). Analyse experimentale de quelques elements de la sensation de poids. *Arch. Physiol. Norm. Pathol.* 3, 122–135.

Chouinard, P., Large, M., Chang, E., and Goodale, M. (2009). Dissociable neural mechanisms for determining the perceived heaviness of objects and the predicted weight of objects during lifting: An fMRI investigation of the size–weight illusion. *Neuroimage* 44, 200–212. doi: 10.1016/j.neuroimage.2008.08.023

Coello, Y., and Grealy, M. A. (1997). Effect of size and frame of visual field on the accuracy of an aiming movement. *Perception* 26, 287–300. doi: 10.1068/p260287

Collins, T., Doré-Mazars, K., and Lappe, M. (2007). Motor space structures perceptual space: evidence from human saccadic adaptation. *Brain Res.* 1172, 32–39. doi: 10.1016/j.brainres.2007.07.040

Conti, P., and Beaubaton, D. (1980). Role of structured visual field and visual reafference in accuracy of pointing movements. *Percept. Mot. Skills* 50, 239–244. doi: 10.2466/pms.1980.50.1.239

Craighero, L., Fadiga, L., Rizzolatti, G., and Umiltà, C. (1999). Action for perception a motor—visual attentional effect. *J. Exp. Psychol. Hum. Percept. Perform.* 25, 1673–1692. doi: 10.1037/0096-1523.25.6.1673

Davoli, C. C., Brockmole, J. R., and Witt, J. K. (2012). Compressing perceived distance with remote tool-use: Real, imagined, and remembered. *J. Exp. Psychol. Hum. Percept. Perform.* 38, 80–89. doi: 10.1037/a0024981

de Brouwer, A. J., Flanagan, J. R., and Spering, M. (2021). Functional use of eye movements for an acting system. *Trends Cogn. Sci.* 25, 252–263. doi: 10.1016/j.tics.2020.12.006

Desmurget, M., Pélisson, D., Rossetti, Y., and Prablanc, C. (1998). "From eye to hand: planning goal-directed movements," in *Neuroscience and Biobehavioral Reviews*, p. 761–788. doi: 10.1016/S0149-7634(98)00004-9

Desmurget, M., Rossetti, Y., Jordan, M., Meckler, C., and Prablanc, C. (1997). Viewing the hand prior to movement improves accuracy of pointing performed toward the unseen contralateral hand. *Exp. Brain. Res.* 115, 180–186. doi: 10.1007/PL00005680

Desmurget, M., Rossetti, Y., Prablanc, C., Jeannerod, M., and Stelmach, G. E. (1995). Representation of hand position prior to movement and motor variability. *Can. J. Physiol. Pharmacol.* 73, 262–272. doi: 10.1139/y95-037

Deubel, H. (1987). "Adaptivity of gain and direction in oblique saccades.," in *Eye movements from physiology to cognition*. (London: Elsevier), p. 181–190. doi: 10.1016/B978-0-444-70113-8.50030-8

Deubel, H., and Schneider, W. X. (1996). Saccade target selection and object recognition: evidence for a common attentional mechanism. *Vision. Res.* 36, 1827–1837. doi: 10.1016/0042-6989(95)00294-4

di Marco, S., Tosoni, A., Altomare, E. C., Ferretti, G., Perrucci, M. G., and Committeri, G. (2019). Walking-related locomotion is facilitated by the perception of distant targets in the extrapersonal space. *Sci. Rep.* 9, 9884. doi: 10.1038/s41598-019-46384-5

Dijker, A. J. M. (2008). Why Barbie feels heavier than Ken: the influence of size-based expectancies and social cues on the illusory perception of weight. *Cognition* 106, 1109–1125. doi: 10.1016/j.cognition.2007.05.009

Duhamel, J.-R., Colby, C. L., and Goldberg, M. E. (1992). The updating of the representation of visual space in parietal cortex by intended eye movements. *Science* 255, 90–92. doi: 10.1126/science.1553535

Elliott, D., Dutoy, C., Andrew, M., Burkitt, J. J., Grierson, L. E. M., Lyons, J. L., et al. (2014). The influence of visual feedback and prior knowledge about feedback on vertical aiming strategies. *J. Mot. Behav.* 46, 433–443. doi: 10.1080/00222895.2014.933767

Elliott, D., Garson, R. G., Goodman, D., and Chua, R. (1991). Discrete vs. continuous visual control of manual aiming. *Hum. Mov. Sci.* 10, 393–418. doi: 10.1016/0167-9457(91)90013-N

Ethier, V., Zee, D. S., and Shadmehr, R. (2008). Changes in control of saccades during gain adaptation. *J. Neurosci.* 28, 13929 LP–13937. doi: 10.1523/JNEUROSCI.3470-08.2008

Fagioli, S., Hommel, B., and Schubotz, R. I. (2007). Intentional control of attention: action planning primes action-related stimulus dimensions. *Psychol. Res.* 71, 22–29. doi: 10.1007/s00426-005-0033-3

Fini, C., Bardi, L., Troje, N. F., Committeri, G., and Brass, M. (2017). Priming biological motion changes extrapersonal space categorization. *Acta. Psychol.* 172, 77–83. doi: 10.1016/j.actpsy.2016.11.006

Fini, C., Brass, M., and Committeri, G. (2015a). Social scaling of extrapersonal space: target objects are judged as closer when the reference frame is a human agent with available movement potentialities. *Cognition* 134, 50–56. doi: 10.1016/j.cognition.2014.08.014

Fini, C., Committeri, G., Müller, B. C. N., Deschrijver, E., and Brass, M. (2015b). How watching pinocchio movies changes our subjective experience of extrapersonal space. *PLoS One* 10, e0120306. doi: 10.1371/journal.pone.0120306

Fini, C., Costantini, M., and Committeri, G. (2014). Sharing space: the presence of other bodies extends the space judged as near. *PLoS One* 9, e114719. doi: 10.1371/journal.pone.0114719

Flanagan, J. R., and Beltzner, M. A. (2000). Independence of perceptual and sensorimotor predictions in the size–weight illusion. *Nat. Neurosci.* 3, 737–741. doi: 10.1038/76701

Flanagan, J. R., Bittner, J. P., and Johansson, R. S. (2008). Experience can change distinct size-weight priors engaged in lifting objects and judging their weights. *Curr. Biol.* 18, 1742–1747. doi: 10.1016/j.cub.2008.09.042

Flanagan, J. R., and Rao, A. K. (1995). Trajectory adaptation to a non-linear visuomotor transformation: evidence of motion planning in visually perceived space. *J. Neurophysiol.* 74, 2174–2178. doi: 10.1152/jn.1995.74.5.2174

Foley, J. M. (1977). Effect of distance information and range on two indices of visually perceived distance. *Perception* 6, 449–460. doi: 10.1068/p060449

Fu, Q., Zhang, W., and Santello, M. (2010). Anticipatory planning and control of grasp positions and forces for dexterous two-digit manipulation. *J. Neurosci.* 30, 9117–9126. doi: 10.1523/JNEUROSCI.4159-09.2010

Garaas, T. W., and Pomplun, M. (2011). Distorted object perception following whole-field adaptation of saccadic eye movements. *J. Vis.* 11, 2. doi: 10.1167/11.1.2

Gibson, J. (1979). *The Ecological Approach to Visual Perception*. New York, NY: Houghton Mifflin.

Gogel, W. C., Loomis, J. M., Newman, N. J., and Sharkey, T. J. (1985). Agreement between indirect measures of perceived distance. *Percept. Psychophys.* 37, 17–27. doi: 10.3758/BF03207134

Gordon, A. M., Westling, G., Cole, K. J., and Johansson, R. S. (1993). Memory representations underlying motor commands used during manipulation of common and novel objects. *J. Neurophysiol.* 69, 1789–1796. doi: 10.1152/jn.1993.69.6.1789

Grandy, M. S., and Westwood, D. A. (2006). Opposite perceptual and sensorimotor responses to a size-weight illusion. *J. Neurophysiol.* 95, 3887–3892. doi: 10.1152/jn.00851.2005

Gray, R. (2013). Being selective at the plate: processing dependence between perceptual variables relates to hitting goals and performance. *J. Exp. Psychol. Hum. Percept. Perform.* 39, 1124–1142. doi: 10.1037/a0030729

Gremmler, S., Bosco, A., Fattori, P., and Lappe, M. (2014). Saccadic adaptation shapes visual space in macaques. *J. Neurophysiol.* 111, 1846–1851. doi: 10.1152/jn.00709.2013

Gutteling, T. P., Kenemans, J. L., and Neggers, S. F. W. (2011). Grasping preparation enhances orientation change detection. *PLoS One* 6, 11. doi: 10.1371/journal.pone.0017675

Hamilton, A., Wolpert, D., and Frith, U. (2004). Your own action influences how you perceive another person's action. *Curr. Biol.* 14, 493–498. doi: 10.1016/j.cub.2004.03.007

Hayhoe, M. M. (2017). Vision and action. *Ann. Rev. Vis. Sci.* 3, 389–413. doi: 10.1146/annurev-vision-102016-061437

Hayhoe, M. M., Shrivastava, A., Mruczek, R., and Pelz, J. B. (2003). Visual memory and motor planning in a natural task. *J. Vis.* 3, 6. doi: 10.1167/3.1.6

Herwig, A., and Schneider, W. X. (2014). Predicting object features across saccades: evidence from object recognition and visual search. *J. Exp. Psychol. Gen.* 143, 1903–1922. doi: 10.1037/a0036781

Herwig, A., Weiß, K., and Schneider, W. X. (2015). When circles become triangular: how transsaccadic predictions shape the perception of shape. *Ann. N Y Acad. Sci.* 1339, 97–105. doi: 10.1111/nyas.12672

Herwig, A., Weiß, K., and Schneider, W. X. (2018). Feature prediction across eye movements is location specific and based on retinotopic coordinates. *J. Vis.* 18, 13. doi: 10.1167/18.8.13

Hoffman, J. E., and Subramaniam, B. (1995). The role of visual attention in saccadic eye movements. *Percept. Psychophys.* 57, 787–795. doi: 10.3758/BF03206794

Hommel, B., Brown, S., and Nattkemper, D. (2016). *Human Action Control*. Cham: Springer. doi: 10.1007/978-3-319-09244-7

Hommel, B., Müsseler, J., Aschersleben, G., and Prinz, W. (2001). The theory of event coding (TEC): a framework for perception and action planning. *Behav. Brain Sci.* 24, 849–878. doi: 10.1017/S0140525X01000103

Honda, H. (1989). Perceptual localization of visual stimuli flashed during saccades. *Percept. Psychophys.* 45, 162–174. doi: 10.3758/BF03208051

Honda, H. (1995). Visual mislocalization produced by a rapid image displacement on the retina: examination by means of dichoptic presentation of a target and its background scene. *Vision. Res.* 35, 3021–3028. doi: 10.1016/0042-6989(95)00108-C

Hopp, J. J., and Fuchs, A. F. (2004). The characteristics and neuronal substrate of saccadic eye movement plasticity. *Prog. Neurobiol.* 72, 27–53. doi: 10.1016/j.pneurobio.2003.12.002

Hutchison, J. J., and Loomis, J. M. (2006). Does energy expenditure affect the perception of egocentric distance? a failure to replicate experiment 1 of proffitt, stefanucci, banton, and epstein (2003). *Span. J. Psychol.* 9, 332–339. doi: 10.1017/S1138741600006235

Jeannerod, M. (1981). Intersegmental coordination during reaching at natural visual objects. *Atten. Perform.* 11, 153–169.

Johansson, R. S., and Westling, G. (1988). Programmed and triggered actions to rapid load changes during precision grip. *Exp. Brain Res.* 2, 71. doi: 10.1007/BF00247523

Johansson, R. S., Westling, G., Bäckström, A., and Flanagan, J. R. (2001). Eye–hand coordination in object manipulation. *J. Neurosci.* 21, 6917–6932. doi: 10.1523/JNEUROSCI.21-17-06917.2001

Kaiser, M., and Lappe, M. (2004). Perisaccadic mislocalization orthogonal to saccade direction. *Neuron* 41, 293–300. doi: 10.1016/S0896-6273(03)00849-3

Kawai, S. (2002a). Heaviness perception: I. constant involvement of haptically perceived size in weight discrimination. *Exp. Brain Res.* 147, 16–22. doi: 10.1007/s00221-002-1209-3

Kawai, S. (2002b). Heaviness perception: II. contributions of object weight, haptic size, and density to the accurate perception of heaviness or lightness. *Exp. Brain. Res.* 147, 23–28. doi: 10.1007/s00221-002-1210-x

Kawai, S. (2003a). Heaviness perception: III. Weight/aperture in the discernment of heaviness in cubes haptically perceived by thumb-index finger grasp. *Exp. Brain Res.* 153, 289–296. doi: 10.1007/s00221-003-1621-3

Kawai, S. (2003b). Heaviness perception: IV. Weight x aperture−1 as a heaviness model in finger-grasp perception. *Exp. Brain Res.* 153, 297–301. doi: 10.1007/s00221-003-1622-2

Kelly, J. W., Donaldson, L. S., Sjolund, L. A., and Freiberg, J. B. (2013). More than just perception–action recalibration: walking through a virtual environment causes rescaling of perceived space. *Atten. Percept. Psychophys.* 75, 1473–1485. doi: 10.3758/s13414-013-0503-4

Kirsch, W. (2015). Impact of action planning on spatial perception: attention matters. *Acta. Psychol. (Amst)* 156, 22–31. doi: 10.1016/j.actpsy.2015.01.002

Kirsch, W., Herbort, O., Butz, M., v., and Kunde, W. (2012). Influence of motor planning on distance perception within the peripersonal space. *PLoS One* 7, e34880. doi: 10.1371/journal.pone.0034880

Kirsch, W., and Kunde, W. (2013). Visual near space is scaled to parameters of current action plans. *J. Exp. Psychol. Hum. Percept. Perform.* 39, 1313–1325. doi: 10.1037/a0031074

Knoblich, G., and Flach, R. (2001). Predicting the effects of actions: interactions of perception and action. *Psychol. Sci.* 12, 467–472. doi: 10.1111/1467-9280.00387

Kojima, Y., Iwamoto, Y., and Yoshida, K. (2005). Effect of saccadic amplitude adaptation on subsequent adaptation of saccades in different directions. *Neurosci. Res.* 53, 404–412. doi: 10.1016/j.neures.2005.08.012

Köller, C. P., Poth, C. H., and Herwig, A. (2020). Object discrepancy modulates feature prediction across eye movements. *Psychol. Res.* 84, 231–244. doi: 10.1007/s00426-018-0988-5

Körding, K. P., and Wolpert, D. M. (2006). Bayesian decision theory in sensorimotor control. *Trends Cogn. Sci.* 10, 319–326. doi: 10.1016/j.tics.2006.05.003

Kunde, W., and Wuhr, P. (2004). Actions blind to conceptually overlapping stimuli. *Psychologic. Res. Psychologische Forschung* 4, 68. doi: 10.1007/s00426-003-0156-3

Kusunoki, M., and Goldberg, M. E. (2003). The time course of perisaccadic receptive field shifts in the lateral intraparietal area of the monkey. *J. Neurophysiol.* 89, 1519–1527. doi: 10.1152/jn.00519.2002

Land, M., Mennie, N., and Rusted, J. (1999). The roles of vision and eye movements in the control of activities of daily living. *Perception* 28, 1311–1328. doi: 10.1068/p2935

Land, M. F. (1992). Predictable eye-head coordination during driving. *Nature* 359, 318–320. doi: 10.1038/359318a0

Land, M. F. (2006). Eye movements and the control of actions in everyday life. *Prog Retin Eye Res* 25, 296–324. doi: 10.1016/j.preteyeres.2006.01.002

Land, M. F. (2009). Vision, eye movements, and natural behavior. *Vis. Neurosci.* 26, 51–62. doi: 10.1017/S0952523808080899

Land, M. F., and Lee, D. N. (1994). Where we look when we steer. *Nature* 369, 742–744. doi: 10.1038/369742a0

Lappe, M., Awater, H., and Krekelberg, B. (2000). Postsaccadic visual references generate presaccadic compression of space. *Nature* 403, 892–895. doi: 10.1038/35002588

Lappe, M., Kuhlmann, S., Oerke, B., and Kaiser, M. (2006). The fate of object features during perisaccadic mislocalization. *J. Vis.* 6, 11. doi: 10.1167/6.11.11

Lavergne, L., Vergilino-Perez, D., Collins, T., and Dore'-Mazars, K. (2010). Adaptation of within-object saccades can be induced by changing stimulus size. *Exp. Brain Res.* 203, 773–780. doi: 10.1007/s00221-010-2282-7

Lee, Y., Lee, S., Carello, C., and Turvey, M. T. (2012). An archer's perceived form scales the "hitableness" of archery targets. *J. Exp. Psychol. Hum. Percept. Perform.* 38, 1125–1131. doi: 10.1037/a0029036

Li, H., and Giudice, N. (2013). "The effects of 2D and 3D maps on learning virtual multi-level indoor environments," in *Proceedings of the 1st ACM SIGSPATIAL International Workshop on Map Interaction* (Orlando: ACM, Orlando, p. 7–12.

Lindemann, O., and Bekkering, H. (2009). Object manipulation and motion perception: Evidence of an influence of action planning on visual processing. *J. Exp. Psychol. Hum. Percept. Perform.* 35, 1062–1071. doi: 10.1037/a0015023

Liversedge, S. P., and Findlay, J. M. (2000). Saccadic eye movements and cognition. *Trends Cogn. Sci.* 4, 6–14. doi: 10.1016/S1364-6613(99)01418-7

Loomis, J. M., da Silva, J. A., Fujita, N., and Fukusima, S. S. (1992). Visual space perception and visually directed action. *J. Exp. Psychol. Hum. Percept. Perform.* 18, 906–921. doi: 10.1037/0096-1523.18.4.906

Loomis, J. M., and Philbeck, J. W. (2008). "Measuring perception with spatial updating and action.," in. *Embodiment, ego-space, and action* (Mahwah, NJ: Erlbaum.), eds R. L. Klatzky, M. Behrmann, and B. MacWhinney, p. 1–43.

Lukos, J., Ansuini, C., and Santello, M. (2007). Choice of contact points during multidigit grasping: effect of predictability of object center of mass location. *J. Neurosci.* 27, 3894–3903. doi: 10.1523/JNEUROSCI.4693-06.2007

Lukos, J. R., Ansuini, C., and Santello, M. (2008). Anticipatory control of grasping: independence of sensorimotor memories for kinematics and kinetics. *J. Neurosci.* 28, 12765–12774. doi: 10.1523/JNEUROSCI.4335-08.2008

Lünenburger, L., Kutz, D. F., and Hoffmann, K.-P. (2000). Influence of arm movements on saccades in humans. *Euro. J. Neurosci.* 12, 4107–4116. doi: 10.1046/j.1460-9568.2000.00298.x

Mark, L. S. (1987). Eyeheight-scaled information about affordances: a study of sitting and stair climbing. *J. Exp. Psychol. Hum. Percept. Perform.* 13, 361–370. doi: 10.1037/0096-1523.13.3.361

Matin, L., and Pearce, D. G. (1965). Visual perception of direction for stimuli flashed during voluntary saccadic eye movements. *Science* 148, 1485–1488. doi: 10.1126/science.148.3676.1485

Matsumiya, K., and Uchikawa, K. (2001). Apparent size of an object remains uncompressed during presaccadic compression of visual space. *Vision Res.* 41, 3039–3050. doi: 10.1016/S0042-6989(01)00174-2

Mattar, M. G., and Lengyel, M. (2022). Planning in the brain. *Neuron.* 110, 914–934. doi: 10.1016/j.neuron.2021.12.018

McConkie, G., PW, K., Reddix, M., Zola, D., and Jacobs, A. (1989). Eye movement control during reading: II. frequency of refixating a word. *Percept. Psychophys.* 46, 245–253. doi: 10.3758/BF03208086

McLaughlin, S. C. (1967). Parametric adjustment in saccadic eye movements. *Percept. Psychophys.* 2, 359–362. doi: 10.3758/BF03210071

Miller, J., Anstis, T., and Templeton, W. (1981). Saccadic plasticity: parametric adaptive control by retinal feedback. *J. Exp. Psychol. Hum. Percept. Perform.* 7, 356–66. doi: 10.1037/0096-1523.7.2.356

Mohler, B. J., Creem-Regehr, S. H., and Thompson, W. B. (2006). "The influence of feedback on egocentric distance judgments in real and virtual environments," in *ACM SIGGRAPH Symposium on Applied Perception in Graphics and Visualization* (Washington, DC: ACM), p. 9–14. doi: 10.1145/1140491.1140493

Morasso, P. (1981). Spatial control of arm movements. *Exp. Brain Res.* 2, 42. doi: 10.1007/BF00236911

Morgado, N., Gentaz, É., Guinet, É., Osiurak, F., and Palluel-Germain, R. (2013). Within reach but not so reachable: Obstacles matter in visual perception of distances. *Psychon. Bull. Rev.* 20, 462–467. doi: 10.3758/s13423-012-0358-z

Morrone, M. C., Ross, J., and Burr, D. (2005). Saccadic eye movements cause compression of time as well as space. *Nat. Neurosci.* 8, 950–954. doi: 10.1038/nn1488

Murray, D. J., Ellis, R. R., Bandomir, C. A., and Ross, H. E. (1999). Charpentier 1891 on the size—weight illusion. *Percept. Psychophys.* 61, 1681–1685. doi: 10.3758/BF03213127

Musseler, J., and Hommel, B. (1997). Blindness to response-compatible stimuli. *J. Exp. Psychol. Hum. Percept. Perform.* 23, 861–872. doi: 10.1037/0096-1523.23.3.861

Nakamura, K., and Colby, C. L. (2002). Updating of the visual representation in monkey striate and extrastriate cortex during saccades. *Proceed. Nat. Acad. Sci.* 99, 4026–4031. doi: 10.1073/pnas.052379899

Neggers, S., Huijbers, W., Vrijlandt, C., Vlaskamp, B., Schutter, D., and Kenemans, J. (2007). TMS pulses on the frontal eye fields break coupling between visuospatial attention and eye movements. *J. Neurophysiol.* 98, 2765–2778. doi: 10.1152/jn.00357.2007

Neggers, S. F., and Bekkering, H. (2000). Ocular gaze is anchored to the target of an ongoing pointing movement. *J. Neurophysiol.* 83, 639–651. doi: 10.1152/jn.2000.83.2.639

Neggers, S. F. W., and Bekkering, H. (1999). Integration of visual and somatosensory target information in goal-directed eye and arm movements. *Exp. Brain. Res.* 125, 97–107. doi: 10.1007/s002210050663

Neggers, S. F. W., and Bekkering, H. (2001). Gaze anchoring to a pointing target is present during the entire pointing movement and is driven by a non-visual signal. *J. Neurophysiol.* 86, 961–970. doi: 10.1152/jn.2001.86.2.961

Neggers, S. F. W., and Bekkering, H. (2002). Coordinated control of eye and hand movements in dynamic reaching. *Hum. Mov. Sci.* 21, 37–64. doi: 10.1016/S0167-9457(02)00120-3

Noel, J.-P., Grivaz, P., Marmaroli, P., Lissek, H., Blanke, O., and Serino, A. (2015). Full body action remapping of peripersonal space: the case of walking. *Neuropsychologia* 70, 375–384. doi: 10.1016/j.neuropsychologia.2014.08.030

Osiurak, F., Morgado, N., and Palluel-Germain, R. (2012). Tool use and perceived distance: when unreachable becomes spontaneously reachable. *Exp. Brain Res.* 218, 331–339. doi: 10.1007/s00221-012-3036-5

Paeye, C., Collins, T., Cavanagh, P., and Herwig, A. (2018). Calibration of peripheral perception of shape with and without saccadic eye movements. *Atten. Percept. Psychophys.* 80, 723–737. doi: 10.3758/s13414-017-1478-3

Patla, A., and Vickers, J. (2003). How far ahead do we look when required to step on specific locations in the travel path during locomotion? *Exp. Brain Res.* 148, 133–138. doi: 10.1007/s00221-002-1246-y

Pelisson, D., Prablanc, C., Goodale, M., and Jeannerod, M. (1986). Visual control of reaching movements without vision of the limb. *Exp. Brain Res.* 62, 303–311.

Pelz, J., Hayhoe, M., and Loeber, R. (2001). The coordination of eye, head, and hand movements in a natural task. *Exp. Brain Res.* 139, 266–277. doi: 10.1007/s002210100745

Pola, J. (2004). Models of the mechanism underlying perceived location of a perisaccadic flash. *Vision Res.* 44, 2799–2813. doi: 10.1016/j.visres.2004.06.008

Prablanc, C., Echallier, J. F., Komilis, E., and Jeannerod, M. (1979). Optimal response of eye and hand motor systems in pointing at a visual target. *Biol. Cybern.* 35, 113–124. doi: 10.1007/BF00337436

Prinz, W. (1990). "A Common Coding Approach to Perception and Action," in *Relationships Between Perception and Action: Current Approaches*, eds. O. Neumann and W. Prinz (Berlin, Heidelberg: Springer Berlin Heidelberg), p. 167–201. doi: 10.1007/978-3-642-75348-0_7

Prinz, W. (1997). Perception and action planning. *Euro. J. Cogn. Psychol.* 9, 129–154. doi: 10.1080/713752551

Proffitt, D. (2008). "An action-specific approach to spatial perception," in R. L. Klatzky, B. MacWhinney and M. Behrmann (Eds.) (New York: Psychology Press.), 179–202.

Proffitt, D. R. (2006). Distance perception. *Curr. Dir. Psychol. Sci.* 15, 131–135. doi: 10.1111/j.0963-7214.2006.00422.x

Rahmouni, S., and Madelain, L. (2019). Inter-individual variability and consistency of saccade adaptation in oblique saccades: amplitude increase and decrease in the horizontal or vertical saccade component. *Vision Res.* 160, 82–98. doi: 10.1016/j.visres.2019.05.001

Richardson, A. R., and Waller, D. (2005). The effect of feedback training on distance estimation in virtual environments. *Appl. Cogn. Psychol.* 19, 1089–1108. doi: 10.1002/acp.1140

Rieser, J. J., Ashmead, D. H., Talor, C. R., and Youngquist, G. A. (1990). Visual perception and the guidance of locomotion without vision to previously seen targets. *Perception* 19, 675–689. doi: 10.1068/p190675

Rieser, J. J., Pick, H. L., Ashmead, D. H., and Garing, A. E. (1995). Calibration of human locomotion and models of perceptual-motor organization. *J. Exp. Psychol. Hum. Percept. Perform.* 21, 480–497. doi: 10.1037/0096-1523.21.3.480

Ross, J., Morrone, M. C., and Burr, D. C. (1997). Compression of visual space before saccades. *Nature* 386, 598–601. doi: 10.1038/386598a0

Rossetti, Y., Stelmach, G., Desmurget, M., Prablanc, C., and Jeannerod, M. (1994). The effect of viewing the static hand prior to movement onset on pointing kinematics and variability. *Exp. Brain. Res.* 101, 323–330. doi: 10.1007/BF00228753

Salimi, I., Hollender, I., Frazier, W., and Gordon, A. M. (2000). Specificity of internal representations underlying grasping. *J. Neurophysiol.* 84, 2390–2397. doi: 10.1152/jn.2000.84.5.2390

Sanz Diez, P., Bosco, A., Fattori, P., and Wahl, S. (2022). Horizontal target size perturbations during grasping movements are described by subsequent size perception and saccade amplitude. *PLoS One* 17, e0264560. doi: 10.1371/journal.pone.0264560

Sarlegna, F. R., and Sainburg, R. L. (2009). *The Roles of Vision and Proprioception in the Planning of Reaching Movements*, p. 317–335. doi: 10.1007/978-0-387-77064-2_16

Schlag, J., and Schlag-Rey, M. (1995). Illusory localization of stimuli flashed in the dark before saccades. *Vision. Res.* 35, 2347–2357. doi: 10.1016/0042-6989(95)00021-Q

Schubö, A., Aschersleben, G., and Prinz, W. (2001). Interactions between perception and action in a reaction task with overlapping S-R assignments. *Psychol. Res.* 65, 145–157. doi: 10.1007/s004260100061

Sedgwick, H. (1986). "Space perception.," in *Handbook of perception and human performance: Vol I. Sensory processes and perception*, eds Thomas (New York, NY: Wiley.), p. 21–57.

Siegel, Z. D., Kelly, J. W., and Cherep, L. A. (2017). Rescaling of perceived space transfers across virtual environments. *J. Exp. Psychol. Hum. Percept. Perform.* 43, 1805–1814. doi: 10.1037/xhp0000401

Stefanucci, J. K., and Geuss, M. N. (2009). Big people, little world: the body influences size perception. *Perception* 38, 1782–1795. doi: 10.1068/p6437

Sutton, R., and Barto, A. (1998). *Reinforcement Learning: An Introduction*. London: The MIT Press. doi: 10.1109/TNN.1998.712192

Symes, E., Tucker, M., Ellis, R., Vainio, L., and Ottoboni, G. (2008). Grasp preparation improves change detection for congruent objects. *J. Exp. Psychol. Hum. Percept. Perform.* 34, 854–871. doi: 10.1037/0096-1523.34.4.854

Taylor, J. E. T., Witt, J. K., and Sugovic, M. (2011). When walls are no longer barriers: perception of wall height in parkour. *Perception* 40, 757–760. doi: 10.1068/p6855

Thut, G., Miniussi, C., and Gross, J. (2012). The functional importance of rhythmic activity in the brain. *Current Biology* 22, R658–R663. doi: 10.1016/j.cub.2012.06.061

Tomassini, A., Ambrogioni, L., Medendorp, W. P., and Maris, E. (2017). Theta oscillations locked to intended actions rhythmically modulate perception. *Elife* 6, e25618. doi: 10.7554/eLife.25618.014

Tomassini, A., Spinelli, D., Jacono, M., Sandini, G., and Morrone, M. C. (2015). Rhythmic oscillations of visual contrast sensitivity synchronized with action. *J. Neurosci.* 35, 7019. doi: 10.1523/JNEUROSCI.4568-14.2015

Valsecchi, M., Cassanello, C., Herwig, A., Rolfs, M., and Gegenfurtner, K. R. (2020). A comparison of the temporal and spatial properties of trans-saccadic perceptual recalibration and saccadic adaptation. *J. Vis.* 20, 2. doi: 10.1167/jov.20.4.2

Valsecchi, M., and Gegenfurtner, K. R. (2016). Dynamic re-calibration of perceived size in fovea and periphery through predictable size changes. *Curr. Biol.* 26, 59–63. doi: 10.1016/j.cub.2015.10.067

van Beers, R. J., Baraduc, P., and Wolpert, D. M. (2002). Role of uncertainty in sensorimotor control. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 357, 1137–1145. doi: 10.1098/rstb.2002.1101

Velay, J., and Beaubaton, D. (1986). Influence of visual context on pointing movement accuracy. *Cahiers de Psychologie Cognitive* 6, 447–456.

Vishwanath, D., and Kowler, E. (2003). Localization of shapes: eye movements and perception compared. *Vision. Res.* 43, 1637–1653. doi: 10.1016/S0042-6989(03)00168-8

Waller, D., and Richardson, A. R. (2008). Correcting distance estimates by interacting with immersive virtual environments: Effects of task and available sensory information. *J. Exp. Psychol. Appl.* 14, 61–72. doi: 10.1037/1076-898X.14.1.61

Warren, W. H. (1984). Perceiving affordances: visual guidance of stair climbing. *J. Exp. Psychol. Hum. Percept. Perform.* 10, 683–703. doi: 10.1037/0096-1523.10.5.683

Warren, W. H., and Whang, S. (1987). Visual guidance of walking through apertures: body-scaled information for affordances. *J. Exp. Psychol. Hum. Percept. Perform.* 13, 371–383. doi: 10.1037/0096-1523.13.3.371

Watanabe, S., Ogino, S., Nakamura, T., and Koizuka, I. (2003). Saccadic adaptation in the horizontal and vertical directions in normal subjects. *Auris Nasus Larynx* 30, 41–45. doi: 10.1016/S0385-8146(02)00119-0

Westling, G., and Johansson, R. S. (1984). Factors influencing the force control during precision grip. *Exp. Brain Res.* 53, 6. doi: 10.1007/BF00238156

Witt, J. (2018). "Perception and Action," in *Stevens' Handbook of Experimental Psychology and Cognitive Neuroscience* (New York, NY: Wiley), p. 489–523. doi: 10.1002/9781119170174.epcn211

Witt, J. K. (2011). Tool use influences perceived shape and perceived parallelism, which serve as indirect measures of perceived distance. *J. Exp. Psychol. Hum. Percept. Perform.* 37, 1148–1156. doi: 10.1037/a0021933

Witt, J. K., and Proffitt, D. R. (2005). See the ball, hit the ball: apparent ball size is correlated with batting average. *Psychol. Sci.* 16, 937–938. doi: 10.1111/j.1467-9280.2005.01640.x

Witt, J. K., and Proffitt, D. R. (2008). Action-specific influences on distance perception: a role for motor simulation. *J. Exp. Psychol. Hum. Percept. Perform.* 34, 1479–1492. doi: 10.1037/a0010781

Witt, J. K., Proffitt, D. R., and Epstein, W. (2004). Perceiving distance: a role of effort and intent. *Perception* 33, 577–590. doi: 10.1068/p5090

Witt, J. K., Proffitt, D. R., and Epstein, W. (2005). Tool use affects perceived distance, but only when you intend to use it. *J. Exp. Psychol. Hum. Percept. Perform.* 31, 880–888. doi: 10.1037/0096-1523.31.5.880

Witt, J. K., and Sugovic, M. (2010). Performance and ease influence perceived speed. *Perception* 39, 1341–1353. doi: 10.1068/p6699

Wittenberg, M., Bremmer, F., and Wachtler, T. (2008). Perceptual evidence for saccadic updating of color stimuli. *J. Vis.* 8, 9. doi: 10.1167/8.14.9

Wohlschläger, A. (2000). Visual motion priming by invisible actions. *Vision. Res.* 40, 925–930. doi: 10.1016/S0042-6989(99)00239-4

Wolpert, D. M., Ghahramani, Z., and Jordan, Michael, I. (1995). Are arm trajectories planned in kinematic or dynamic coordinates? an adaptation study. *Exp. Brain. Res.* 5, 103. doi: 10.1007/BF00241505

Woodworth, R. S. (1899). Accuracy of voluntary movement. *Psychologic. Rev. Monograp. Suppl.* 3, i—114. doi: 10.1037/h0092992

Wühr, P., and Müsseler, J. (2001). Time course of the blindness to response-compatible stimuli. *J. Exp. Psychol. Hum. Percept. Perform.* 27, 1260–1270. doi: 10.1037/0096-1523.27.5.1260

Wykowska, A., Hommel, B., and Schubo, A. (2011). Action-induced effects on perception depend neither on element-level nor on set-level similarity between stimulus and response sets. *Atten. Percept. Psychophys.* 73, 1034–1041. doi: 10.3758/s13414-011-0122-x

Wykowska, A., and Schubö, A. (2012). Action intentions modulate allocation of visual attention: electrophysiological evidence. *Front. Psychol.* 3, 12. doi: 10.3389/fpsyg.2012.00379

Wykowska, A., Schubö, A., and Hommel, B. (2009). How you move is what you see: action planning biases selection in visual search. *J. Exp. Psychol. Hum. Percept. Perform.* 35, 1755–1769. doi: 10.1037/a0016798

Zelinsky, G. J., Rao, R. P. N., Hayhoe, M. M., and Ballard, D. H. (1997). Eye movements reveal the spatiotemporal dynamics of visual search. *Psychol. Sci.* 8, 448–453. doi: 10.1111/j.1467-9280.1997.tb00459.x

Zimmermann, E., and Lappe, M. (2010). Motor signals in visual localization. *J. Vis.* 10, 1–11. doi: 10.1167/10.6.2

Zimmermann, E., Morrone, M. C., and Burr, D. (2015). Visual mislocalization during saccade sequences. *Exp. Brain. Res.* 233, 577–585. doi: 10.1007/s00221-014-4138-z

Zimmermann, E., Morrone, M. C., and Burr, D. C. (2014). The visual component to saccadic compression. *J. Vis.* 14, 13. doi: 10.1167/14.12.13

Zwickel, J., Grosjean, M., and Prinz, W. (2007). Seeing while moving: measuring the online influence of action on perception. *Q. J. Experiment. Psychol.* 60, 1063–1071. doi: 10.1080/17470210701288722

Zwickel, J., Grosjean, M., and Prinz, W. (2010). On interference effects in concurrent perception and action. *Psychologic. Res. Psychologische Forschung* 74, 152–171. doi: 10.1007/s00426-009-0226-2

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Hippocampal beta rhythms as a bridge between sensory learning and memory-guided decision-making

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A pillar of systems neuroscience has been the study of neural oscillations. Research into these oscillations spans brain areas, species, and disciplines, giving us common ground for discussing typically disparate fields of neuroscience. In this review, we aim to strengthen the dialog between sensory systems research and learning and memory systems research by examining a 15–40 Hz oscillation known as the beta rhythm. Starting with foundational observations based largely in olfactory systems neuroscience, we review evidence suggesting beta-based activity may extend across sensory systems generally, as well as into the hippocampus and areas well known for coordinating decisions and memory-guided behaviors. After evaluating this work, we propose a framework wherein the hippocampal beta oscillation and its diverse coupling with other brain areas can support both sensory learning and memory-guided decision-making. Using this framework, we also propose circuitries that may support these processes, and experiments to test our hypothesis.

KEYWORDS

beta oscillations, neural oscillations, decision-making, sensory learning, hippocampus

Introduction

When researchers studying olfaction started recording from the hippocampus in the 1990s and 2000s they found that hippocampal activity could oscillate coherently with activity in early olfactory regions. The rhythmic coupling between these structures was strongest in the 15–40 Hz frequency band–the frequency of a classic olfactory system oscillation known as the beta rhythm. Prior work had indicated that beta rhythms occurred in other early sensory systems, such as the visual and auditory systems, and work since then has reaffirmed the existence of hippocampal beta in contexts that seemingly have nothing to do with active olfaction.

At the core of systems neuroscience is the promise of illuminating relationships between typically distinct sub-disciplines. Thus the goal of this review is to examine and relate the literature describing beta rhythms in sensory systems to beta rhythms in

hippocampal processing. After briefly summarizing historical reports of beta, both in early sensory regions and the hippocampus, we will discuss new evidence suggesting cross-regional interactions between the hippocampus and a number of areas at beta frequencies. Based on these results, we will suggest that hippocampal beta is a distinctive rhythm that may have dual roles in sensory- and memory-guided behaviors.

Since this review will focus on sensory-cortical and hippocampal beta, as well as hippocampal beta coupling with other brain regions, we will not be reviewing all aspects of the beta rhythm. Instead, for reviews on beta rhythms in (primate) cortical information processing, we refer the reader to Spitzer and Haegens (2017) and Miller et al. (2018). To learn more about beta rhythms in motor systems, and how they become pathological in neurodegenerative diseases (see Stein and Bar-Gad, 2013; Singh, 2018; Barone and Rossiter, 2021). For general descriptions of how beta fits into circuit and system-wide oscillatory dynamics (see Kay et al., 2009; Kay, 2014; Kopell et al., 2014).

Before exploring the early work on beta, we should note that beta is not always defined in the same way, and its definition has changed over time. Fortunately, sensory systems work has been relatively consistent with its definition of beta as an often brief, 15–40 Hz rhythm. In contrast, early hippocampal research often separated rhythms into regular slow activity (often recognized as theta) and fast rhythms, which we would now call gamma, without consistent reference to their frequency content (Leung, 1992). To maintain consistency we will adopt the 15–40 Hz definition from the sensory systems literature in this review.

Early reports of beta in sensory systems

Reports of beta rhythms in mammalian sensory systems extend at least as far back as the 1940s, when Adrian (1942) reported breathing- and scent-related 15–20 and 30–40 Hz rhythms in the hedgehog and rabbit olfactory bulb, hedgehog piriform cortex, and lateral olfactory tract of cats. Amplitude modulated sounds were shown to evoke 15–30 Hz responses in parts of the canine auditory cortex (Tielen et al., 1969), and recordings from the visual cortex of dogs trained to detect sinusoidally modulated light also showed beta oscillations (Lopes da Silva et al., 1970). As quantification of coordinated activity between neural systems became more precise, researchers began describing how different areas interacted with one another (Boudreau, 1964; Abraham et al., 1973; Holsheimer et al., 1979; Bressler, 1984; Boeijinga and Lopes da Silva, 1989; Wróbel et al., 1994). For example, Boeijinga and Lopes da Silva (1989) showed beta coherence between the piriform cortex and entorhinal cortex in cats exploring two different smells, especially as they sniffed an odor associated with reward. Others suggested that beta activity in the visual cortex during attention to visual stimuli propagated to the lateral geniculate nucleus (Wróbel et al., 1994). It's unclear if there was consensus about general roles of the beta observed throughout sensory cortical areas. However, an attempt to summarize the role of beta oscillations specifically in visual processing suggested that inter-areal beta activity was a marker of attention, and posited that the same could be true of any sensory processing areas (Wróbel, 2000).

Early reports of hippocampal beta

Explicit observations of a hippocampal beta rhythm in early research were scarce, but there were several notable exceptions. First, Boudreau showed hippocampal auto- and cross- spectral peaks in the 15–20 Hz range of awake cats (Boudreau, 1966). Comparing theta and beta generation in the hippocampus and overlying neocortex of the rat, one group concluded that, while there were many similarities between hippocampal theta and beta, they also appeared independently of one another (Holsheimer et al., 1979). Soon after, a report in awake rats proposed three main hippocampal rhythmic states–theta or regular slow activity, irregular slow activity, and fast waves. While this research described irregular slow activity as occurring partially in the beta range, it also attributed much of the energy in the beta range to theta harmonics (Leung et al., 1982), which is somewhat at odds with the reports of Holsheimer et al. (1979). In sum, early work on hippocampal beta described its similarities to theta, but suggested there were grounds to think of it as a separate rhythm.

Beta coupling between the hippocampus and sensory cortices

A series of papers in the 1990s helped bridge the gap between sensory systems and hippocampal work by studying hippocampal and olfactory bulb processing in tandem. Hippocampal dentate gyrus recordings showed that 15–40 Hz "fast waves" were triggered when rats were coaxed to sniff toluene, xylene, or several predator-mimicking odors (Vanderwolf, 1992; Heale et al., 1994). Though not quantified, the authors also claimed the dentate fast wave was not necessarily correlated with olfactory bulb beta. Similar results were also obtained by Chapman et al. (1998), who also showed beta in the entorhinal and piriform cortices. Other researchers described a series of bidirectional interactions between the dentate gyrus, olfactory bulb, entorhinal cortex, and piriform cortex throughout the course of an odor discrimination (Kay et al., 1996; Kay and Freeman, 1998). With respect to beta, they described a so-called "preafferent" beta signal, originating in the entorhinal cortex and sent to the olfactory bulb prior to olfactory stimulus presentation. Overall, these authors suggested that beta in limbic structures could bias attention in early olfactory areas to detect learned stimuli, but it was still hard to say how the hippocampus factored into this process.

Following up on these results, Martin et al. (2007) recorded from the olfactory bulb and dentate gyrus while rats learned to distinguish between different pairs of odors. They found increased beta power in both structures during odor sampling, but beta coherence reliably increased only when rats learned the distinction between new odor pairs. Re-examination of these results with different mathematical techniques suggested that beta coherence flowed from the olfactory bulb to the hippocampus during odor sampling (Gourévitch et al., 2010). Looking deeper into the link between intra-limbic beta activity during odor identification, Igarashi et al. (2014) showed strong coherence between the lateral entorhinal cortex and dorsal CA1 region of the hippocampus during odor sampling. These authors also showed that learning was accompanied by increased beta coherence between these areas,

which coincided with the formation of odor representations in cell populations. Further, they showed that error trials and changes of odor contingencies were accompanied by reduced coherence and reduced ensemble selectivity between areas. Together, these reports suggested that beta during sensory sampling can, but does not necessarily, coincide with beta in limbic structures, while increased entorhinal-hippocampal beta coupling tracks learning and task performance.

Building on olfactory-hippocampal beta coupling and early sensory systems work, one recent study demonstrated beta-based hippocampal interactions with non-olfactory sensory areas. To clarify how rhythmic activity was patterned across sensory cortices, Vinck et al. (2016) recorded from a primary somatosensory area (barrel cortex), primary visual cortex, perirhinal cortex, and dorsal CA1 of rat hippocampus. The strongest coupling between areas was in the beta range. This was different from local synchrony measures, which were strongest in the gamma range. Beta coupling was also stronger while animals were moving, but the authors did not study how rhythms correlated with other aspects of behavior. This study provided new evidence that the hippocampus could couple with a variety of cortical sensory regions in the beta frequency range, not just olfactory and higher-order limbic regions like the entorhinal cortex.

Though it's not yet clear how beta between the hippocampus and sensory cortices becomes coordinated, one possible candidate is through interactions with the basal forebrain (**Figure 1**). The basal forebrain has modular anatomical connections throughout the neocortex and with the hippocampus (Woolf, 1991; Záborszky et al., 2018). Further, beta-rhythmic basal forebrain local field potential (LFP) has been reported to change throughout learning (Quinn et al., 2010), and both cell assembly formation and oscillatory dynamics in the basal forebrain have been shown to occur at beta-rhythmic frequencies throughout the course of a trial in complex sensory-motor tasks (Tingley et al., 2015, 2018).

Hippocampal beta in learning and memory

Recent work has provided more details on how hippocampal beta relates to learning and memory. Using a task that combined sensory-guided behavior with sequence-memory, Allen et al. (2016) showed the magnitude of rhythmic hippocampal activity in the 20–40 Hz range was stronger when odors were presented in a correctly learned sequence. Additionally, the magnitude increase correlated with task performance. Importantly, because they presented the same odors for correct and incorrect sequences, the authors argued that changes in beta were tied to the sequences themselves and not sensory aspects of the odor identities. Similar results in the same paradigm further demonstrated that this elevated hippocampal beta response tends to occur late in the odor-sampling process, particularly for odors correctly identified as being presented in the correct sequence (Gattas et al., 2022).

Interested in characterizing the relationship between hippocampal cell classes and LFP dynamics with respect to behavior, Rangel et al. (2016) recorded from dorsal CA1 during an odor-place association task. Similar to Allen et al. (2016), they found that beta-rhythmic activity was most strongly related to successful task performance. Specifically, the vast majority of putative interneurons and principal cells that phase-locked to the hippocampal LFP in the beta range did so only when animals chose correctly. Notably, beta-coherent principal cells were the only cells to selectively carry information about odor-place associations, and only during the period coinciding with their decision. From these data, the authors concluded that beta-rhythmic activity might be uniquely situated to process information required for memory-guided associations. This mirrors other findings that hippocampal LFP beta power increased in response to reward-predictive cues, concurrent with decreased theta, in a variety of cue-reward association tasks (Rangel et al., 2015).

While most research on hippocampal beta has come from studies using olfactory stimuli, Berke et al. (2008) demonstrated dorsal hippocampal beta power increasing in response to novel environments. These authors showed that strong beta oscillations in CA1 and CA3 emerged early in sessions where mice had been introduced to novel environments, with spiking phase-locked to the beta LFP oscillation, and spatial specificity in place cells emerging during the elevated beta period. These results provided evidence that the hippocampus could exhibit beta-rhythmic activity during behaviors that were not explicitly sensory-guided. In sum, work focused on hippocampal beta has shown that its prevalence extends beyond a simple role in olfactory learning by linking it with novelty (Berke et al., 2008), sequence memory (Allen et al., 2016; Gattas et al., 2022), and cue-reward associations (Rangel et al., 2015, 2016).

Beta coupling between the hippocampus and "non-sensory" areas

Showing that beta oscillations could link the hippocampus and non-sensory areas, Lansink et al. (2016) reported increased beta (and theta) activity between the hippocampus and ventral striatum during cue-driven navigation. Similar to Rangel et al. (2015), they showed that entry into a cued location associated with reward caused increases in hippocampal beta/theta LFP power and intra-hippocampal coherence. Additionally, spike timing in the ventral striatum showed beta-rhythmic phase-locking to the dorsal CA1 LFP, which, again, was stronger when the animal approached a cued reward. Therefore, the authors suggested that beta and theta rhythmic interactions between the dorsal hippocampus and ventral striatum were important when anticipating reward and guiding behavior based on learned associations to cues.

Although the hippocampus and medial prefrontal cortex (mPFC) are classically known for their theta oscillatory coupling (Jones and Wilson, 2005; Siapas et al., 2005; Benchenane et al., 2010; Hyman et al., 2010; Colgin, 2011; Gordon, 2011), recent studies have shown beta-based interactions between the two. In an odor-place association task, beta coherence between the mPFC and hippocampus increased as rats were sampling odors and making decisions about where they would navigate (Symanski et al., 2022). Cells that phase-locked to the local beta rhythm in either mPFC or hippocampus did so more strongly before correct decisions, but no clear differences in LFP coherence between areas was observed. It's worth noting that these authors also saw beta

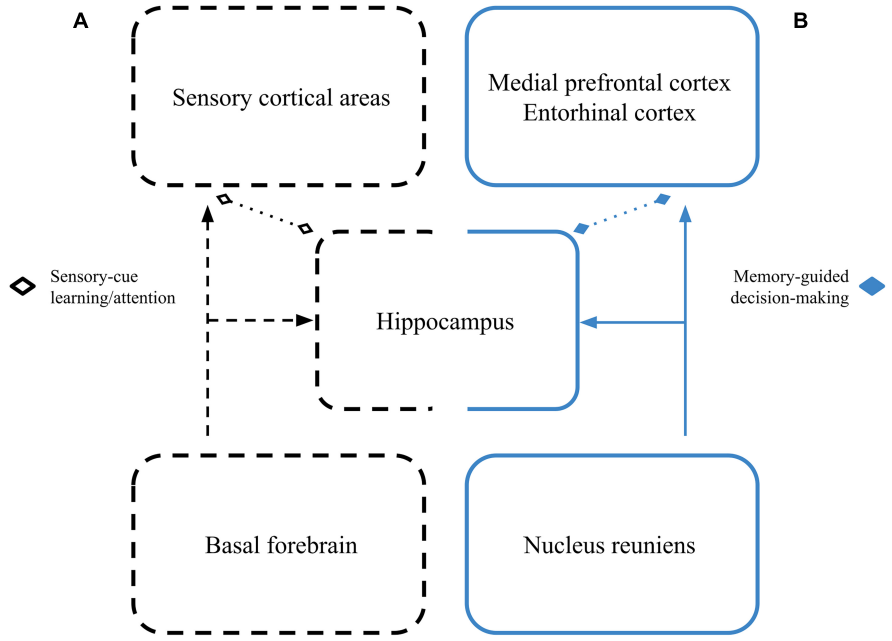

FIGURE 1
Dual roles for hippocampal beta networks. **(A)** Cues driving beta in sensory cortical areas may become coherent with cue-driven hippocampal beta through beta-related activity of cell assemblies in the basal forebrain as learning progresses and cues are selectively attended to. This network is represented by the black dashed boxes. **(B)** During memory-guided decision-making, the reuniens may coordinate beta between the hippocampus, prefrontal/association cortices, and their efferent action selection areas. This network is represented by the solid blue boxes. Dotted lines with diamond tips signify that these beta-based interactions may happen with or without direct anatomical connectivity.

coherence between both structures (mPFC and hippocampus) and the olfactory bulb during the same odor sampling and decision-making period, suggesting that this network is engaged during active sensation at beta frequency as well. This is somewhat at odds with prior reports showing only occasional coherence between the olfactory bulb and hippocampus during odor sampling, but in accordance with suggestions that different behaviors and behavioral strategies may alter beta dynamics (Gourévitch et al., 2010; Kay and Beshel, 2010; Frederick et al., 2016).

In another study using the previously mentioned olfactory sequence-memory task, Jayachandran et al. (2022) found that hippocampal beta during sequence-memory is coherent with mPFC beta. Accurate identification of correctly ordered sequences showed higher beta coherence than sequences that were incorrectly ordered or misidentified. Interestingly, these authors also found beta bursts in recordings from the reuniens that began just prior to beta in the mPFC and hippocampus, and showed that optogenetic stimulation of reuniens projections to the hippocampus caused beta in the hippocampus and mPFC.

Taken together, these results show that coordinated beta-rhythmic activity can exist between the hippocampus and areas not traditionally considered sensory processing regions, such as the mPFC and ventral striatum. Beta coupling between the hippocampus and mPFC seems to be linked to successful memory-based decision-making (Igarashi et al., 2014; Jayachandran et al., 2022; Symanski et al., 2022), beta-rhythmic activity between the ventral striatum and hippocampus is strongest during cue-triggered reward expectation (Lansink et al., 2016), and hippocampal-entorhinal beta seems to track learning (Igarashi et al., 2014). All of these results suggest that increased beta between the hippocampus and higher-order cortical or action planning areas is important for successful memory-guided behavior.

Dual roles for hippocampal beta networks

What remains unclear is whether beta-based interactions between the hippocampus and sensory areas have the same characteristics as beta-based interactions between the hippocampus and "non-sensory" areas (**Figure 1**). The olfactory system, for example, seems to reliably exhibit beta oscillations during active sensation, but that activity is not always coherent with hippocampal beta activity (Kay and Freeman, 1998; Martin et al., 2007; Gourévitch et al., 2010), even when animals are engaging in a learned behavior. On the other hand, there are increases in beta coherence between the hippocampus and olfactory sensory areas during rule transfers to new stimuli (Martin et al., 2007; Gourévitch et al., 2010), and freely moving rats can show beta-rhythmic activity between the hippocampus and a variety of sensory areas even if they are not engaged in any structured task (Vinck et al., 2016).

Resolving this ambiguity will require more studies that record concurrently from the hippocampus and sensory areas during active sensation, as has been done in the olfactory system. Analogous tests of the visual system could be done using tasks that change which visual cues are associated with reward. Presumably, visual cortex and hippocampus would show beta during cue presentations, but coherence between areas would only significantly increase while learning cue-reward associations or after they change. The test could be made even stronger using a task

that switched reward contingencies between different modalities of sensory cue (e.g., visual and olfactory/auditory). If beta coherence between the hippocampus and sensory structures switched based on rewarded sensory modality, it would support the idea that beta coherence enables sensory-driven, cue-reward association. Additionally, if the cross-regional coherence increases were specific to transition periods, it would suggest that learned sensory cues *per se* do not drive the interaction, but the flexible contingency re-learning or attentional shift required to update behavior does.

We also have reason to believe that hippocampal beta coupling with non-sensory areas has relevance for task performance, learning, and memory (Igarashi et al., 2014; Lansink et al., 2016; Jayachandran et al., 2022; Symanski et al., 2022). The tasks from these studies, however, are all explicitly tied to sensory stimuli, and it's clear that hippocampal beta can occur under conditions not specifically locked to reward (Berke et al., 2008; Vinck et al., 2016). Recordings from hippocampus and areas linked to higher-order association and decision-making during tasks that do not require sensory-driven behavioral responses would help clarify how beta coupling unfolds between hippocampus and non-sensory areas. For example, spatial working memory tasks often require hippocampal-prefrontal interactions (Floresco et al., 1997; Wang and Cai, 2006; Eichenbaum, 2017), but there do not seem to be experiments directly asking whether beta-based activity correlates with spatial working memory or decision-making. We would expect to see brief elevations in hippocampal-prefrontal beta coherence as decisions are made about where to navigate. Care should also be taken to ensure the task requires allocentric navigation. This would prevent simple cue-based strategy use, which we already suspect causes hippocampal beta.

Conclusion

We hypothesize that one role for hippocampal-based beta is to coherently oscillate with sensory areas and promote cue-reward associations, while another is to coherently oscillate with decision-making and action selection areas, enabling successful memory-guided behavior. Continued study of neural coordination within and across sensory and memory systems could reveal new insights into the nature and significance of beta-based activity across disparate brain structures (Kopell et al., 2000).

Author contributions

JM, KK, and SM contributed to the conceptualization of the review. JM wrote the initial drafts of the document, proposed the model, and made the associated figure. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

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References

Abraham, F., Bryant, H., Mettler, M., Bergerson, B., Moore, F., Maderdrut, J., et al. (1973). Spectrum and discriminant analyses reveal remote rather than local sources for hypothalamic EEG: Could waves affect unit activity? *Brain Res.* 49, 349–366. doi: 10.1016/0006-8993(73)90427-7

Adrian, E. D. (1942). Olfactory reactions in the brain of the hedgehog. *J. Physiol.* 100, 459–473.

Allen, T. A., Salz, D. M., McKenzie, S., and Fortin, N. J. (2016). Nonspatial sequence coding in CA1 Neurons. *J. Neurosci.* 36, 1547–1563. doi: 10.1523/JNEUROSCI.2874-15.2016

Barone, J., and Rossiter, H. E. (2021). Understanding the role of sensorimotor beta oscillations. *Front. Syst. Neurosci.* 15:655886. doi: 10.3389/fnsys.2021.655886

Benchenane, K., Peyrache, A., Khamassi, M., Tierney, P. L., Gioanni, Y., Battaglia, F. P., et al. (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. *Neuron* 66, 921–936. doi: 10.1016/j.neuron.2010.05.013

Berke, J. D., Hetrick, V., Breck, J., and Greene, R. W. (2008). Transient 23–30 Hz oscillations in mouse hippocampus during exploration of novel environments. *Hippocampus* 18, 519–529. doi: 10.1002/hipo.20435

Boeijinga, P. H., and Lopes da Silva, F. H. (1989). Modulations of EEG activity in the entorhinal cortex and forebrain olfactory areas during odour sampling. *Brain Res.* 478, 257–268. doi: 10.1016/0006-8993(89)91506-0

Boudreau, J. C. (1964). Computer analysis of electrical activity in the olfactory system of the cat. *Nature* 201, 155–158. doi: 10.1038/201155a0

Boudreau, J. C. (1966). Computer measurements of hippocampal fast activity in cats with chronically implanted electrodes. *Electroencephalogr. Clin. Neurophysiol.* 20, 165–174. doi: 10.1016/0013-4694(66)90160-X

Bressler, S. L. (1984). Spatial organization of EEGs from olfactory bulb and cortex. *Electroencephalogr. Clin. Neurophysiol.* 57, 270–276. doi: 10.1016/0013-4694(84)90128-7

Chapman, C. A., Xu, Y., Haykin, S., and Racine, R. J. (1998). Beta-frequency (15–35Hz) electroencephalogram activities elicited by toluene and electrical stimulation in the behaving rat. *Neuroscience* 86, 1307–1319. doi: 10.1016/S0306-4522(98)00092-X

Colgin, L. L. (2011). Oscillations and hippocampal–prefrontal synchrony. *Curr. Opin. Neurobiol. Behav. Cogn. Neurosci.* 21, 467–474. doi: 10.1016/j.conb.2011.04.006

Eichenbaum, H. (2017). Prefrontal-hippocampal interactions in episodic memory. *Nat. Rev. Neurosci.* 18, 547–558. doi: 10.1038/nrn.2017.74

Floresco, S. B., Seamans, J. K., and Phillips, A. G. (1997). Selective roles for hippocampal, prefrontal cortical, and ventral striatal circuits in radial-arm maze tasks with or without a delay. *J. Neurosci.* 17, 1880–1890. doi: 10.1523/JNEUROSCI.17-05-01880.1997

Frederick, D. E., Brown, A., Brim, E., Mehta, N., Vujovic, M., and Kay, L. M. (2016). Gamma and beta oscillations define a sequence of neurocognitive modes present in odor processing. *J. Neurosci.* 36, 7750–7767. doi: 10.1523/JNEUROSCI.0569-16.2016

Gattas, S., Elias, G. A., Janecek, J., Yassa, M. A., and Fortin, N. J. (2022). Proximal CA1 20–40 Hz power dynamics reflect trial-specific information processing supporting nonspatial sequence memory. *eLife* 11:e55528. doi: 10.7554/eLife.55528

Gordon, J. A. (2011). Oscillations and hippocampal–prefrontal synchrony. *Curr. Opin. Neurobiol. Behav. Cogn. Neurosci.* 21, 486–491. doi: 10.1016/j.conb.2011.02.012

Gourévitch, B., Kay, L. M., and Martin, C. (2010). Directional Coupling from the olfactory bulb to the hippocampus during a Go/No-Go odor discrimination task. *J. Neurophysiol.* 103, 2633–2641. doi: 10.1152/jn.01075.2009

Heale, V. R., Vanderwolf, C. H., and Kavaliers, M. (1994). Components of weasel and fox odors elicit fast wave bursts in the dentate gyrus of rats. *Behav. Brain Res.* 63, 159–165. doi: 10.1016/0166-4328(94)90087-6

Holsheimer, J., Feenstra, B., and Nijkamp, J. (1979). "Distribution of field potentials and their relationships during theta and beta activity in the hippocampus and the overlying neocortex of the rat," in *Origin of cerebral field potentials*, eds E. J. Speckmann and H. Caspers (Stuttgart: Thieme), 98–114.

Hyman, J., Zilli, E., Paley, A., and Hasselmo, M. (2010). Working memory performance correlates with prefrontal-hippocampal theta interactions but not with prefrontal neuron firing rates. *Front. Integr. Neurosci.* 4:2. doi: 10.3389/neuro.07.002.2010

Igarashi, K. M., Lu, L., Colgin, L. L., Moser, M.-B., and Moser, E. I. (2014). Coordination of entorhinal–hippocampal ensemble activity during associative learning. *Nature* 510, 143–147. doi: 10.1038/nature13162

Jayachandran, M., Viena, T. D., Garcia, A., Veliz, A. V., Leyva, S., Roldan, V., et al. (2022). Reuniens transiently synchronizes memory networks at beta frequencies. *bioRxiv* [Preprint]. doi: 10.1101/2022.06.21.497087

Jones, M. W., and Wilson, M. A. (2005). Theta rhythms coordinate hippocampal–prefrontal interactions in a spatial memory task. *PLoS Biol.* 3:e402. doi: 10.1371/journal.pbio.0030402

Kay, L. M. (2014). "Circuit Oscillations in Odor Perception and Memory," in *Progress in Brain Research, Odor Memory and Perception*, Chap. 9, eds E. Barkai and D. A. Wilson (Amsterdam: Elsevier), 223–251. doi: 10.1016/B978-0-444-63350-7.00009-7

Kay, L. M., and Beshel, J. (2010). A beta oscillation network in the rat olfactory system during a 2-alternative choice odor discrimination task. *J. Neurophysiol.* 104, 829–839. doi: 10.1152/jn.00166.2010

Kay, L. M., and Freeman, W. J. (1998). Bidirectional processing in the olfactory-limbic axis during olfactory behavior. *Behav. Neurosci.* 112, 541–553. doi: 10.1037/0735-7044.112.3.541

Kay, L. M., Beshel, J., Brea, J., Martin, C., Rojas-Líbano, D., and Kopell, N. (2009). Olfactory oscillations: The what, how and what for. *Trends Neurosci.* 32, 207–214. doi: 10.1016/j.tins.2008.11.008

Kay, L. M., Lancaster, L. R., and Freeman, W. J. (1996). Reafference and attractors in the olfactory system during odor recognitioN. *Int. J. Neur. Syst.* 07, 489–495. doi: 10.1142/S0129065796000476

Kopell, N. J., Gritton, H. J., Whittington, M. A., and Kramer, M. A. (2014). Beyond the Connectome: The Dynome. *Neuron* 83, 1319–1328. doi: 10.1016/j.neuron.2014.08.016

Kopell, N., Ermentrout, G. B., Whittington, M. A., and Traub, R. D. (2000). Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. U.S.A.* 97, 1867–1872. doi: 10.1073/pnas.97.4.1867

Lansink, C. S., Meijer, G. T., Lankelma, J. V., Vinck, M. A., Jackson, J. C., and Pennartz, C. M. A. (2016). reward expectancy strengthens CA1 theta and beta band synchronization and hippocampal-ventral striatal coupling. *J. Neurosci.* 36, 10598–10610. doi: 10.1523/JNEUROSCI.0682-16.2016

Leung, L. S. (1992). Fast (Beta) Rhythms in the hippocampus: A review. *Hippocampus* 2, 93–98.

Leung, L.-W. S., Da Silva, F. H. L., and Wadman, W. J. (1982). Spectral characteristics of the hippocampal EEG in the freely moving rat. *Electroencephalogr. Clin. Neurophysiol.* 54, 203–219. doi: 10.1016/0013-4694(82)90162-6

Lopes da Silva, F. H., van Rotterdam, A., Storm van Leeuwen, W., and Tielen, A. M. (1970). Dynamic characteristics of visual evoked potentials in the dog. II. Beta frequency selectivity in evoked potentials and background activity. *Electroencephalogr. Clin. Neurophysiol.* 29, 260–268. doi: 10.1016/0013-4694(70)90138-0

Martin, C., Beshel, J., and Kay, L. M. (2007). An olfacto-hippocampal network is dynamically involved in odor-discrimination learning. *J. Neurophysiol.* 98, 2196–2205. doi: 10.1152/jn.00524.2007

Miller, E. K., Lundqvist, M., and Bastos, A. M. (2018). Working Memory 2.0. *Neuron* 100, 463–475. doi: 10.1016/j.neuron.2018.09.023

Quinn, L. K., Nitz, D. A., and Chiba, A. A. (2010). Learning-dependent dynamics of beta-frequency oscillations in the basal forebrain of rats. *Eur. J. Neurosci.* 32, 1507–1515. doi: 10.1111/j.1460-9568.2010.07422.x

Rangel, L. M., Rueckemann, J. W., Riviere, P. D., Keefe, K. R., Porter, B. S., Heimbuch, I. S., et al. (2016). Rhythmic coordination of hippocampal neurons during associative memory processing. *eLife* 5:e09849. doi: 10.7554/eLife.09849

Rangel, L., Chiba, A., and Quinn, L. (2015). Theta and beta oscillatory dynamics in the dentate gyrus reveal a shift in network processing state during cue encounters. *Front. Syst. Neurosci.* 9:96. doi: 10.3389/fnsys.2015.00096

Siapas, A. G., Lubenov, E. V. and Wilson, M. A. (2005). Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46, 141–151. doi: 10.1016/j.neuron.2005.02.028

Singh, A. (2018). Oscillatory activity in the cortico-basal ganglia-thalamic neural circuits in Parkinson's disease. *Eur. J. Neurosci.* 48, 2869–2878. doi: 10.1111/ejn.13853

Spitzer, B., and Haegens, S. (2017). Beyond the status quo: A role for beta oscillations in endogenous content (re)activation. *eNeuro* 4, 1–15. doi: 10.1523/ENEURO.0170-17.2017

Stein, E., and Bar-Gad, I. (2013). Beta oscillations in the cortico-basal ganglia loop during parkinsonism. *Exp. Neurol. Spec. Issue* 245, 52–59. doi: 10.1016/j.expneurol.2012.07.023

Symanski, C. A., Bladon, J. H., Kullberg, E. T., Miller, P., and Jadhav, S. P. (2022). Rhythmic coordination and ensemble dynamics in the hippocampal-prefrontal network during odor-place associative memory and decision making. *eLife* 11:e79545. doi: 10.7554/eLife.79545

Tielen, A. M., Kamp, A., da Silva, F. H. L., Reneau, J. P., and van Leeuwen, W. S. (1969). Evoked responses to sinusoidally modulated sound in unanaesthetized dogs. *Electroencephalogr. Clin. Neurophysiol.* 26, 381–394. doi: 10.1016/0013-4694(69)90088-1

Tingley, D., Alexander, A. S., Quinn, L. K., Chiba, A. A., and Nitz, D. (2018). Multiplexed oscillations and phase rate coding in the basal forebrain. *Sci. Adv.* 4:eaar3230. doi: 10.1126/sciadv.aar3230

Tingley, D., Alexander, A. S., Quinn, L. K., Chiba, A. A., and Nitz, D. A. (2015). Cell Assemblies of the Basal Forebrain. *J. Neurosci.* 35, 2992–3000. doi: 10.1523/JNEUROSCI.4432-14.2015

Vanderwolf, C. H. (1992). Hippocampal activity, olfaction, and sniffing: An olfactory input to the dentate gyrus. *Brain Res.* 593, 197–208. doi: 10.1016/0006-8993(92)91308-2

Vinck, M., Bos, J. J., Van Mourik-Donga, L. A., Oplaat, K. T., Klein, G. A., Jackson, J. C., et al. (2016). Cell-type and state-dependent synchronization among rodent somatosensory, visual, perirhinal cortex, and hippocampus CA1. *Front. Syst. Neurosci.* 9:187. doi: 10.3389/fnsys.2015.00187

Wang, G. -W. and Cai, J. -X. (2006). Disconnection of the hippocampal-prefrontal cortical circuits impairs spatial working memory performance in rats. *Behav. Brain Res.* 175, 329–336. doi: 10.1016/j.bbr.2006.09.002

Woolf, N. J. (1991). Cholinergic systems in mammalian brain and spinal cord. *Prog. Neurobiol.* 37, 475–524. doi: 10.1016/0301-0082(91)90006-M

Wróbel, A. (2000). Beta activity: A carrier for visual attention. *Acta Neurobiol. Exp.* 60, 247–260.

Wróbel, A., Bekisz, M., and Waleszczyk, W. (1994). "20 Hz Bursts of Activity in the Cortico-Thalamic Pathway During Attentive Perception," in *Oscillatory Event-Related Brain Dynamics, NATO ASI Series*, eds C. Pantev, T. Elbert, and B. Lütkenhöner (Boston, MA: Springer US), 311–324. doi: 10.1007/978-1-4899-1307-4_22

Záborszky, L., Gombkoto, P., Varsanyi, P., Gielow, M. R., Poe, G., Role, L. W., et al. (2018). Specific Basal forebrain–cortical cholinergic circuits coordinate cognitive operations. *J. Neurosci.* 38, 9446–9458. doi: 10.1523/JNEUROSCI.1676-18.2018

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How far neuroscience is from understanding brains

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The cellular biology of brains is relatively well-understood, but neuroscientists have not yet generated a theory explaining how brains work. Explanations of how neurons collectively operate to produce what brains can do are tentative and incomplete. Without prior assumptions about the brain mechanisms, I attempt here to identify major obstacles to progress in neuroscientific understanding of brains and central nervous systems. Most of the obstacles to our understanding are conceptual. Neuroscience lacks concepts and models rooted in experimental results explaining how neurons interact at all scales. The cerebral cortex is thought to control awake activities, which contrasts with recent experimental results. There is ambiguity distinguishing task-related brain activities from spontaneous activities and organized intrinsic activities. Brains are regarded as driven by external and internal stimuli in contrast to their considerable autonomy. Experimental results are explained by sensory inputs, behavior, and psychological concepts. Time and space are regarded as mutually independent variables for spiking, post-synaptic events, and other measured variables, in contrast to experimental results. Dynamical systems theory and models describing evolution of variables with time as the independent variable are insufficient to account for central nervous system activities. Spatial dynamics may be a practical solution. The general hypothesis that measurements of changes in fundamental brain variables, action potentials, transmitter releases, post-synaptic transmembrane currents, etc., propagating in central nervous systems reveal how they work, carries no additional assumptions. Combinations of current techniques could reveal many aspects of spatial dynamics of spiking, post-synaptic processing, and plasticity in insects and rodents to start with. But problems defining baseline and reference conditions hinder interpretations of the results. Furthermore, the facts that pooling and averaging of data destroy their underlying dynamics imply that single-trial designs and statistics are necessary.

KEYWORDS

understanding brains, neuroscience concepts, spatial brain dynamics, intrinsic activity, spontaneous ongoing activity, brain mechanisms, dendrites, axons

1. Introduction

Understanding how a system works, usually means to understand the mechanisms by which its elements interact. If the major interaction mechanisms are known and ideally described mathematically, one has a theory of the system. So, the reason why neuroscientists do not understand how brains and central nervous systems work is that there is no theory of brains and central nervous systems. A scientific theory of a central nervous system (CNS) is an experimentally based general set of explanations of how the elements in a CNS interact at all scales of observation, i.e., from the molecular to the macroscopic scale. At the molecular scale neuroscience is guided by the theory of molecular biology. Although molecular neuroscience does not have a mathematical framework, it identifies molecules, provides rules explaining genetic replication, transcription, synthesis, interactions,

and transformation of organic molecules. However, at the cellular, and especially supracellular scales of observation, neuroscience is far from having a guiding theory.

The purpose of this article is to identify why it is so difficult to build a theory of brains and point to domains where neuroscience seems stuck in that process. Indeed, experimental neuroscience produce a rapidly increasing number of results. Based on the current structure of (systems) neuroscience, I will argue, it is impossible to put all results together to a theory of a CNS. The reasons are not primarily lack of experimental data, nor lack of methods. So, those who expect a review of how far neuroscience has reached and expect to find a list of what we do not yet know, please stop reading here. Rather the reasons for lack of progress are obstacles inherent in current neuroscientific practice which hinder us from knowing more about brains.

In this paper I use a theory of science approach to locate weaknesses in neuroscientific practices.

Neuroscience works, as other scientific disciplines, with a scientific scheme (Figure 1). Normally theory would be at the top in Figure 1. However, in the absence of a guiding theory, neuroscientists form hypotheses guided by concepts. If a concept used in neuroscience does not match brain activities, neuroscience will not progress in that direction. This is the danger of not having a theory in which relations among concepts are defined without inconsistencies. Figure 1 may serve as a roadmap for this paper, dealing with obstacles in the neuroscientific process.

Within the realms in Figure 1, one can identify obstacles of progress. The obstacles of progress indirectly identify frontiers in (systems) neuroscience. In many cases, it is possible to give suggestions that could circumvent an obstacle, push it, or eliminate it. In this effort, I build on results provided by many wise colleagues during workshops aimed to understand how brains and central nervous systems work (see Acknowledgments). This article, however, is my personal extract.

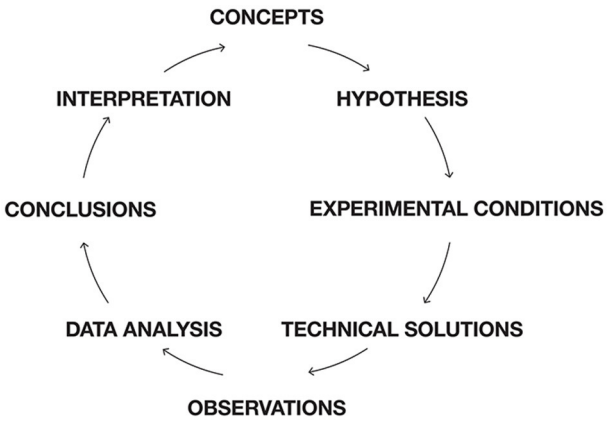

FIGURE 1
Scientific scheme for neuroscience. Roadmap for this paper. Instead of having theory on top, neuroscience have a set of concepts guiding hypothesis formation. Most of the obstacles for progress are conceptual. Conceptual glitches propagate to hypotheses, creations of experimental conditions, data analysis, and interpretations of results. First, concepts, which cannot efficiently relate to brain activities are identified. Then obstacles for models of brain functions based on brain structure and assumptions of connectivity are exposed. It is shown that cognitive tasks are not localized to specific sets of cortical areas. Unchartered issues and obstacles in understanding dendritic processing in single neurons and populations of neurons are discussed. Difficulties of distinguishing task related bran activities from spontaneous and intrinsic activities are discussed and so is the relation between autonomous and stimulus driven brain activities. The assumption that time is the independent variable for brain activities is analyzed and experimental results incompatible with this hypothesis are presented. Dynamic systems theory and models are blind to spatial interactions, limiting this approach. These obstacles are followed by suggestions to overcome them. Technically, experimental neuroscience is mostly challenged by revealing fast processes at the single neuron scale and limited by difficulties of including primates. Experimental practice neglects difficulties of finding true reference conditions, neglects the problematic assumptions that experimental animals always are naïve, and trials are statistically independent. Similarly, data are analyzed by bandwidth filters, temporal and spatial averaging removing important aspects of brain mechanisms. Finally, avoiding these many obstacles could make it easier to reliably interpret experimental results.

2. Conceptual obstacles

2.1. Lack of neuroscientific concepts

Anyone studying neuroscience and reading textbooks and neuroscientific literature gets introduced to the concepts that neuroscientists use to explain how central nervous systems are anatomically constructed and how neurons work. Some concepts are rooted in reproducible experimental results from neuroscience itself: synapse, transmitter release, membrane currents, action potentials, ion-channels, excitation, inhibition, etc. Some concepts are more loosely used: top-down, bottom-up, dorsal and ventral streams, parallel processing, or recurrent processing with reference to anatomical schemes of connectivity.

Many concepts, however, are borrowed from other scientific disciplines (Figure 2). The concepts shown in Figure 2 are used to explain how the systems in their mother disciplines work technically and (often) mathematically. These borrowed concepts are used as analogies in neuroscience. But the borrowed concepts are not tailored to explain (more complex) biological systems such as brains. Logically, analogies cannot and do not explain how neurons collaborate to achieve the whole repertoire of CNS activities. Psychological concepts have been a rich source for importing brain functions into neuroscience. Psychological concepts are made to explain and link human behavior to particular social or environmental conditions, but not fitted to explain the mechanisms by which neurons produce this behavior.

Recently, dynamics and tools from dynamical systems theory are used to characterize the collective activities of neurons (see later). The analogies shown in Figure 2 are also used as assumptions, as part of scientific hypotheses, and to interpret experimental results. If we remove all analogies and metaphors as attempts to explain brain mechanisms in neuroscience, will we lose understanding of brains? Logically, the answer is no. But one may claim that brains have certain properties which could be labeled by psychological concepts. For example, brains can show attention. In this case, which is not the rule, it is possible to hypothesize and experimentally identify physiological mechanisms creating a pre-stimulus activity making it possible to detect, say near threshold stimuli (see later). When this is experimentally supported, it would be scientifically efficient to refer to this brain mechanism,

Concepts in neuroscience borrowed from other disciplines

feedback, gain (control theory)
signal, noise, signal energy, circuit (radio engineering)
computations, inout, buffers (computer engineering)
code, encoding, decoding, information, transmission (information theory)
input, output, readout (computer science)
dynamics, states, state space (physics)
attention, motivation, reward, representation, working memory and many more (psychology)

FIGURE 2
Examples of concepts in neuroscience borrowed from other disciplines. These concepts are analogies explaining how other systems work. In neuroscience, these concepts are attempts to explain how brains work by explaining how other non-brain systems work. Analogies cannot explain brain mechanisms because they lack ontological connection to measurable brain variables. In other words, it is obscure how the concepts relate to brain variables. To remedy this, neuroscientists sometimes make new definitions of the concept. For example, gain gets re-defined as the relative increase in spike rate for a neuron. In other instances, raw data get transformed to comply with borrowed concepts. For example, oscillations are rare in *in vivo* measurements. The irregular field potentials and EEG recordings then gets filtered to produce band limited oscillations (see further under Experimental obstacles and data analysis). In short, the use of borrowed concepts implies unnecessary troubles and uncertainties in the whole neuroscientific process (Figure 1).

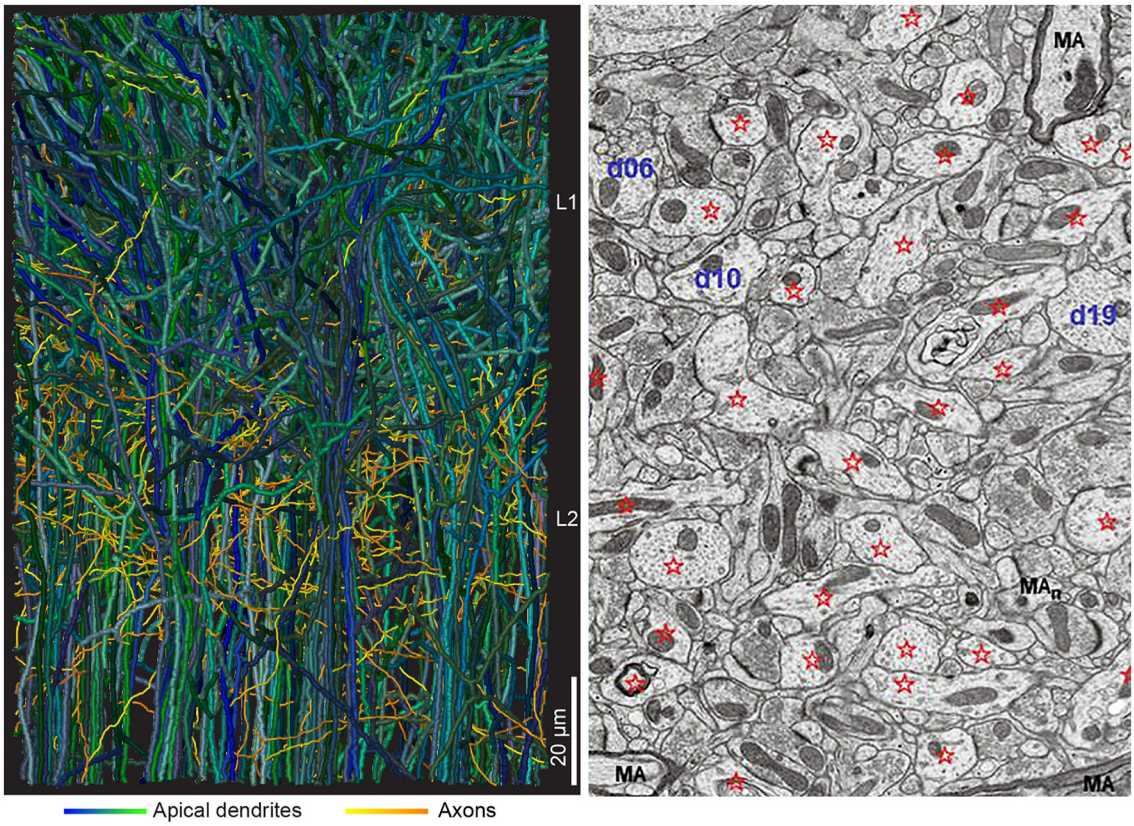

FIGURE 3
Interdigitating dendrites. **(Left)** Two hundred thirteen reconstructed apical dendrites from layer 2 (61 gray dendrites) and layers 3, 4, and 5 (152 dendrites) from mouse anterior cingulate cortex (from Karimi et al., 2020, with permission). In the volume, ~2,000 dendrites from adjacent neurons and multiple axonal branches from adjacent local and distal neurons will complete the picture. **(Right)** Electron microscopic image, 10 × 12 µm, from adult rat CA1 stratum radiatum, with dendrites identified by stars and d (number). MA, myelinated axon (from Harris et al., 2022, with permission).

rather than referring to a psychological concept with unclear ontological connection to brains. This replacement gives a precise definition that can be experimentally tested. Neuroscience should explore all possible conditions with no conceptual restrictions (see later). When we abandon the analogies, neuroscientists would be forced to analytically form concepts and hypotheses of brain mechanisms based on experimental results. Lack of concepts explaining collective interactions of neurons at all spatial scales of observation is a real obstacle for neuroscience.

Conceptual frontier 1: Develop concepts strongly rooted in experimental results explaining how neurons (and glia) interact at all scales.

2.2. Brain structure and models

Connectomics produce reconstructions showing the challenging microstructure of cortical networks (Figure 3). The challenge is to extract the functionally most relevant connectivity to build models of CNS activities. An alternative is to simulate the whole connectome. Currently insect (*Drosophila*) and mammalian connectomes available are partial connectomes showing synaptic connections of only a part of the CNS (Scheffer et al., 2020). So, in practice, simulations still evolve in a local network (for example Markram et al., 2016; Schmidt et al., 2018). Apart from the trouble of building the model, the model must also be validated against experimental results, which would be quite an undertaking.

So far CNS models have no lasting eigen activity. There are some relatively detailed models of cerebral cortex (Izhikevich and Edelmann, 2008; Kumar et al., 2008; Eliasmith et al., 2012; Markram et al., 2016; Schmidt et al., 2018). These models are started by injecting noise, stimuli, or Poisson spike trains. However, when the afferent stimulation ceases, the spiking activity dies out. Mammalian brains, and most likely also insect and zebrafish CNS, have eigen activity as ever-changing ongoing spiking and membrane currents no matter whether they are stimulated or not, awake or at sleep (Rudolph et al., 2007; Yap et al., 2017; Stringer et al., 2019; Davis et al., 2020; Marques et al., 2020; McCormick et al., 2020; Siegle et al., 2021; Willumsen et al., 2022).

Conceptual frontier 2: Build a brain model with modifiable, but everlasting ongoing changes of membrane potentials and spiking like that in mammalian brains.

2.3. Functions and CNS activities

Except in mathematics, the word function assumes activity to fulfill a purpose or obtain a goal. Following the line of thinking in the lack of concepts section, one ought to be careful reading purposes or psychology into CNS activities (Buzsaki, 2020). A more neutral description is CNS activities. CNS activities can be measured directly as changes of trans-membrane currents (which includes action potentials), transmitter release and binding, receptor induced biochemical changes, synthesis of brain specific proteins and other compounds, activity of transmembrane pumps and transporters. CNS activities can be measured indirectly as field potentials, changes in magnetic fields (see technical obstacles). What people and animals experience, think, memorize, and how they behave, as a general hypothesis, are consequences of CNS activities at many scales. Arriving at a full description transcending all scales of observation it the task of neuroscience. This task meets further obstacles.

2.3.1. Are CNS activities carried out by separate loops, circuits, modules, or one large network?

The ideas that chains of neurons (sometimes organized in cortical-subcortical loops), micro-circuits, and modular organized cortical columns are responsible for brain activities have been criticized. The reasons were unrealistic simplifications of the actual synaptic connectivity neglecting actual dendritic and axonal anatomy (Figures 3, 4). These ideas also neglect divergence of connections to other structures than the members of the loops, micro-circuits, or columns (Alito and Usrey, 2005; Rockland, 2010, 2021; Foster et al., 2021; Shepherd and Yamawaki, 2021).

Studies of cortical neurons operating *in vivo* show widely spreading depolarizations, excitations, and spiking. These results leave no support for activity restricted to a circumscribable location, to a specialized microcircuit or to columns (see following sections). Rather the spreading mechanisms may relate to the actual neuron anatomy with interdigitating multiple dendritic and axonal branches (Figures 3, 4). In a CNS perspective, large populations of neurons spike in many areas of cortex, sectors of basal ganglia, thalamus, other parts of the diencephalon, brain stem nuclei, cerebellum, and spinal cord, even during simpler tasks (Steinmetz et al., 2019; Wagner et al., 2019; Li and Mrsic-Flogel, 2020; Peters et al., 2021; Grün et al., 2022). Moreover, diencephalic and mesencephalic nuclei contribute significantly to choices and specific behaviors, showing that brain activities are results of interacting brain stem, cerebellar, basal ganglia, thalamic, and cortical networks (Figure 5).

Conceptual frontier 3: Rather the crucial issue is whether the whole CNS is active, and if not, which (biophysical) mechanisms determine how far depolarizations and spiking spread in CNS?

2.4. Single neuron activities

2.4.1. Action potentials are for interaction: the bulk of processing in neurons take place in the dendrites

As axons only conduct action potentials, the post-synaptic current transformations, processing, and plasticity in a neuron takes place in its dendrites (and in soma constituting the smaller part). Processing of synaptic excitatory post-synaptic potentials (EPSPs) in dendrites is complex (Figure 6). Roughly, excitatory transmitters elicit a localized EPSP in the post-synaptic spine, spreading only sparsely into the local dendrite. However, synaptic EPSPs, close in space and time, may open Ca^{2+} channels and NMDA channels in the dendrites to produce Ca^{2+} spikes or Ca^{2+}

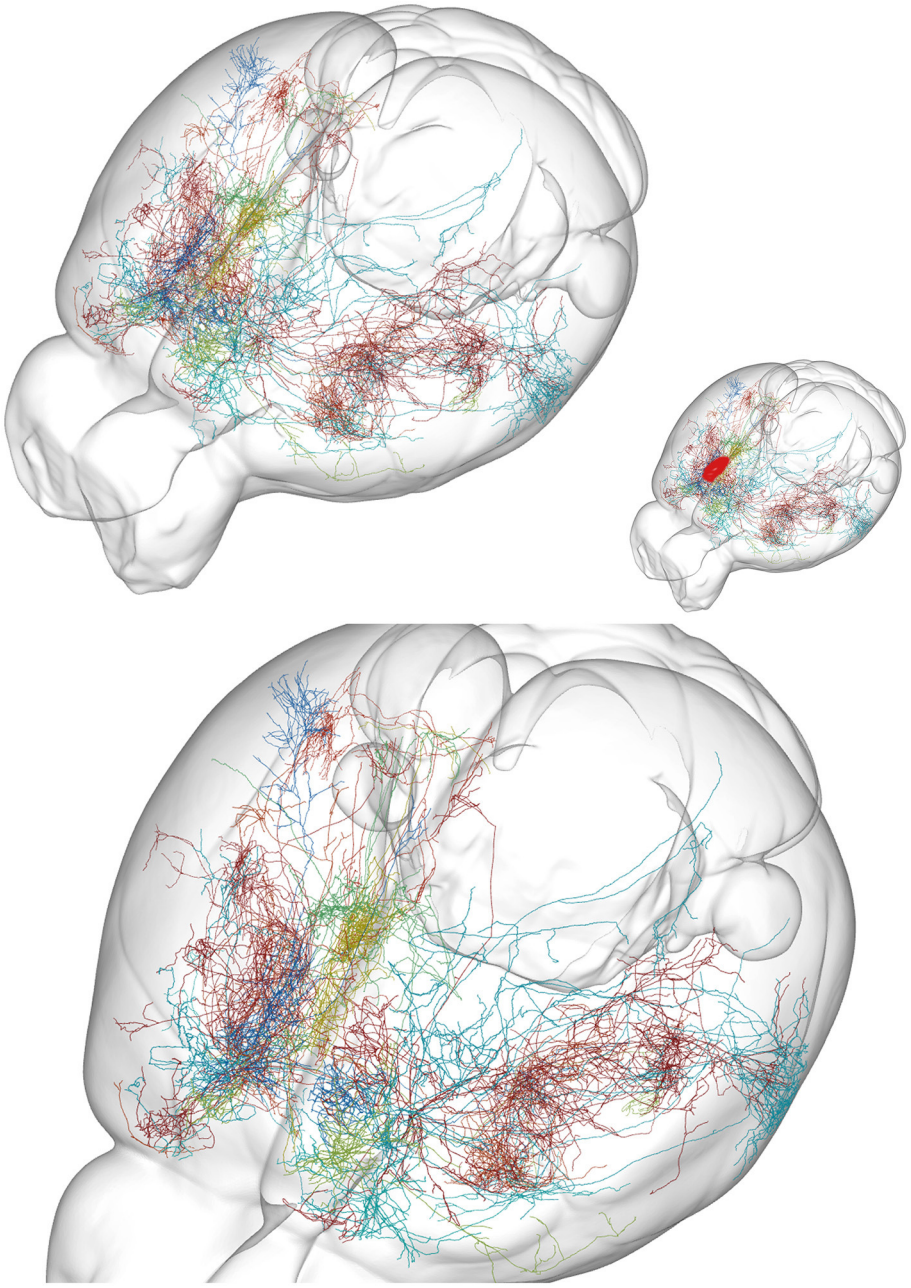

FIGURE 4
Examples of axon anatomy. Ten axons targeting prelimbic area in the mouse. The prelimbic area is small, located at the rostral and mesial surface of the frontal lobe (approximate location red in insert). **(Top)** Overview of the mouse brain. **(Bottom)** Close view. Each axon targeting the area branches at successive positions to produce an exponentially increasing number of axonal branches. An axon can have 1,000 branches (Wu et al., 2014). A single action potential (AP) in the initial part of such an axon then at each branch point give rise to two APs, one traveling in each branch. With no failures (Alcami and El Hady, 2019) this gives around 500 action potentials traveling in the roughly 500 terminal branches. Although several branches of one axon target the prelimbic area, many of its branches also end in several other cortical areas. From the MouseLight database, http://mlneuronbrowser.janelia.org. Axons belong to the following single neurons in series AA: 0138, 0241, 0344, 0397, 0402, 0802, 0842, 0883, 0897, and 1425. Four axons originate from motor cortex layer 2/3, two from motor cortex layer 5, one from adjacent anterior cingulate cortex, one from visual association area AM, one from ventral anterior nucleus of thalamus, and one from the intralaminar rhomboid nucleus of thalamus. The finest axonal branches (Figure 3) are not visible with this method.

plateau potentials and NMDA spikes or NMDA plateau potentials. These spikes and plateau potentials can propagate locally in one or a few adjacent dendrites without propagating to the soma and generate action potentials (Larkum et al., 2022; Moore et al., 2022; Stuyt et al., 2022). Depending on the spatial interactions, the plateau potentials or larger spikes can also propagate to the soma and elicit an action potential (Otor et al., 2022).

Another scenario is that synaptic EPSPs close in space and time to distal dendrites may produce Ca^{2+} plateau potentials or NMDA spikes in many or all apical dendrites. Alternatively, this

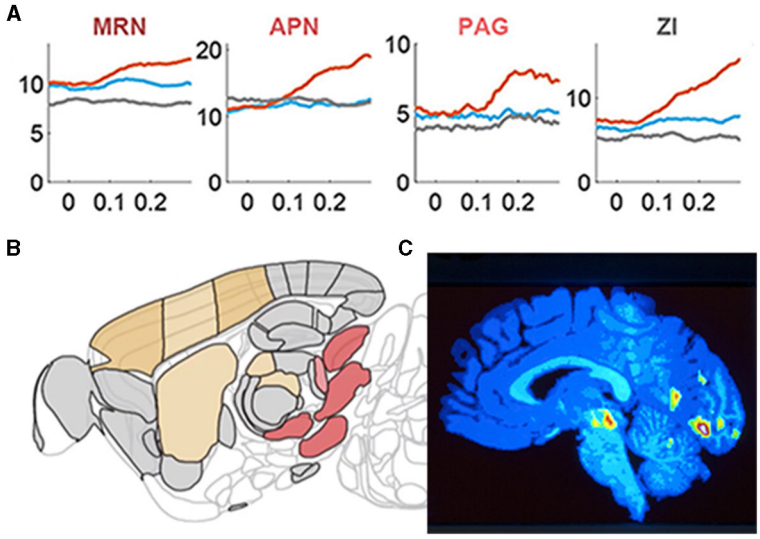

FIGURE 5
Brain stem nuclei participate in cognitive tasks. **(A)** *Y*-axis: population mean firing rates in task go trials (orange), task missed trials (blue), and passive sensory stimulation (gray). *X*-axis time 0 s stimulus onset/ target onset that the mice must bring into the center of the field of view. Note the different pre-stimulus rates in the midbrain reticular nucleus (MRN) and the zona incerta (ZI) and how these nuclei and the anterior pretectal nucleus (APN) and peri-aqueductal gray matter (PAG) become engaged in the action selection. **(B)** Sagittal section of the mouse brain showing these nuclei (red-brown) in the right brain stem specifically engaged in the right motor response (action selection; adapted from Steinmetz et al., 2019) with permission. **(C)** Sagittal section of the human brain showing the right side of the brain stem when normal subjects with their right thumb or right index finger respond to a faint increase in a visual or somatosensory stimulus, respectively. The color-coded significant increases in regional cerebral blood flow are located in the right midbrain reticular nucleus (and in the visual cortex; adapted from Kinomura et al., 1996) with permission.

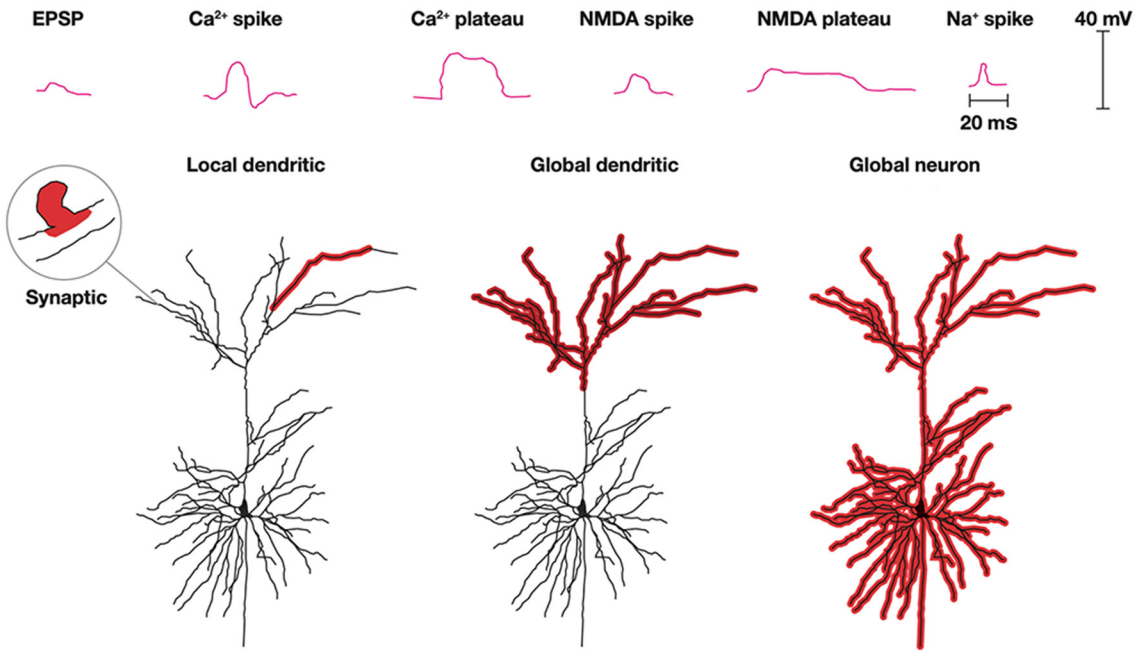

FIGURE 6
Dendritic processing. Post-synaptic processing can be an EPSP localized to a single synapse and a small part adjacent dendrite. Na^{+}, NMDA, and Ca^{2+} spikes and NMDA, and Ca^{2+} plateau potentials with limited progress depolarize one or a few dendrites. Multiple spikes and plateau potentials with larger spatial progress depolarize all apical (shown) or all basal dendrites (not shown) or globally excite all dendrites and the soma (Modified from Stuyt et al., 2022) with permission.

can happen in basal dendrites. Neither of these processes may lead to any action potentials, but nevertheless induce or restore plasticity in the active dendrites (d'Aquin et al., 2022). Similarly, apical or basal dendrites, at least in pyramidal excitatory neurons, may stay globally depolarized for up to a few seconds without this leading to a spike (Larkum et al., 2022; Stuyt et al., 2022). In addition to

the Ca^{2+} and NMDA spikes, dendrites can also produce smaller Na^{+} spikes (spikelets) locally in the dendrites without this leading to action potentials (Goetz et al., 2021).

Propagation of dendritic spikes and plateau potentials to the soma often induce action potentials (Larkum et al., 2022; Moore et al., 2022; Stuyt et al., 2022). The combination of apical-somatic plateau potentials and action potentials may elicit a back-propagating action potential to many or all apical or basal dendrites. This is a mechanism that is also likely to induce or modify the plasticity of the dendrites.

The single (pyramidal) neuron can support several processes in parallel with or without spiking. Consequently, an action potential could be the result of many different dendritic processes.

> *Conceptual frontier 4: Understand the local and global in vivo processing in dendrites of single neurons and their consequences for emission or withholding action potentials. This also addresses the question of which processing leads to the spike emitted.*

With rare exceptions (Mel, 1993; Jones and Kording, 2022) dendritic processing is an important fact that is neglected in models of CNS networks (Shepherd and Grillner, 2018).

2.5. Larger scale network activities

2.5.1. Spontaneous and task-related activity

During an experimental task, e.g., 40% of the neurons in the brain and mesencephalon may increase their spiking, and up to 20% of neurons decrease their spiking, whereas the remaining 40% of the neurons do not change their ongoing spiking (Steinmetz et al., 2019; Siegle et al., 2021). However, a large proportion of neurons (up to 40% of all neurons) may not spike at all (Shoham et al., 2006; Barth and Poulet, 2012; Wohrer et al., 2013). These non-spiking neurons could also participate in the task, for example by depolarizing or hyperpolarizing their dendrites (Roland et al., 2006, 2017; Mohajerani et al., 2010; Esteves et al., 2021; Liang et al., 2021). In the future, it might be possible to estimate the proportion of neurons participating in a task in mammals by changing their transmembrane currents (see technical obstacles). For spiking, the above results might be illustrative. Thus, there are task related activities, but most studies report many spiking neurons seemingly unrelated to tasks (Urai et al., 2022). In the literature this is often called spontaneous activity.

The usual distinction is between task related activity and "spontaneous ongoing activity,' i.e., CNS activities that may co-exist, but are unrelated to task and task behavior. This distinction must be made for any of the activity variables measured (spiking, synaptic, postsynaptic activity variables as defined in section 3). In practice the distinction is often set by sorting the neurons in two groups. One group for which changes in measured variables correlate with parameters of the task. The other group for which this is not so. This strategy may overlook neurons which are necessary for solving the tasks but unrelated to the stimulation and behavioral parameters (see later). The spontaneous activity may be seemingly random fluctuations of the measured variables in space and time. For example, the continuous local spatial and temporal irregular changes from slight excitation to slight inhibition prior to the stimulation as in Supplementary Video 1. This CNS activity is easy to distinguish from task CNS activity. However, during the experiment there may be neurons supporting intrinsic (cognitive) CNS activities un-related to the task (Figure 7). Separating task related activity from such "spontaneous" or more precisely self-organized intrinsic cognitive activity is difficult and may only be possible under assumptions. For example, two tasks depending on activities engaging the same part of the CNS network interfere and cannot be performed simultaneously (Herath et al., 2001) (Figure 7).

> *Conceptual frontier 5: Separate self-organized intrinsic activity in CNS from task dependent activity.*

This may require examination of the whole CNS (Figure 5). Larger scale CNS activities may also be classified according to their causes. The questions raised in this section are all related to how brains and a central nervous systems self-organize their activities.

2.5.2. Are brains driven or autonomous?

Until recently, neuroscience has been mainly oriented to explain how changes in the surrounds and behavioral conditions change transmembrane currents (including action potentials) and synaptic efficacy in brain neurons. Recently, there is accumulating evidence contesting this view that spiking and post-synaptic dynamics in brains are predominantly externally driven (Figure 7) (Millner, 1999; Fried et al., 2011; Buzsaki, 2019; Steinmetz et al., 2019; Cowley et al., 2020; Marques et al., 2020; Clancy and Mrsic-Flogel, 2021; Grün et al., 2022). The alternative is self-organized intrinsic activities. *Intrinsic* activity is independent of external stimuli, internal stimuli, demands and tasks, which also distinguish it from CNS activities related to bodily internal functions such as thirst, hunger, and sexual desire.

Brains are not in direct contact with the surroundings. Strictly, all spikes generated in a central nervous system are intrinsically generated. Brains can self-organize their everchanging intrinsic activity to generate slow waves, spindles, sharp wave ripples, faster irregular membrane fluctuations, dreams, and, in awake conditions, thoughts, plans, strategies, overt behavior, and (some brains) language (Figure 7). Even in primary visual and auditory cortical areas, only 5%–15% of the spikes carry information about the surround (Richmond and Optican, 1990; Heller et al., 1995; Olshausen and Field, 2006; Keyser et al., 2010; Urai et al., 2022). Similarly, the correlation of spike trains with external visual stimuli is low, typically around 0.1 in the primary visual cortex (Eriksson et al., 2010). These results are well known and indicate that 85%–95% of the spikes in a brain are autonomous. A recent large-scale study showed that external stimuli and various experimental conditions could modify fluctuations in the (multidimensional) human cortical field potential, but not perturb the underlying dynamics generating the fluctuations (Willumsen et al., 2022).

> *Conceptual frontier 6: describe and classify CNS activities by how they engage the CNS network by changing CNS activities*

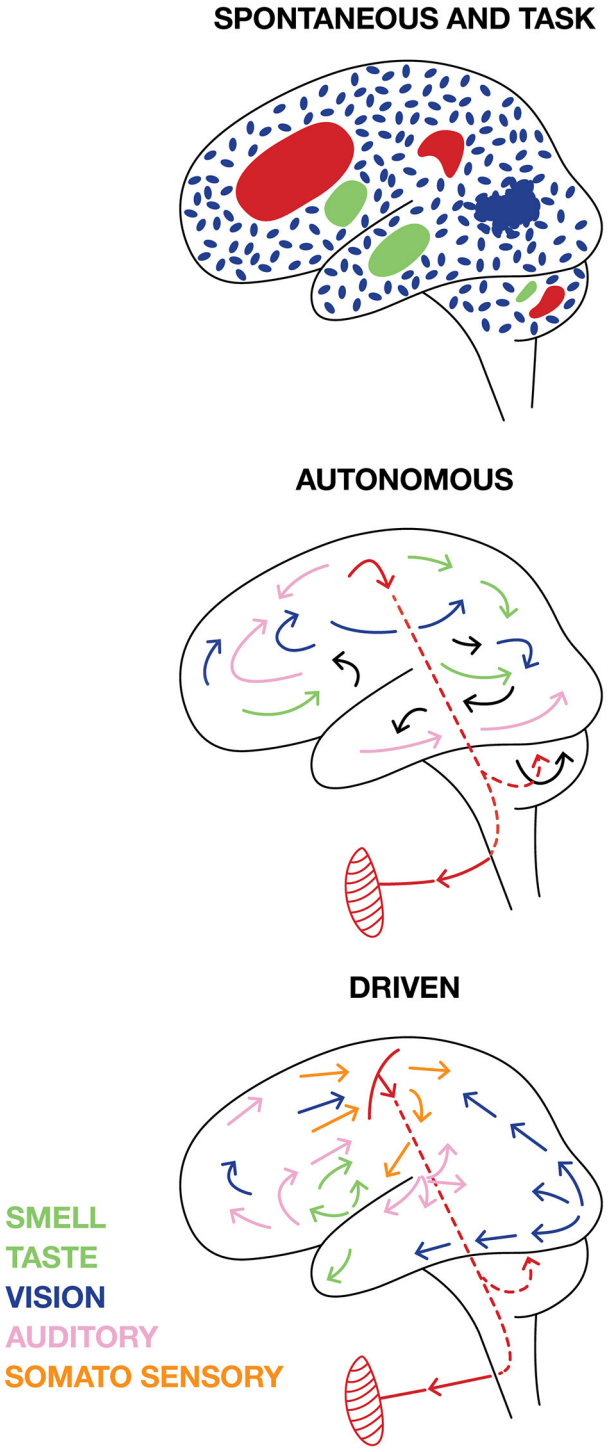

FIGURE 7
Cartoon illustrating different views on brain activities. SPONTANEOUS activities are independent of external signals and TASK activities. Spontaneous brain activity can be (blue) fluctuating irregular "background" activity spatially independent at scales < 1 mm^3 when the brain is awake, but idle and not producing any motor activity. In other parts of the brain, INTRINSIC cognitive activities (green) not leading to any behavior engaging the network in several parts from the microscopic to macroscopic scales may co-exist with the TASK activity (red). AUTONOMOUS. The brain could be autonomous with self-organized intrinsic activities engaging the network at all scales that external stimuli and demands cannot change, but only slightly modify. The autonomous brain self-organizes motor behavior (symbolically pictured as a muscle). *(Continued)*

FIGURE 7 (Continued)
DRIVEN. Task related activity and external sensory stimuli and internal stimuli from the body drive brains away from spontaneous activity into sensory and cognitive activities at all scales, which eventually result in some motor behavior.

(defined in section 3). (Referring to sensory input, behavior, and psychological concepts may have limited explanatory power).

On the other hand, in awake conditions, focused attention and exclusion or suppression of own (intrinsic) activities can entrain field potentials partly or globally over the cerebral cortex. For example, in humans and other primates exposed to rhythmic visual or auditory stimuli, each stimulus produces a single time-locked oscillation. These time-locked oscillations can spread, with different lags, to cover the whole cortex (Besle et al., 2011; Gomez-Ramirez et al., 2011; Spaak et al., 2014; Merchant and Averbeck, 2017; Willumsen et al., 2022). Also, unexpected stimuli may elicit spreading excitation and spiking globally over cortical areas (Ferezou et al., 2007; Salkoff et al., 2020). Thus, under such circumstances, cortical networks are largely externally driven.

Most likely, brains have a certain degree of autonomy. In addition, brains regulate their sensitivity to external sensory impact. Autonomy may be distributed over different CNS structures and be differentially regulated in each structure. Even respiratory inspiration can be voluntarily modulated. Similarly, in subjects planning a motor effort, the motor system can increase the heart rate and blood pressure in advance of the motor action (Pfurtscheller et al., 2013).

Conceptual frontier 7: Measure regulation of CNS autonomy.

2.5.3. How does intrinsic activity in brains emerge?

Conceptual frontier 8: Find principles for how intrinsic activity in brains emerge.

Drosophila and zebrafish larvae possess neurons (P1 neurons and dorsal raphe neurons, respectively) which by increased spiking mobilize several structures to produce complex behavior lasting minutes. The number of neurons triggering these behaviors is less than 100 (Jung et al., 2020; Marques et al., 2020). Details of how the trigger neurons recruit a large part of the CNS are still lacking. The changes in spiking and recruitment of many populations of neurons are examples of an intrinsically organized activity spreading to large parts of a CNS.

From mammals, there are examples of how the spiking of one or very few neurons can change the behavior and performance of an animal (Romo et al., 1998; Houweling and Brecht, 2008). However, in these examples, the animals were engaged in a task; therefore, they do not qualify as intrinsic activity (see also the text later). But the fundamental questions are still pending. For example, how many neurons are required to generate intrinsic dynamics? How many neurons are required to generate intrinsic dynamics leading to overt behavior? Dreaming is yet another example

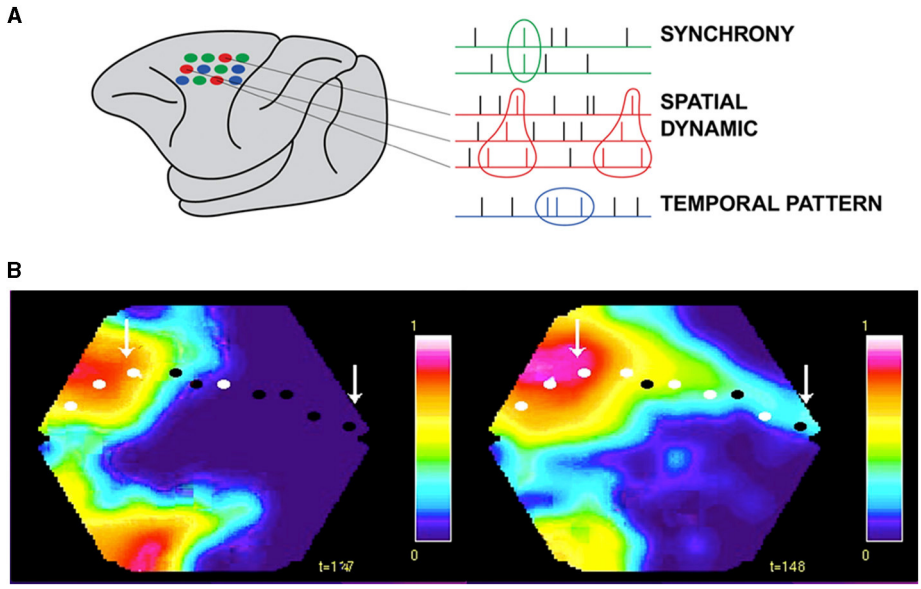

FIGURE 8
Spatial dynamics of spiking. **(A)** Small groups of individual neurons spike in the same spatial order in single trials from the macaque pre-motor and motor cortex (in contrast to synchrony and temporal patterns, Grün et al., 2022). **(B)** Excitatory sweeps elicited by spiking exciting the dendrites post-synaptically in a spatial order. Left: Excitatory sweep, 122 ms after the appearance of an object moving in the field of view, in areas 19/21 and feedback to areas 17/18. Right: Significant spiking in areas 17/18, mostly in layers 3 and 5, shown by the white spots and excitatory sweep here at 148 ms, ahead of the retinotopical mapping of the moving object (arrow to bright red). The spiking estimating where the object will be mapped in the future (right arrow) and hence where its position in the field of view will be. See the full spatial dynamics in Supplementary Video 2 (isoflurane anesthetized ferret, Harvey et al., 2009).

of intrinsic brain activity. How dreams start is unknown, i.e., how changes in spiking and transmembrane currents organize to produce dreams.

Conceptual frontier 9: Reveal how changes in crucial variables (membrane potentials, transmembrane currents, and spiking) evolve to encompass larger populations of neurons in multiple structures of the CNS.

2.6. Is time an independent variable for CNS operations?

An independent variable is a variable that does not depend on other variables. Time is invented by humans. Time is composed of equal units that add linearly. Time is an independent variable in Newtonian physics, but in the theory of relativity and quantum mechanics, time is not an independent variable (Rovelli, 2018). Time in neuroscience is usually regarded as an independent variable for fundamental brain processes. As external observers, scientists can timestamp every spike. Similarly, one can create mathematical functions of other measured fundamental (dependent) variables, potentials, transmembrane currents, transmitter releases, and plasticity variables using time as the exclusive independent variable. From a scientific point of view, the question is whether time is the only independent variable for operations in neurons and for CNS processes.

Conceptual frontier 10: Examine if time is an independent variable for any activity of neurons and brains.

2.6.1. Experimental results incompatible with time as independent variable in brain activities

Spike trains have traditionally been analyzed with time as the independent variable. This could be a list of the times spikes are emitted from neurons according to an external (computer) clock or transforming the spike train to a continuous rate function of time. However, claiming that all activities in brains all evolve according to external clock time only (i.e., with time as the independent variable) is a strong hypothesis that can be proven wrong. Regarding spike trains as temporal codes carrying information to be decoded by the brain is assuming that this type of brain activity depends on time as the independent variable (Figure 2). Decades have been spent to find temporal patterns carrying the code (Barlow, 1961; Bialeck et al., 1997; Rao and Ballard, 1999; Dayan and Abbott, 2001; Bassett et al., 2020). Also simultaneously recorded neurons have been analyzed for synchrony (Gray and Singer, 1989; Abeles, 1991; Singer et al., 2019).

Working in the premotor and motor cortex of the monkey, Sonja Grün and associates, using rigorous statistics, observed that the same set of neurons in every single trial fired in the same spatial order while the monkey reached out and grasped an object (Grün, 2021; Grün et al., 2022). Subsets of 2–6 neurons elicited from 2 to 6 spikes always in the same spatial order (Figure 8A). These spatial sequences were specific to the components of the reaching task, i.e., related to the cue, delay, preparation, reaching, and grasping (Grün, 2021; Grün et al., 2022). These results show spatial dynamics at the microscopic and single neuron scale. These results cannot be explained as a brain activity using clock time as the independent variable. In contrast, they demonstrate that the timing and order of

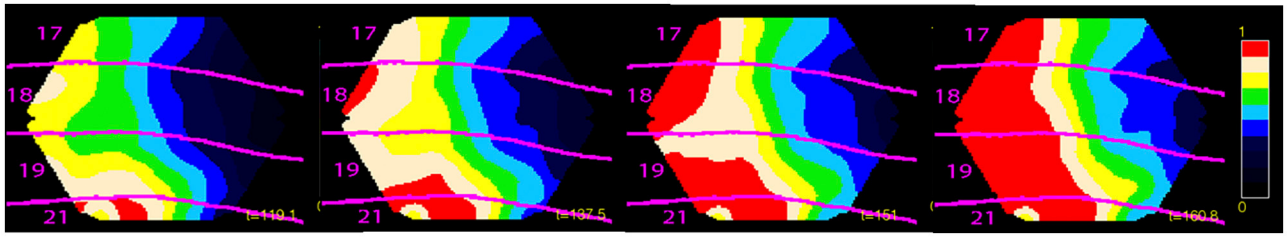

FIGURE 9
Moving visual object and phase alignment. Object moving downwards from time 0 ms. Phase plot of depolarisation in areas 17, 18, 19, and 21 from six ferrets aligned by their cytoarchitectural borders. Note the leading depolarization in areas 19 and 21 at 119 ms **(left)**. Feedback 137 ms and phase alignment canceling the delays between areas 160.8 ms **(right)** (Harvey et al., 2009).

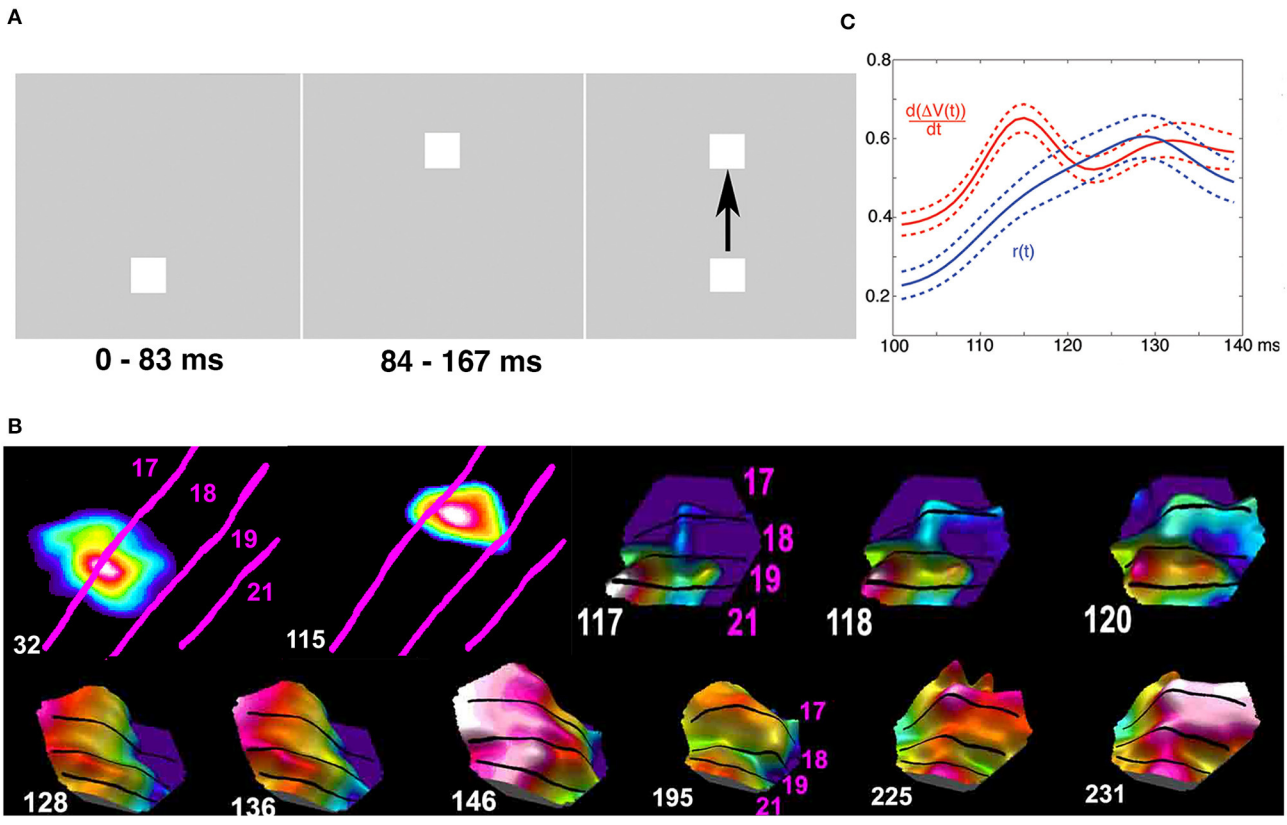

FIGURE 10
Cortical operations at the mesoscopic scale incompatible with time as an independent variable (apparent motion). Spatial dynamics underlying apparent motion illusion. **(A)** At time 0 ms, the lower object appears. Spiking (not shown) and **(B)** excitation increases map the lower object retinotopically at area 17/18 border at 32 ms. At 83 ms, the upper object appears, and the lower object disappears. The upper object gets mapped at 115 ms retinotopically at a different spatial location along the 17/18 border. At 117 ms, the spiking induces a directed excitation along the 19/21 border (like that for moving objects in Figure 8B) and a feedback excitation to the 17/18 border in between the mapping of the now-extinct lower object and the new upper object. **(C)** At 118 ms, this elicits a directional excitation $d[\Delta V(t)]/dt$ and spiking $r(t)$ at the 17/18 border progressing 120 ms to 160 ms in between the former object mapping site and the new (top right). **(B)** The feedbacks then quench the delays between areas, and the cortical excitation proceeds in phase from 146 ms over the 4 areas. The processing in the cortex smoothed space and time and converted two external spatial and temporal distinct objects to one moving object **(A)** (top; modified from Ahmed et al., 2008, licensed under CC BY-NC 2.0).

the spikes depend on the spatial positions of the collaborating single neurons.

Another example violating time as the independent variable in brain processing is when the retinotopic mapping of a moving object co-exists with the mapping of the prediction of its future external position in the visual areas (Figure 8B and Supplementary Video 2).

If an external object moves in the field of view, it is mapped, with different delays, in each retinotopically organized visual area (Supplementary Video 3). So, initially, multiple versions, separated in space and time in the brain, exists of one and the same object. However, higher visual areas convey excitatory feed-back sweeps to lower visual areas aligning the excitation phase between the areas. This cancels their initial separation in brain time and produce

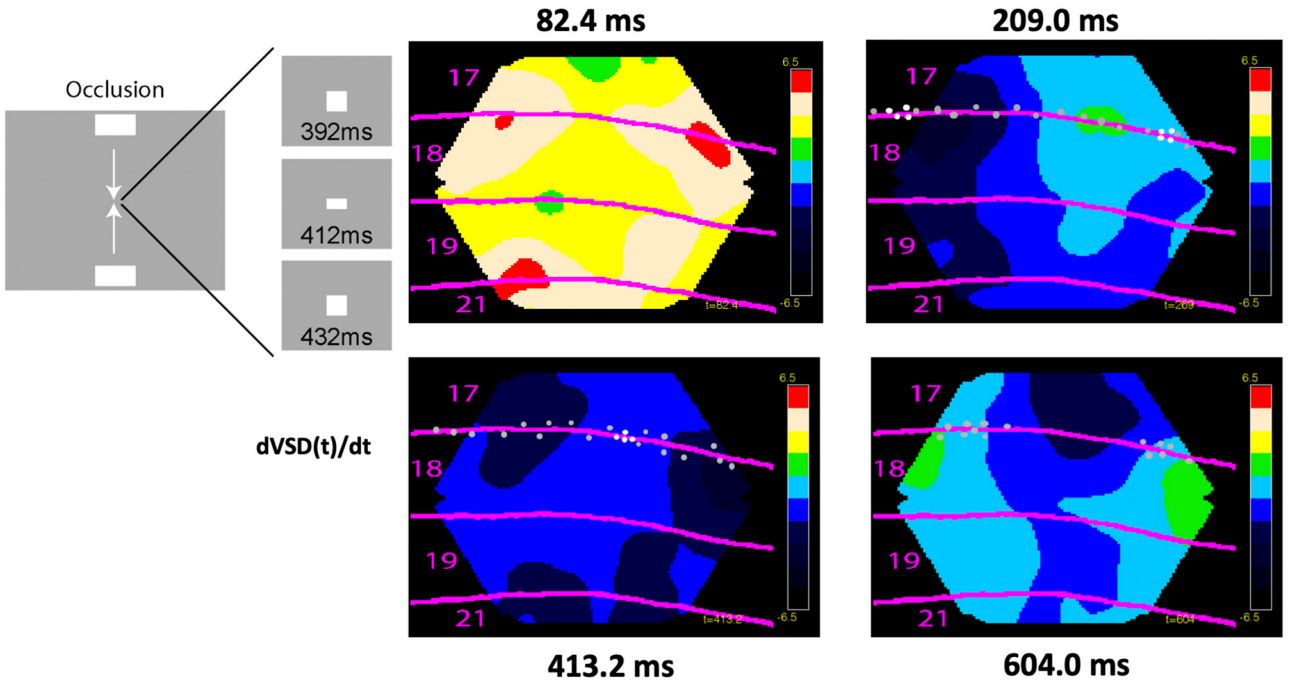

FIGURE 11
Cortical spiking, excitation, and inhibition at the mesoscopic scale incompatible with time as an independent variable. Excitation, inhibition, and spiking in ferrets exposed to two bars moving to occlude one another in the center of the field of view at 412 ms. Dots show significant spiking and white dots maximal spiking rates, otherwise conventions as in Figure 10. Notice the predictive excitations of the future retinotopic mappings of the objects in areas 17/18 and 19/21 at 82 ms, the maximal spiking at the cortex representing the center of the field of view at 413 ms in an inhibitory regimen of cortical layers 1–3 (data from Harvey and Roland, 2013).

unified motion of the object in retinotopical visual areas. This is likely to contribute the experience to perceive only one object moving in the field of view (Figure 9).

Brains do not always process stationary objects that are separate in time and space as stationary in time and space (Figure 10A). When first a stationary object appears at one position in the field of view, this is mapped in its retinotopical position in visual areas as explained above. If the first object then disappears and a second stationary object is flashed at another position in the field of view, the second object is mapped (correctly) in its different retinotopical position in the first visual area (Figure 10B). However, the mapping of the second object in higher visual areas elicits spatial-temporal excitatory dynamics smoothing the mapping of the previous object with the present object in brain space (Figure 10B). After this fusion to one object, its dynamics in space and time in the brain is identical to that of a moving object. This elicits the illusion that the first object moved to the new position (Figure 10). Thus, external objects stationary and separate in space and time by brain processing become united to one moving object (apparent motion).

In vision, there is a delay between the appearance of an object until the spiking increases in the first visual area: the retino-cortical delay (Supplementary Video 1). Figure 11 shows how excitatory, inhibitory, and spiking mechanisms in space and time in the brain can quench the perceptual delay by maximizing spiking in the cortex when two oppositely moving objects occlude one-another in the field of view. In the examples shown in Figures 8–11, the ferrets were anesthetized (isoflurane) showing that these brain dynamics were automatic.

These examples demonstrate that all brain activities cannot be explained as evolving with clock time as the independent variable. The examples also illustrate that spiking at the microscopic scale and postsynaptic depolarizations, excitations and inhibitions at the mesoscopic scale evolve with time and space as mutually dependent. The idea of time as an independent variable for brain processes has been criticized from different theoretical points of views (Buzsáki and Tingley, 2018; Gao, 2020; Le Bihan, 2020). For example, interpreting both the meaning of brain responses as measured against the clock in the computer and the meaning of the clock units-might be a fundamental confound in current experimental approach (Buzsáki and Tingley, 2018). Unnecessary assumptions conceptually restrict neuroscience from developing further.

2.6.2. Stationarity

It is often assumed, or claimed, that brain variables end up in some form of stationarity. If this happens, the variable has the same probability distribution over time, i.e., mean, variance, and autocorrelation are invariant over time. If time is not an independent variable for brain processes, the stationarity concept loses its importance in neuroscience. Although stationarities are convenient and simplify mathematics and statistics, are they necessary for understanding brain activities? One may ask then, if the concept of stationarity as defined is invalid for brains, how do brains determine whether external objects are stationary? For vision, Supplementary Video 4 might give a clue. Some 90 ms

after the appearance of a stationary object, the spiking, despite continuously changing rates, is confined to the retinotopic map of the object in the primary and secondary visual areas (see also Lamme, 1995). This cannot be explained by statistical and dynamical systems definitions (e.g., fixed point) of stationarity. This is another kind of stationarity, an example of a brain spatial stationarity.

2.6.3. Dynamical systems theory explaining brain activities

A dynamical system is composed of a state space and rules describing the *evolution of the system over time* in this state space. Treating central nervous systems as complex dynamical systems as complex dynamical systems has had some success explaining collective operations of neurons. *In vivo* studies of different spiking networks in the cerebral cortex but also spinal, hypothalamic, and thalamo-cortical networks show the collective spiking dynamics of the network neurons progress as trajectories along low-dimensional, stable manifolds in state space (Churchland et al., 2010; Gallego et al., 2017; Lindén et al., 2022). On the post-synaptic side, field potential, MEG, and EEG studies show state space dynamics like that of strange (chaotic) higher dimensional attractors (Babloyantz and Destexhe, 1986; Stam, 1996; Baria et al., 2017; Willumsen et al., 2022). This dynamic may be identical for all local networks in the human cerebral cortex. However, since the trajectories expand and contract, the dynamic is incompatible with the mathematical definition of attractors (Strogatz, 2018; Willumsen et al., 2022).

Importantly, to be a truly higher dimensional (chaotic) dynamical complex system, the CNS must show sensitivity to initial conditions (Strogatz, 2018). This means that one must determine the initial conditions for a CNS. This requires that for "one point in time," say within a fraction of a ms, we must know how many variables there are at each point of each neuron (say a point is a membrane surface of 0.1 μm^2) and which order they have (e.g., higher derivatives of the variables as a result of spatial interaction; Figure 6). We must know exactly where and in which axon or axonal branches action potentials are and know the conduction velocities of each branch (Figure 4). Moreover, as we cannot be sure whether a neuron only has spontaneous ongoing unorganized activity or participates in intrinsic or task-related organized activity, we must know the values of all these variables for all neurons of the CNS within this ms. To define an initial condition in a CNS having ever-ongoing changes of its variables at all spatial scales seems impossible.

Dynamical systems analysis gives the temporal evolution of the collected neurons or local network and neglects spatial interactions. However, one can preserve the locations of the neurons in the data and instead observe the spatial evolution as trajectories in state space (neglecting the temporal evolution) (Roland et al., 2017). Both these approaches thus have limitations. As shown here, dynamical systems theory might not always fit brain activities. The examples in section 2.6.1 show that one can directly observe and measure spatial temporal interactions in the cerebral cortex, instead of analysing temporal and spatial trajectories in abstract state space.

2.7. Spatial dynamics, a general hypothesis

The fundamental mechanism of interaction in CNS of most species is spatiotemporal: each neuron sends action potentials through all axon branches to its two–three orders of magnitude more numerous target neurons (Figure 4). This fundamental mechanism creates spatial dynamics in the network of neurons. Postsynaptically, the spatial progress of currents in the dendrites determine plasticity and spike production (Figure 6, section 4.1). Spatial dynamics is a general hypothesis that can be tested experimentally. The hypothesis states that changes in activity variables (section 3) propagate through the network of neurons that makes up a central nervous system. These propagations reveal spatial and temporal interactions underlying CNS activities at different scales (Roland, 2017; Grün et al., 2022). The forces driving the spatio-temporal interactions thus are transmembrane currents, receptor driven, and biochemical. The word dynamics refer to these biophysical and biochemical forces driving the interactions. Thus, spatial dynamics is not related to dynamical systems theories and do not carry any further assumptions about brain activity variables and their interactions.

2.7.1. Spatial dynamics at different scales of observation

Spatial dynamics is not a new idea. Tasaki et al. (1968) used a voltage sensitive dye to follow the course of an action potential. Spatial dynamics has been slowly progressing since then but boosted by recent techniques permitting simultaneous measurements of CNS activity variables in large parts or a whole CNS (see technical obstacles). Figures 8–11 and Supplementary Videos 1–4 are concrete examples of spatial dynamics of spiking and postsynaptic changes in excitation and inhibition leading to visual object perception and the apparent motion illusion. Spatial dynamics of spiking and postsynaptic activities operate in single neurons (Figures 6, 8A) small groups of neurons (Figures 8B, 11), and larger populations of neurons (Figures 8B–12). Spatial derivatives are needed to distinguish different forms of postsynaptic processing at the network scale (Supplementary Videos 1, 5). Spatial dynamics of the activity variables progress though the low-dimensional geometry of a CNS and are therefore wellsuited to reveal mechanisms of neuron interactions at the population (mesoscopic) scale. Its challenge is to find principles to form theories of interactions between multiple neurons.

> *Conceptual frontier 10: Use spatial dynamics to find principles of interactions of neurons at all scales of observation.*

2.7.2. Cortical spatial dynamics

Spatial dynamics in the cerebral cortex relate directly to detection, prediction, perception, illusions, retrieval, and consolidation of memories in rodents, carnivores, and primates (Grün et al., 2022) (Figures 8–12). Here it is not the purpose to review spatial dynamics, only to give some concrete examples.

Postsynaptic excitations propagating over dendritic fields may have many shapes and speeds (Supplementary Videos 1–5) (Xu et al., 2007; Mohajerani et al., 2010; Denker et al., 2018; Dickey et al., 2021). Broad postsynaptic net-excitations followed by local net-inhibitions give the impression of a wave propagation though the cortical network. The different forms of (mesoscopic) postsynaptic changes have different roles in brain activities. For example, frequency-modulated sounds elicit a depolarization sweep over the relevant tonalities in the first and secondary auditory areas (Horikawa et al., 1998; Farley and Norena, 2013; Horikawa and Ojima, 2017). Retinal excitatory sweeps induced by a saccade elicit a cortical sweep in V1 matching the direction of motion over the retinal photoreceptors (Slovin et al., 2002).

Waves in different directions appear in mesoscopic recordings of current changes in upper layers of cortex with fast voltage indicators (Prechtl et al., 1997; Senseman, 1999; Roland et al., 2006, 2017; Xu et al., 2007; Mohajerani et al., 2010; Denker et al., 2018; Davis et al., 2020) (Figures 9–11), or in genetically labeled pyramidal excitatory neurons, or as changes in glutamate release (Berger et al., 2007; Song et al., 2018; Abadshi et al., 2020; Zhu et al., 2021). The examples in Figures 8B–11 and Supplementary Videos 1–5 were recordings from isoflurane anesthetized ferrets receiving a visual stimulus. Although the visual stimulus initially drives the cortical neurons after some 28 ms, the cortex does not produce a spatial pattern of the stimulus in each visual area. Rather autonomous cortical spiking and postsynaptic spatial dynamics take over producing lateral spreading excitation, feedback waves and local inhibitions. This dynamics after some 90–120 ms converge to a spatio-temporal "interpretation of the visual surround" in the visual areas. Similarly, the moving visual stimulus initially likely drives the retinotopical depolarization, but autonomus spatial dynamics take over and produce predictive depolarizations and spiking and further spatial dynamics (Supplementary Videos 2, 3).

Conceptual frontier 11: form hypotheses of how different forms of spatial dynamics distinguish different organized CNS activities.

2.7.3. Learning dependent spatial dynamics in awake animals

In animals trained to perform a task, intracellular Ca^{2+} can stay increased for longer periods, while in other areas intracellular Ca^{2+} stays decreased for longer periods. These changes are learning and task dependent (Gilad and Helmchen, 2020; Salkoff et al., 2020; Clancy and Mrsic-Flogel, 2021; Liang et al., 2021) (Figure 12). The optical signals reporting these changes stem mainly from the upper, supragranular, layers of cortex. However, there are several examples of discrepancies between spiking and mesoscopic post-synaptic activity, even in supragranular layers. This could be spiking under inhibitory regimes (Orsolic et al., 2021) (see also Figure 11), or no spiking under excitatory post-synaptic regimes, pre-excitation (Roland, 2010) (Figure 12). These discrepancies are in accordance with the earlier mentioned observations that dendrites may be well depolarized without giving rise to action potentials or apical dendrites inhibited while neurons are spiking (section 3.1).

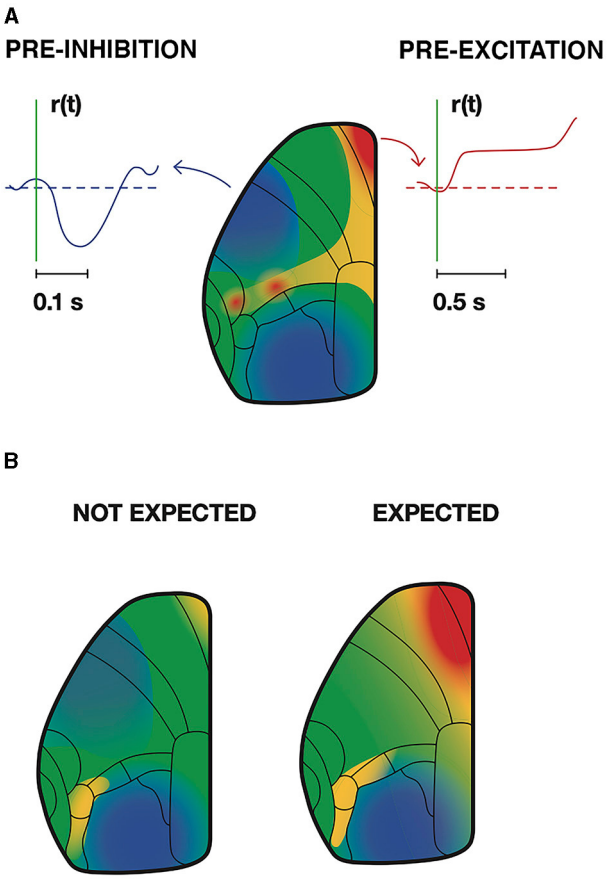

FIGURE 12
Trained mice inhibit and excite relevant cortical areas prior to stimulation and motor response. **(A)** At the time indicated by the vertical green line, a weak whisker stimulus is given. Intracellular Ca^{2+} and spiking rate, *r(t)*, decreased in pyramidal neurons in motor and visual areas, but increased in anterior cingulate and pre-motor cortex. However, the mouse must wait 1,000 ms until a beep tells that it can obtain its reward by licking (redrawn from Esmaeili et al., 2021, licensed under CC-BY 4.0). **(B)** Mice continuously watch a moving grating for a sustained change in speed and respond by licking their reward. At periods when such a change was unlikely, this elicited moderate intracellular Ca^{2+} increases in premotor and motor areas in contrast to when the change was expected. Note the intracellular Ca^{2+} decrease in pyramidal neurons' primary visual cortex and increase in visual association areas in advance of the stimulus change (redrawn from Orsolic et al., 2021, licensed under CC-BY 4.0).

Conceptual frontier 12: Measuring the spatial dynamics in CNS structures and relate this to measures of excitation and inhibitory spatial postsynaptic dynamics in the same structures and vice versa.

Generally, spatial dynamics are causal. In naïve animals weak or moderate stimuli may not give rise to a local excitation and spiking in primary sensory areas. If it does, the excitation and spiking do not progress to other areas and structures. This contrasts with well-trained animals. In trained animals, failure of a trial specific spatial dynamics to progress from the

primary sensory area to other areas and subcortical structures leads to failure to respond (Gilad and Helmchen, 2020; Salkoff et al., 2020; Esmaeili et al., 2021; Orsolic et al., 2021). Thus, spatial dynamics is likely to propagate such that changes in the activity variables propagate from microscopic scales to engage larger parts of a CNS. However, this does not exclude more restricted local forms of spatial dynamics. Details of how spatial interactions evolve in and between subcortical structures are not known (Figure 5).

Conceptual frontier 13: reveal the spatial dynamics of subcortical structures at all spatial scales.

3. Technical obstacles

The lack of techniques to follow the course of action potentials through a CNS is often claimed the reason for the lack of progress in systems neuroscience (Bargmann et al., 2014). Given the premise that many parts of a CNS, the brain stem, thalamus, basal ganglia, cerebellum, and the brain itself do seem to participate even in simpler tasks, global access to a CNS seems a must. The axonal diameters of primate cortico-cortical axons range from 0.2 to 4 μm (Liewald et al., 2014). This gives conduction velocities up to 35 mm ms^{-1} (Waxman and Bennett, 1972). In addition, the relevant sampling space in humans range from synapses 0.5 μm^3 to a human brain hemisphere 700 cm^3, i.e., 14 orders of magnitude. In comparison, Zebrafish larvae with their translucent CNS and 100,000 neurons with slower axonal conduction of action potentials seem an ideal species for studying spatial CNS dynamics.

The physiologically relevant techniques are electro-physiological, magnetic, and optical. Applications of these techniques in multiple recordings simultaneously from CNS are well described in recent reviews (Engel and Steinmetz, 2019; Cardin et al., 2020; Moreaux et al., 2020; Machado et al., 2022; Urai et al., 2022). So here the focus is on limitations that cannot be solved by combinations of electrophysiological and optical techniques.

Modern multi-electrodes can in principle access all parts of the CNS, yielding spiking from 20,000 to 100,000 neurons simultaneously in animals, and humans with sampling frequencies >20 kHz (Jun et al., 2017; Steinmetz et al., 2019; Paulk et al., 2021). Spike recordings do not reveal the type of neurons involved (excitatory glutamatergic, inhibitory GABAergic, and glycine-ergic sub-types). Moreover, extracellular spike recordings are blind to the dendritic contributions.

Optical recordings can capture dendritic contributions in relevant space-time scales, with voltage-sensitive dyes or genetically encoded voltage sensors (GEVI) with sampling rates op to 2 kHz (Roland et al., 2017; Song et al., 2018; Villette et al., 2019; Moreaux et al., 2020). Intracellular Ca^{2+} changes in single dendrites and single synapses can be detected with recent GCaMP reporters, which are able to capture changes currently at 20 ms scale (50 Hz). This captures slow spatial dynamics, but not the fast (Ferezou et al., 2007; Muller et al., 2016; Grün et al., 2022) (Figures 8–12, Supplementary Videos 1–5). The local interdigitation of dendrites from thousands of neurons (Figure 3) implies that post-synaptic transformation by individual neurons cannot be resolved with one-photon, two-photon, or three-photon optical recordings, because it is difficult to match the active dendritic branches with the right neuron. Labeling all dendritic and axonal terminal branches with voltage sensors gives an overcrowded picture in which this problem takes immense dimensions. In addition, it is a challenge to trace action potentials in thin axonal branches and their origin from neurons in other areas (Figures 3, 4).

Technical frontier 1: Reveal the spatial dynamics in axonal branches and of synaptic and dendritic processing and connect this to the appropriate neurons.

Genetically encoded voltage sensors specifically expressed in only one-subclass of neurons make this problem easier to tackle (Abdelfattah et al., 2019; Piatkevich et al., 2019; Villette et al., 2019). In these neurons, one can follow the depolarizations, hyperpolarizations, and progress of action potentials in single trials *in vivo* with 1 kHz sampling rates. It is possible to implant fiber optics and even optical probes providing excitation light and detection of fluorescence along multiple sites on the same probe. However, recordings of dendritic excitation and inhibition dynamics are restricted to the narrow space along the implanted optic probe (Moreaux et al., 2020).

At high resolution, it is possible to selectively examine subclasses of excitatory and inhibitory neurons. However currently, no coherent recordings of a whole insect or mammalian CNS is possible at any spatial scale (Piatkevich et al., 2019; Villette et al., 2019; Cardin et al., 2020; Moreaux et al., 2020; Machado et al., 2022; Urai et al., 2022). Moreover, the genetic incorporation of reporters of membrane current changes, and contributions from neuron subclasses is limited to a few species.

Technical frontier 2: Including primates is so far out of reach for comprehensive spatial dynamic recordings.

It is difficult to envisage a noninvasive technique for primates with physiologically relevant sampling frequency. Perhaps, novel MEG-techniques with quantum field sensors and improved depth resolution may develop into tomographic MEG for primate brains (Bezsudnova et al., 2022).

4. Experimental obstacles

Ordinarily, experiments are performed on a CNS to test a hypothesis. The hypothesis is the prediction of the outcome of the experiment. Sometimes, the hypothesis can be quite general. In most experiments, the experimenter determines and manipulates the independent variables. For example, controlling the surround to minimize confounding factors and specifying the behavioral conditions (see conceptual frontier 5; Figure 13).

4.1. Baseline and control conditions

Animals must be trained to perform tasks. In the example in Figure 12A, deflection of the whisker at an early stage of

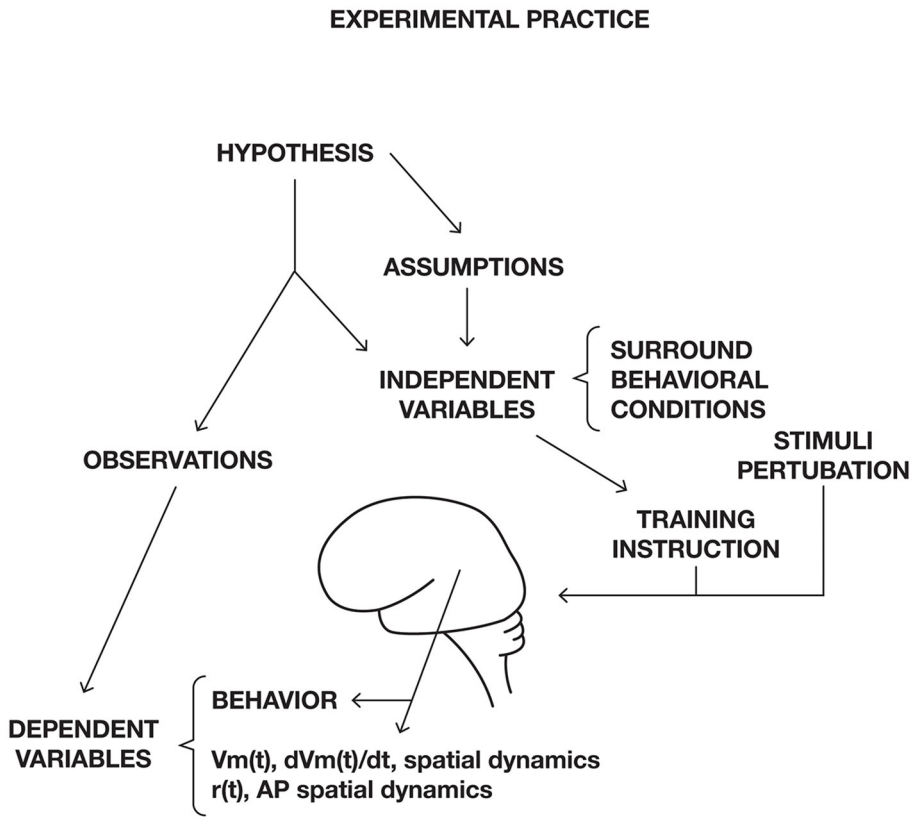

FIGURE 13
Experimental practice in neuroscience. Dependent variables, for example Membrane potential, *Vm*(*t*), trans-membrane currents *dVm*(*t*)/*dt*, spike rate *r*(*t*), or action potentials, AP, and their spatial dynamics. The experimental trial can start with a cue or a stimulus. During the trial, the experimenter measures dependent variables, for example spike trains and membrane currents or membrane potential changes. The recorded dependent variables are then compared to recordings of the same dependent variables during a baseline or control condition.

training will give no change in intracellular Ca^{2+} in the cortex. After many training trials, intracellular Ca^{2+} and spiking will increase in the primary sensory (barrel) cortex and spread to the secondary sensory cortex and from there to the premotor and motor cortex (Esmaeili et al., 2021; Gallero-Salas et al., 2021). Thus, the prerequisite for the task-induced spatial dynamics is successful learning.

When mice have learned a task, spiking increases prior to the experimental trial in CA3 of the hippocampus, dentate gyrus, basal ganglia, zona incerta, substantia nigra, midbrain reticular formation and anticipatory Ca^{2+} increases may appear in specific cortical areas (Steinmetz et al., 2019; Salkoff et al., 2020; Orsolic et al., 2021) (Figure 12). Humans are usually verbally instructed to perform experimental tasks. If they understand the instruction, the regional cerebral blood flow increases in cortical areas engaged in the processing of the sensory stimuli, prior to the experimental trial (Figure 14).

Awake-trained animals and humans are not naïve. In contrast, they are specifically engaged in performing the task *prior* to the experimental trial. Prior to the experimental trial, spatial dynamics evolves in the brain stem, hippocampus, basal ganglia, and cortex. This experimental-related preparatory spatial dynamic probably fine tune the excitability in structures and cortical areas relevant for executing the task (Roland, 1981; Steinmetz et al., 2019; Gilad and Helmchen, 2020; Salkoff et al., 2020; Esmaeili et al., 2021; Orsolic et al., 2021) (Figures 12, 14). These preparatory spatial dynamics may explain how micro-stimulation of singe neurons can control the choice of an animal (Romo et al., 1998; Houweling and Brecht, 2008). Changes in brain variables in most cases are measured relative to a biased pre-stimulus or pre-trial measurements in which the CNS structures to investigate are already active or specifically inhibited.

Experimental frontier 1: Which reference should measurements from brains have?

Historically, the field of human brain imaging tried to establish a commonly agreed reference, a defined rest condition. This is a behavioral reference, during which there are no changes in sensory input and no voluntary motor activity, and with physiologically defined reference values of blood pressure, heart rate, galvanic skin response, and EEG pattern (Roland and Larsen, 1976). But the rest condition is also a consequence of an instruction. The assumption that this "rest state" is stationary and valuable as a reference for trials done immediately before or after the rest measurement is most likely false. So, if there are no external or internal stationary references, how should we measure changes in spiking and currents

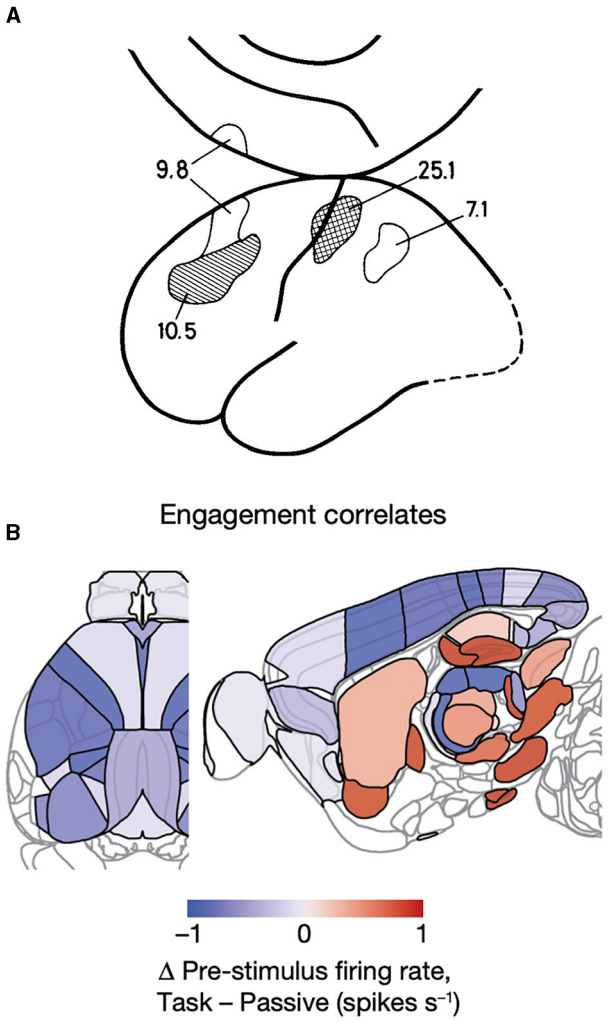

FIGURE 14
Pre-trial CNS activity. **(A)** Regional cerebral blood flow increases in percent in prefrontal, primary, and parietal somatosensory areas prior to a single trial in which the subject expects a threshold stimulus on the tip of the right index finger compared to physiological defined rest condition (see text) (Roland, 1981). **(B)** Changes in spiking rates prior to experimental trials. Spiking prior to trials (indicating task engagement) of neurons in visual, somatosensory, primary motor, retrosplenial, ACA cortex, and posterior thalamus (LP, PU) correlates negatively with the engagement, but the spiking in nucleus accumbens, globus pallidus ext., CA3 of the hippocampus, dentate gyrus, parafasicular nucleus of thalamus, midbrain reticular formation, and substantia nigra correlates positively with task engagement, if "passive" visual stimulation is taken as baseline condition (from Steinmetz et al., 2019).

and magnetic signals from brains? Also, how should we interpret the measured changes?

A practical solution is that one could measure where and when changes in membrane currents, magnetic fields, and spiking occur without any internal or prior brain reference. This could also be done during the training of the animals and while humans receive the task instructions.

Experimental frontier 2: Distinguish different operations in the brain, for example by their spatial dynamics at all scales and in single trials.

Theoretically, at least, one could get a rough classification of brain activities to start with. Secondly one could relate these data to other changes in brain variables in space and time.

4.2. Experimental design, single trials

Single-trial design and analysis is mandatory because brains organize behavior with differences in single trials. The spiking dynamics reflects a single-trial variability (Riehle et al., 2018; Steinmetz et al., 2019; Cowley et al., 2020; Salkoff et al., 2020; Williams and Linderman, 2021). Spatial spiking dynamics is a single-trial dynamics (Grün et al., 2022).

Averaging across neurons, single trials, single areas, or other CNS structures hides the underlying spatial dynamics (Riehle et al., 2018; Davis et al., 2020; Grün et al., 2022). The concepts behind this praxis, behind the experimental design, and behind the interpretation of results are influenced by the separation of time and space. For example, this holds for concepts such as representation, spike pattern, temporal codes, maps, place cell, and synchrony.

The assumptions underlying temporal and spatial averaging, multi-trial statistics, and statistical independence of trials are most likely wrong. So, neuroscientists are forced to design single-trial experiments and analyze single trials statistically (Lee et al., 2010; Rey et al., 2015; Williams and Linderman, 2021).

Experimental frontier 3: Single-trial statistics.

Current single-trial statistics make use of a dynamical systems approach. The key to observe differences between single trials is to record simultaneously from many positions/neurons. Often, spike data, membrane, and field potentials are of lower dimensionalities than the number of neurons/positions recorded. So, first one needs to estimate the true dimensionality of the data at hand.

Dimensionality is the number of dimensions one needs to get an exhaustive description of the dynamics of variables in state space. There are several methods by which one can find the dimensionality of time series data. The best method is the Grassberger and Procaccia (1983) method (Camastra, 2003). The end-product is a trajectory of the single-trial behavior in a multidimensional state space of the found true dimensions. Trials with different dynamics evolve in partly different parts of this multidimensional state space (Churchland et al., 2010).

The drawback of this method is that the dimensionality of the state space must be constant for all single trials (Spaak et al., 2017; Willumsen et al., 2022).

5. Obstacles in interpretation and explaining CNS operations

In experimental neuroscience, scientists usually measure changes in some dependent brain variables induced by experimental manipulations of independent variables (Figure 13). The measured changes in the observed dependent variables, spiking, membrane potentials, field potentials, magnetic and electrical fields, blood flow, and BOLD signals are interpreted

related to external, optogenetic, or direct brain stimulation, particular behaviors, rewards, memory retention, overt behavior, and changes in performance. Careful analyses of the measurements often show that only minor proportions of the variance or information in the data can be explained as related to stimuli, motor behavior, reward behavior, and performance (Urai et al., 2022). This opens several fundamental questions for the interpretation of CNS measurements.

Summarizing the conclusions from the analysis of the barriers hampering progress, the premises for the interpretation of experimental results in systems neuroscience are:

1. Lack of reference or baseline conditions.
2. The continuously changing spiking and changing transmembrane currents everywhere in a CNS implies that one cannot apply a classical cause-effect analysis: if A, t_1 then B, t_2.
3. Central nervous systems, in contrast to complex dynamical systems, have no clear initial state definition, neither locally nor globally. This implies that we cannot explain the future states of the system from local or global initial states.
4. Neither can we assume any pre-existing dimensional state space, because dimensionalities change concurrently in many locations in a CNS. This implies that dynamical systems theory may be of limited value.
5. Time is probably not an independent variable for CNS operations. In a CNS, dynamics are space and time dependent, i.e., spatial dynamics. This implies that pooling data from different neurons or locations and temporal and spatial averaging destroy the spatial dynamics. Repeated observations show that spatial dynamics can vary from trial to trial. This in turn implies that conclusions must be drawn from the outcomes of single trials. Moreover, since external clock time does not uniquely relate to the activities of neurons, other types of causality, e.g., Granger causality, are of no help. Assumptions of statistical stationarities of spiking or transmembrane currents are most likely invalid.
6. Referring to external input or motor, behavioral, output has limited explanatory power, because many CNS processes are intrinsic and relatively autonomous.
7. Separating task related activities from spontaneous and intrinsic cognitive activities in a CNS is still difficult.
8. For experiments in humans, introspection is invalid to explain CNS activities, because brains produce experience and motor activity as results of processes lasting from some 120 ms to more than 1,000 ms (Fried, 2022). These spatial dynamics processes, which initially are logically in-accessible, must arrive to some stage of organization before the human subject can report.
9. Current neuroscience is limited to observe spatial dynamics in discrete parts of CNS only.

Theoretical frontier 1: How can we reliably interpret our results? Theoretical frontier 2: How can we reliably explain our results? Theoretical frontier 3: How can we start to make theories of brains?

A scientific brain theory would be an experimentally based general explanation on how the elements in brains interact at all scales of observation under all conditions. A theory must serve as a conceptual structure in which gaps of knowledge and inconsistencies can be isolated. It must offer rules and coherent explanations, to some extent encompassing different scales of observation. With the recent technical advances, neuroscience now is free to explore complex brain tasks and conditions in many species. Hopefully, scientists could use their experimental results to find principles which could be part of a brain or CNS theory.

Author's note

Despite a century of anatomical, physiological, and molecular biological efforts scientists do not know how neurons by their collective interactions produce percepts, thoughts, memories, and behavior. Scientists do not know and have no theories explaining how brains and central nervous systems work. The usual explanations are that scientists lack methods, techniques, and efficient data analysis to obtain this goal. These are no longer the main reasons. The main obstacles for systems neuroscience seem to be conceptual. That is lack of concepts rooted in solid experimental results, unnecessary assumptions, and focus on analogies from other disciplines (information theory, computer science, physics, and psychology). Brains cannot be understood treating time and space as independent variables. Methods are now available for measuring spatial dynamics at microscopic to mesoscopic scales, also in single trials. This paper summarizes the conceptual, theoretical, statistical, and experimental practice obstacles which need to be eliminated to efficiently use and interpret results with these new methods.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnsys.2023.1147896/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Single trial recording of temporal derivative of the voltage signal (showing excitation and inhibition) over visual areas 17, 18, 19, and 21 (see Figures 7, 8). From −180 ms to +20 ms the movie shows spontaneous un-organized spatial fluctuations. From 21 to 200 ms organized spatial excitation and inhibition dynamics in response to a 3° × 3° stationary square at 0 ms, exposed for 133 ms.

SUPPLEMENTARY VIDEO 2
Statistically significant ($p < 0.01$ after Bonferroni correction) depolarization in visual areas of a ferret in response to a bar moving downwards starting in the peripheral field of view. The retina is stationary. Note that the bar then is mapped as moving excitation over the cortex. However, at 104 ms the neurons in area s 19/21 compute an excitation far ahead of the bar mapping. After feedback to areas 17/18 this repeats here. The black holes show the electrode penetration sites along the border between areas 17 and 18 corresponding to the vertical meridian. When the spiking at any layer of the cortex becomes statistically significant ($p < 0.01$) the hole turns white. Note the mapping of the future bar trajectory when the bar representation on the cortex has reached the left white arrow (155 ms). Note also how the object mapping, defined by the hot spot in area 17/18 actually follows the cortical route predicted already at 160 ms. Animal 410 (from Harvey et al., 2009).

SUPPLEMENTARY VIDEO 3
Three-dimensional visualization of derivative of the voltage signal showing excitation (orange to red) and inhibition (dark green to blue) in areas 17, 18, 19, 21 of a ferret to an object moving down from time 0 ms in the field of view. For localization of area borders (see Figure 9) (from the top areas 17, 18, 19, and 21). Note the non-linear spatial dynamics, feedback from areas 21 and 19 to 18 and 17 at 115 ms, predictive excitation 135-195 ms and inhibition chasing the excitations from 500 ms (from Harvey et al., 2009).

SUPPLEMENTARY VIDEO 4
Spiking in layer 4 of areas 17 and 18 of 8 ferrets. Electrode positions are marked with white circles. Color scale shows the proportion of trials giving rise to significant increases (compared to pre-trial baseline). Note that significant spiking gets restricted to the retinotopic mapping after 90 ms (time on top) (from Roland et al., 2017).

SUPPLEMENTARY VIDEO 5
Spatial derivatives in areas 17, 18, 19, 21, to a 3° × 3° stationary square at 0 ms, exposed for 250 ms. Compare with Supplementary Video 1.

References

Abadshi, J. K., Nazari-Ahangarkolaee, M., Gattas, S., Bermudez-Contreras, E., Luzak, A., McNaughton, B. L., et al. (2020). Spatiotemporal patterns of neocortical activity around hippocampal sharp-wave ripples. *Elife* 9, e51972. doi: 10.7554/eLife.51972

Abdelfattah, A. S., Kawashima, T., Singh, A., Novak, O., Liu, H., Shuai, Y., et al. (2019). Bright and photostable chemigenetic indicators for extended *in vivo* voltage imaging. *Science* 365, 699–704. doi: 10.1126/science.aav6416

Abeles, M. (1991). *Corticotronics*. Cambridge: Cambridge University Press, 280.

Ahmed, B., Hanazawa, A., Undeman, C., Eriksson, D., Valentiniene, S., and Roland, P. E. (2008). Cortical dynamics subserving visual apparent motion. *Cereb. Cortex* 18, 2796–2810. doi: 10.1093/cercor/bhn038

Alcami, P., and El Hady, A. (2019). Axonal computations. *Front. Cellular Neurosci.* 13:413. doi: 10.3389/fncel.2019.00413

Alito, H. J., and Usrey, W. M. (2005). Dynamic prope3rties of thalamic neurons for vision. *Prog. Brain Res.* 149, 83–90. doi: 10.1016/S0079-6123(05)49007-X

Babloyantz, A., and Destexhe, A. (1986). Low-dimensional chaos in an instance of epilepsy. *Proc. Natl. Acad. Sci. U. S. A.* 83, 35613–33517. doi: 10.1073/pnas.83.10.3513

Bargmann, C., Newsome, W., Anderson, D., Brown, E., Deisseroth, K., Donoghue, J., et al. (2014). *BRAIN 2025*. National Institutes of Health, June 5. Available online at: https://braininitiative.nih.gov/sites/default/files/documents/brain2025_508c_2.pdf

Baria, A. T., Maniscalco, B., and He, B. J. (2017). Initial-state-dependent, robust, transient neural dynamics encode conscious visual perception. *PLoS Comput. Biol.* 13, e1005806. doi: 10.1371/journal.pcbi.1005806

Barlow, H. R. (1961). "Possible principles underlying the transformations of sensory messages," in *Sensory Communication*, ed W. A. Rosenblith (Cambridge, MA: MIT Press), 217–234.

Barth, A. L., and Poulet, J. F. A. (2012). Experimental evidence for sparse firing in the neocortex. *Trends Neurosci.* 35, 345–355. doi: 10.1016/j.tins.2012.03.008

Bassett, D. S., Cullen, K. E., Eickhoff, S. B., Farah, M. J., Goda, Y., Haggard, P., et al. (2020). Reflections on the past two decades of neuroscience. *Nat. Rev. Neurosci.* 21, 524–534. doi: 10.1038/s41583-020-0363-6

Berger, T., Borgdorff, A., Crochet, S., Neubauer, F. B., Lefort, S., Fauvet, B., et al. (2007). Combined voltage and calcium epiflourescence imaging *in vitro* and *in vivo* reveals subthreshold and suprathreshold dynamics of mouse barrel cortex. *J Neurophysiol.* 97, 3751–3762. doi: 10.1152/jn.01178.2006

Besle, J., Shevon, C. A., Mehta, A. D., Lakatos, P., Goodman, R. R., McKhan, G. M., et al. (2011). Tuning of the human neocortex to the temporal dynamics of attended events. *J. Neurosci.* 31, 3176–3185. doi: 10.1523/JNEUROSCI.4518-10.2011

Bezsudnova, Y., Koponen, L. M., Barontini, G., Jensen, O., and Kowalczyk, A. U. (2022). Optimising the sensing volume of OPM sensors for MEG source reconstruction. *Neuroimage* 264, 119747. doi: 10.1016/j.neuroimage.2022.119747

Bialeck, W., van Steveninck, R. R., Rieke, F., and Warland, D. (1997). *Spikes, Exploring the Neural Code*. Cambridge, MA: MIT Press, 414.

Buzsaki, G. (2019). *The Brain Inside Out*. Cambridge, MA: MIT Press. doi: 10.1093/oso/9780190905385.001.0001

Buzsaki, G. (2020). The brain-cognitive behavior problem: a retrospective. *eNeuro* 7, ENEURO.0069-20.2020. doi: 10.1523/ENEURO.0069-20.2020

Buzsáki, G., and Tingley, D. (2018). The hippocampus as a sequence generator. *Trends Cogn. Sci.* 22, 853–869. doi: 10.1016/j.tics.2018.07.006

Camastra, F. (2003). Data dimensionality estimation methods: a survey. *Pattern Recogn.* 36, 2945–2954. doi: 10.1016/S0031-3203(03)00176-6

Cardin, J. A., Crair, M. C., and Hogley, M. J. (2020). Mesoscopic imaging: shining a wide light on large-scale neural dynamics. *Neuron* 108, 33–43. doi: 10.1016/j.neuron.2020.09.031

Churchland, M. M., Yu, B. M., Cunningham, J. P., Sugrue, L. P., Cohen, M. R., Corrado, G. S., et al. (2010). Stimulus onset quenches neural variability: a widespread cortical phenomenon. *Nat. Neurosci.* 13, 369–378. doi: 10.1038/nn.2501

Clancy, K. R., and Mrsic-Flogel, T. D. (2021). The sensory representation of causally controlled objects. *Neuron* 109, 677–689. doi: 10.1016/j.neuron.2020.12.001

Cowley, B. R., Snyder, A. C., Acar, K., Williamson, R. C., Yu, B. M., and Smith, M. A. (2020). Slow drift of neural activity as a signature of impulsivity in macaque visual and pre-fronal cortex. *Neuron* 108, 551–567. doi: 10.1016/j.neuron.2020.07.021

d'Aquin, S., Szonyi, A., Mahn, M., Krabbe, S., Gründemann, J., and Lüthi, A. (2022). Compartmentalized dendritic plasticity during associative learning. *Science* 376, 266. doi: 10.1126/science.abf7052

Davis, Z. W., Muller, L., Martinez-Trujillo, J., Sejnowski, T. J., and Reynolds, J. H. (2020). Spontaneous travelling cortical waves gate perception in behaving primates. *Nature* 587, 432–436. doi: 10.1038/s41586-020-2802-y

Dayan, P., and Abbott, L. F. (2001). *Theoretical Neuroscience*. Cambridge, MA: MIT Press.

Denker, M., Zehl, L., Kilavik, B. E., Diesmann, M., Brochier, T., Riehle, A., et al. (2018). LFP beta amplitude is linked to mesoscopic spatio-temporal phase patterns. *Sci. Rep.* 8, 5200. doi: 10.1038/s41598-018-22990-7

Dickey, C. W., Sargsyan, A., Madsen, J. R., Eskandar, E. N., Cash, S. S., and Halgren, E. (2021). Traveling spindles create necessary conditions for spike -timing-dependent plasticity in humans. *Nat. Commun.* 12, 1027. doi: 10.1038/s41467-021-21298-x

Eliasmith, C., Stewart, T. C., Choo, X., Bekolay, T., DeWolf, T., Tang, Y., et al. (2012). A large-scale model of the brain. *Science* 338, 1202–1205. doi: 10.1126/science.1225266

Engel, T. A., and Steinmetz, N. A. (2019). New perspectives on dimensionality and variability from large-scale cortical dynamics. *Curr. Opin. Neurobiol.* 58, 181–190. doi: 10.1016/j.conb.2019.09.003

Eriksson, D., Valentiniene, S., and Papaioannou, S. (2010). Relating information, encoding and adaptation: decoding the population firing rate in visual areas 17/18 in response to a stimulus transition. *PLoS ONE* 5, e10327. doi: 10.1371/journal.pone.0010327

Esmaeili, V., Tamura, K., Muscinelli, S. P., Modirshanechi, A., Boscaglia, M., Lee, A. B., et al. (2021). Rapid suppression and sustained activation of distinct cortical regions for a delayed sensory-triggered motor response. *Neuron* 109, 2183–2201. doi: 10.1016/j.neuron.2021.05.005

Esteves, I. M., Chang, H. R., Neumann, A. R., Sun, J. J., Mohajerani, M. H., and McNaughton, B. L. (2021). Spatial information encoding across multiple neocortical regions depends on an intact hippocampus. *J. Neurosci.* 41, 307–319. doi: 10.1523/JNEUROSCI.1788-20.2020

Farley, B. J., and Norena, A. J. (2013). Spatiotemporal cordiunation of slow-wave ongoing activity across auditory areas. *J. Neurosci.* 33, 3299–3310. doi: 10.1523/JNEUROSCI.5079-12.2013

Ferezou, I., Haiss, F., Gentet, L. J., Aronoff, R., Weber, B., Petersen, C. C. H., et al. (2007). Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. *Neuron* 56, 907–923. doi: 10.1016/j.neuron.2007.10.007

Foster, N. N., Barry, J., Korobkova, L., Garcia, L., Gao, L., Becerra, M., et al. (2021). The mouse cortico-basal ganglia-thalamic network. *Nature* 598, 188–194. doi: 10.1038/s41586-021-03993-3

Fried, I. (2022). Neurons as will and representation. *Nat. Rev. Neurosci.* 23, 104–114. doi: 10.1038/s41583-021-00543-8

Fried, I., Mukamel, R., and Kreiman, G. (2011). Internally generated preactivation of single neurons in human medial frontal cortex predicts volition. *Neuron* 69, 548–562. doi: 10.1016/j.neuron.2010.11.045

Gallego, J. A., Perich, M. G., Miller, L. E., and Solla, S. A. (2017). Neural manifolds for the control of movement. *Neuron* 94, 978–984. doi: 10.1016/j.neuron.2017.05.025

Gallero-Salas, Y., Han, S., Sych, Y., Voigt, F. F., Laurenczy, B., Gilad, A., et al. (2021). Sensory and behavioral components of neorcortical signal flow in discrimination with short-term memory. *Neuron* 109, 135–148. doi: 10.1016/j.neuron.2020.10.017

Gao, R. (2020). Neuronal timescales are functionally dynamic and shaped by cortical microarchitecture. *Elife* 9, e61277. doi: 10.7554/eLife.61277.sa2

Gilad, A., and Helmchen, F. (2020). Spatiotemporal refinement of signal flow through assocoiation cortex during learning. *Nat. Commun.* 11, 1744. doi: 10.1038/s41467-020-15534-z

Goetz, L., Roth, A., and Häusser, M. (2021). Active dendrites enable strong but sparse input to determine orientation selectivity. *Proc. Natl. Acad. Sci. U. S. A.* 118, e2017339118. doi: 10.1073/pnas.2017339118

Gomez-Ramirez, M., Kelly, S. P., Molholm, S., Schatpour, P., Schwartz, T. H., Foxe, J. J., et al. (2011). Oscillatory sensory selection mechanisms during intersensory attention to rhythmic auditory and visual inputs: a human electrocorticographic investigation. *J. Neurosci.* 31, 18556–18567. doi: 10.1523/JNEUROSCI.2164-11.2011

Grassberger, P., and Procaccia, I. (1983). Characterization of strange attractors. *Phys. Rev. Lett.* 50, 346–349. doi: 10.1103/PhysRevLett.50.346

Gray, C. M., and Singer, W. (1989). Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 86, 1698–1702. doi: 10.1073/pnas.86.5.1698

Grün, S. (2021). Significant spatio-temporal spike patterns in macaque monkey motor cortex. *J. Comput. Neurosci.* 49(Suppl 1), S4–S5. doi: 10.1007/s10827-021-00801-9

Grün, S., Li, J., McNaughton, B., Petersen, C., McCormick, D., Robson, D., et al. (2022). Emerging principles of spacetime in brains: meeting report on spatial neurodynamics. *Neuron* 110, 1894–1898. doi: 10.1016/j.neuron.2022.05.018

Harris, K. M., Hubbard, D. D., Kuwajima, M., Abraham, W. C., Bourne, J. N., Bowden, J. B., et al. (2022). Dendritic spine density scales with microtubule number in rat hippocampal dendrites. *Neuroscience* 489, 84–97. doi: 10.1016/j.neuroscience.2022.02.021

Harvey, M. A., and Roland, P. E. (2013). Laminar firing and membrane dynamics in four visual areas exposed to two objects moving to occlusion. *Front. Syst. Neurosci.* 7, 23. doi: 10.3389/fnsys.2013.00023

Harvey, M. A., and Valentiniene, S., and Roland, P. E. (2009). Cortical membrane potential dynamics and laminar firing during object motion. *Front. Syst. Neurosci.* 3, 7. doi: 10.3389/neuro.06.007.2009

Heller, J., Hertz, J. A., Kjær, T. W., and Richmond, B. J. (1995). Information flow and temporal coding in primate pattern vision. *J. Comp. Neurosci.* 2, 175–193. doi: 10.1007/BF00961433

Herath, P., Klingberg, T., Young, J., Amunts, K., and Roland, P. (2001). Neural correlates of dual task interference can be dissociated from those of divided attention: an fMRI study. *Cereb Cortex.* 11, 796–805. doi: 10.1093/cercor/11.9.796

Horikawa, J., Nasu, M., and Taniguchi, I. (1998). Optical recording of responses to grequency-modulated sounds in the auditory cortex. *Neuroreport* 9, 799–802. doi: 10.1097/00001756-199803300-00006

Horikawa, J., and Ojima, H. (2017). Cortical activation patterns evoked by temporally asymmetric sounds and their modulation by learning. *eNeuro* 4, ENEURO.0241-16.2017. doi: 10.1523/ENEURO.0241-16.2017

Houweling, A. R., and Brecht, M. (2008). Behavioral report of single neuron stimulation in somatosensory cortex. *Nature* 451, 65–68. doi: 10.1038/nature06447

Izhikevich, E. M., and Edelmann, G. M. (2008). Large-scale model of mammalian thalamocortical systems. *Proc. Natl. Acad. Sci. U. S. A.* 105, 3593–3598. doi: 10.1073/pnas.0712231105

Jones, I. S., and Kording, K. P. (2022). Do biological constraints impair dendritic computation? *Neuroscience* 489, 282–274. doi: 10.1016/j.neuroscience.2021.07.036

Jun, J., Steinmetz, N. A., Harris, K. D., Koch, C., O'Keefe, J., Harris, T. D., et al. (2017). Fully integrated silicon probes for high-density recording of neural activity. *Nature* 551, 232–236. doi: 10.1038/nature24636

Jung, Y., Kennedy, A., Chiu, H., Mohammed, F., Claridge-Chang, A., and Anderson, D. J. (2020). Neurons that function within an integrator to promote a persistent behavioral state in *Drosophila*. *Neuron* 105, 322–333. doi: 10.1016/j.neuron.2019.10.028

Karimi, A., Odenthal, J., Drawitsch, F., Boergens, K. M., and Helmstaedter, M. (2020). Cell-type specific innervation of cortical pyramidal cells at their apical dendrites. *Elife* 9, e46876. doi: 10.7554/eLife.46876.sa2

Keyser, C., Logothetis, N. K., and Panzieri, S. (2010). Millisecond encoding precision of auditory cortex neurons. *Proc. Natl. Acad. Sci. U. S. A.* 107, 16976–16981. doi: 10.1073/pnas.1012656107

Kinomura, S., Larsson, J., Gulyás, B., and Roland, P. E. (1996). Attention activates the midbrain reticular formation and thalamic intralaminar nuclei in man. *Science* 271, 512–515. doi: 10.1126/science.271.5248.512

Kumar, A., Schrader, S., and Aertsen, A. (2008). The high conductance state of cortical networks. *Neural Comp.* 20, 1–43. doi: 10.1162/neco.2008.20.1.1

Lamme, V. A. F. (1995). The neurophysiology of figure-ground segregation in primary visual cortex. *J. Neurosci.* 15, 1605–1615. doi: 10.1523/JNEUROSCI.15-02-01605.1995

Larkum, M. E., Wu, J., Duverdin, S. A., and Gidon, A. (2022). The guide to dendritic spikes of the mammalian cortex *in vitro* and *in vivo*. *Neuroscience* 489, 15–33. doi: 10.1016/j.neuroscience.2022.02.009

Le Bihan, D. (2020). On time and space in the brain: a relativistic Pseudo-diffusion framework. *Brain Multiphys.* 1, 100016. doi: 10.1016/j.brain.2020.100016

Lee, J., Kim, H. R., and Lee, C. (2010). Trial-to-trial variability of spike response of V1 and saccadic response time. *J. Neurophysiol.* 104, 2556–2572. doi: 10.1152/jn.01040.2009

Li, N., and Mrsic-Flogel, T. D. (2020). Cortic-cerebellar interactions during goal-directed behavior. *Curr. Opin. Neurobiol.* 65, 27–37. doi: 10.1016/j.conb.2020.08.010

Liang, Y., Song, C., Liu, M., Gong, P., Zhou, C., and Knöpfel, T. (2021). Cortex-wide dynamics of intrinsic electrical activities: propagating waves and their interactions. *J. Neurosci.* 41, 3665–3678. doi: 10.1523/JNEUROSCI.0623-20.2021

Liewald, D., Miller, R., Logothetis, N., Wagner, H.-J., and Schüz, A. (2014). Distribution of axon diameters in cortical white matter. An electron-microscopic study on three human brains and a macaque. *Biol. Cybern.* 108, 541–537. doi: 10.1007/s00422-014-0626-2

Lindén, H., Petersen, P. C., Vestergaard, M., and Berg, R. W. (2022). Movement is governed by rotational population dynamics in spinal motor networks. *Nature* 610, 526–531. doi: 10.1038/s41586-022-05293-w

Machado, T. A., Kauvar, I. V., and Deisserroth, K. (2022). Multiregion neuronal activity: the forrest and the trees. *Nat. Rev. Neurosci.* 23, 683–704. doi: 10.1038/s41583-022-00634-0

Markram, H., Muller, E., Ramaswamy, S., Reimann, M. W., Abdellah, M., Sanchez, C. A., et al. (2016). Reconstruction and simulation of neocortical microcircuity. *Cell* 163, 456–492. doi: 10.1016/j.cell.2015.09.029

Marques, J. C., Li, M., Schaak, D., Robson, D. N., and Li, J. M. (2020). Internal state dynamics shape brainwide activity and foraging behaviour. *Nature* 577, 239–243. doi: 10.1038/s41586-019-1858-z

McCormick, D. A., Nestvogel, D. B., and He, B. J. (2020). Neuromodulation of brain state and behavior. *Ann. Rev. Neurosci.* 43, 391–415. doi: 10.1146/annurev-neuro-100219-105424

Mel, B. (1993). Synaptic integration in an excitable dendritic tree. *J. Neurophysiol.* 70, 1086–1101. doi: 10.1152/jn.1993.70.3.1086

Merchant, H., and Averbeck, B. R. (2017). The computational and neural basis of rhythmic timing in medial premotor cortex. *J. Neurosci.* 37, 4552–4564. doi: 10.1523/JNEUROSCI.0367-17.2017

Millner, P. M. (1999). *The Autonomous Brain: A Neural Theory of Attention and Learning*. Mawah, NJ: Lawrence Earlbaum Ass. Publishers. doi: 10.4324/9781410602985

Mohajerani, M. H., McVea, D. A., Fingas, M., and Murphy, T. H. (2010). Mirroed bilateral slow-wave cortical activity within local circuits revealed by fast bihemispheric voltage-sensitive dye imaging in anesthetized and awake mice. *J. Neurosci.* 30, 3745–3751. doi: 10.1523/JNEUROSCI.6437-09.2010

Moore, J. J., Robert, V., Rashid, S. K., and Basu, J. (2022). Assessing local and branch-specific activity in dendrites. *Neuroscience* 489, 143–164. doi: 10.1016/j.neuroscience.2021.10.022

Moreaux, L. C., Yatsenko, D., Sacher, W. D., Choi, J., Lee, C., Kubat, N. J., et al. (2020). Integrated neurophotonics: toward dense volumetric interrogation of brain circuit activity-at depth and in real time. *Neuron* 108, 66–92. doi: 10.1016/j.neuron.2020.09.043

Muller, L., Plantoni, G., Koller, D., Cash, S. S., Halgren, E., and Sejnowski, T. J. (2016). Rotating waves during human sleep organize global patterns of activity that repeat precisely though the night. *Elife* 5, e17267. doi: 10.7554/eLife.17267

Olshausen, B. A., and Field, D. J. (2006). "What is the other 85 percent of V1 doing?" in *23 Problems in Systems Neuroscience*, eds J. L. van Hemmen, and T. J. Sejnowski (New York, NY: Oxford University Press), 182−−221. doi: 10.1093/acprof:oso/9780195148220.003.0010

Orsolic, I., Rio, M., Mrsic-Flogel, T. D., and Znamensky, P. (2021). Mesoscale dynamics reflect the interaction and temporal expectation during perceptual decision-making. *Neuron* 109, 1–15. doi: 10.1016/j.neuron.2021.03.031

Otor, Y., Achvat, S., Cermak, N., Benisty, H., Abboud, M., Barak, O., et al. (2022). Dynamic compartmental computations in tuft dendrites of layer 5 neurons during motor behavior. *Science* 376, 267–275. doi: 10.1126/science.abn1421

Paulk, A. C., Kfir, Y., Khanna, A. R., Mustroph, M. L., Trautmann, E. M., Soper, D. J., et al. (2021). Large-scale neural recordings with single neuron resolution using Neuropixels probes in huiman cortex. *Nat. Neurosci.* 25, 252–263. doi: 10.1038/s41593-021-00997-0

Peters, A. J., Fabre, J. M. J., Steinmetz, N. A., Harris, K. D., and Carandini, M. (2021). Striatal activity topographically reflects cortical activity. *Nature* 591, 420–425. doi: 10.1038/s41586-020-03166-8

Pfurtscheller, G., Solis-Escalante, T., Barry, R. J., Klobassa, D. S., Neuper, C., and Müller-Putz, G. R. (2013). Brisk heart rate and EEG changes during execution and withholding of cue-paced foot motor imagery. *Front. Hum. Neurosci.* 7, 379. doi: 10.3389/fnhum.2013.00379

Piatkevich, K. D., Bensussen, S., Tseng, H.-A., Shroff, S. N., Lopez-Huerta, V. G., Park, D., et al. (2019). Population imaging of neural activity in awake behving mice. *Nature* 574, 413–417. doi: 10.1038/s41586-019-1641-1

Prechtl, J. C., Cohen, L. B., Pesaran, B., Mitra, P. P., and Kleinfeld, D. (1997). Visual stimuli induce waves of electrical activity in turtle cortex. *Proc. Natl. Acad. Sci. USA* 94, 7621–7626. doi: 10.1073/pnas.94.14.7621

Rao, R. P. N., and Ballard, D. H. (1999). Predictive coding in the visual cortex. a functional interpretation of some extra-classical receptive-field effects. *Nat. Neurosci.* 2, 79–87. doi: 10.1038/4580

Rey, H. G., Ahmadi, M., and Quiroga, R. Q. (2015). Single trial analysis of field potentials in perception, learning and memory. *Curr. Opin. Neurobiol.* 31, 148–155. doi: 10.1016/j.conb.2014.10.009

Richmond, B. J., and Optican, L. M. (1990). Temporal encoding of two-dimensional patterns by single units in primate primary visual cortex. II. Information transmission. *J. Neurophysiol.* 64, 370–380. doi: 10.1152/jn.1990.64.2.370

Riehle, A., Brochier, T., Nawrot, M., and Grün, S. (2018). Behavioral context determines network state and variability dynamics in monkey motor cortex. *Front. Neural Circuits* 12, 52. doi: 10.3389/fncir.2018.00052

Rockland, K. S. (2010). Five points on columns. *Front. Neuroanat.* 4, 22. doi: 10.3389/fnana.2010.00022

Rockland, K. S. (2021). A closer look at cortico-thalamic "loops". *Front. Neural Circuits* 15, 632668. doi: 10.3389/fncir.2021.632668

Roland, P. E. (1981). Somatotopical tuning on the postcentral gyrus during focal attention in man. A regional cerebral blood flow study. *J. Neurophysiol.* 46, 744–754. doi: 10.1152/jn.1981.46.4.744

Roland, P. E. (2010). Six principles of visual cortical dynamics. *Front. Syst. Neurosci.* 4, 28. doi: 10.3389/fnsys.2010.00028

Roland, P. E. (2017). Space-time dynamics of membrane currents evolve to shape excitation, spiking, and inhibition in the cortex at small and large scales. *Neuron* 94, 934–942. doi: 10.1016/j.neuron.2017.04.038

Roland, P. E., Bonde, L. H., Forsberg, L., and Harvey, M. (2017). Breaking the excitation-inhibition balance makes the cortical network's space-time dynamics distinguish simple visual scenes. *Front. Syst. Neurosci.* 11, 14. doi: 10.3389/fnsys.2017.00014

Roland, P. E., Hanazawa, A., Undeman, C., Eriksson, D., Tompa, T., Nakamura, H., et al. (2006). Cortical feedback depolarization waves: a mechanism of top-down influence on early visual areas. *Proc. Natl. Acad. Sci. USA* 103, 12586–12591. doi: 10.1073/pnas.0604925103

Roland, P. E., and Larsen, B. (1976). Focal increase of cerebral blood flow during stereognostic testing in man. *Arch. Neurol.* 33, 551–558. doi: 10.1001/archneur.1976.00500080029005

Romo, R., Hernández, A., Zainos, A., and Salinas, E. (1998). Somatosensory discrimination based on cortical microstimulation. *Nature* 392, 387–390. doi: 10.1038/32891

Rovelli, C. (2018). *The Order of Time*. London: Penguin Random House.

Rudolph, M., Pospischil, M., Timofeev, I., and Destexhe, A. (2007). Inhibition determines membrane potential dynamics and controls action potential generation in awake and sleeping cat cortex. *J Neurosci.* 27, 5280–5290. doi: 10.1523/JNEUROSCI.4652-06.2007

Salkoff, D. A., Zagha, E., McCarthy, E., and McCormick, D. (2020). Movement and performance explain widespread cortical activity in a visual detection task. *Cereb. Cortex* 30, 421–437. doi: 10.1093/cercor/bhz206

Scheffer, L. K., Xu, C. S., Januszewski, M., Lu, Z., Takemura, S.-Y., Hayworth, K. J., et al. (2020). A connectome and analysis of the adult *Drosophila* central brain. *Elife* 9, e57443. doi: 10.7554/eLife.57443.sa2

Schmidt, M., Bakker, R., Shen, K., Bezgin, G., Diesmann, M., and van Albada, S. J. (2018). A multi-scale layer-resolved spiking network model of resting-state dynamics in macaque visual cortical areas. *PLoS Comput. Biuol.* 14, e1006359. doi: 10.1371/journal.pcbi.1006359

Senseman, D. M. (1999). Spatiotemporal structure of depolarization spread in cortical pyramidal cell populations evoked by diffuse retinal light flashes. *Vis. Neurosci.* 16, 65–79. doi: 10.1017/S0952523899161030

Shepherd, G. M., and Grillner, S. (2018). *Handbook of Brain Microcircuits*. New York, NY: Oxford University Press, 599. doi: 10.1093/med/9780190636111.001.0001

Shepherd, G. M., and Yamawaki, N. (2021). Untangling the cortico-thalamo-cortical loop: cellular pieces of a knotty circuit puzzle. *Nat. Rev. Neurosci.* 22, 389–406. doi: 10.1038/s41583-021-00459-3

Shoham, S., O'Connor, D. H., and Segev, R. (2006). How silent is the brain: is there a "dark matter" problem in neuroscience? *J. Comp. Physiol. A* 192, 777–784. doi: 10.1007/s00359-006-0117-6

Siegle, J. H., Jia, X., Durand, S., Gale, S., Bennett, C., Graddis, N., et al. (2021). Survey of spiking in the mouse visual system reveals functional hierarchy. *Nature* 592, 86–92. doi: 10.1038/s41586-020-03171-x

Singer, W., Sejnowski, T. J., and Rakic, P. (eds) (2019). *The Neocortex*. Cambridge, MA: MIT Press. doi: 10.7551/mitpress/12593.001.0001

Slovin, H., Arieli, A., Hildesheim, R., and Grinvald, A. (2002). Long-term voltage-sensitive dye imaging reveals cortical dynamics in behaving monkeys. *J. Neurophysiol.* 88, 3421–3438. doi: 10.1152/jn.00194.2002

Song, C., Piscopo, D. M., Niell, C. M., and Knöpfel, T. (2018). Cortical signatures of wakeful somatosensory processing. *Sci. Rep.* 8, 11977. doi: 10.1038/s41598-018-30422-9

Spaak, E., de Lange, F. P., and Jensen, O. (2014). Local entrainment of alpha oscillations by visual stimuli causes cyclic modulation of perception. *J. Neurosci.* 34, 3636–3544. doi: 10.1523/JNEUROSCI.4385-13.2014

Spaak, E., Watanabe, K., Funahashi, S., and Stokes, M. G. (2017). Stable and dynamic coding for working memory in primate prefrontal cortex. *J. Neurosci.* 37, 6502–6516. doi: 10.1523/JNEUROSCI.3364-16.2017

Stam, C. J. (1996). Non-linear dynamic analysis of EEG and MEG: review of an emerging field. *Clin. Neurophysiol.* 116, 2266–2301. doi: 10.1016/j.clinph.2005.06.011

Steinmetz, N. A., Zatka-Haas, P., Carandini, M., and Harris, K. D. (2019). Distributed coding of choice, action and engagement across the mouse brain. *Nature* 576, 266–273. doi: 10.1038/s41586-019-1787-x

Stringer, C., Pachitariu, M., Steinmetz, N., Carandini, M., and Harris, K. D. (2019). High-dimensional geometry of population responses in visual cortex. *Nature* 571, 361–365. doi: 10.1038/s41586-019-1346-5

Strogatz, S. H. (2018). *Nonlinear Dynamics and Chaos*, 2 ed. New York, NY: CRC Press. doi: 10.1201/9780429492563

Stuyt, G., Godenzini, L., and Palmer, L. M. (2022). Local and global dynamics of dendritic activity in the pyramidal neuron. *Neuroscience* 489, 176–184. doi: 10.1016/j.neuroscience.2021.07.008

Tasaki, I., Watanabe, A., Sandlin, R., and Carnay, L. (1968). Changes in in fluoresence, turbidity, birefringence, associated with nerve excitation. *Proc. Natl. Acad. Sci. U.S.A.* 61, 883–888. doi: 10.1073/pnas.61.3.883

Urai, A. E., Doiron, B., Leifer, A. M., and Churchland, A. K. (2022). Large-scale neural recordings call for new insights to link brain and behavior. *Nat. Neurosci.* 25, 11–19. doi: 10.1038/s41593-021-00980-9

Villette, V., Chavarha, M., Dimov, I. K., Bradley, J., Pradhan, L., Mathieu, B., et al. (2019). Ultrafast two-photon imaging of a high-gain voltage indicator in awake behaving mice. *Cell* 179, 1590–1608. doi: 10.1016/j.cell.2019.11.004

Wagner, M. J., Kim, T. H., Kadmon, J., Nguyen, N. D., Ganguli, S., Schnitzer, M. J., et al. (2019). Shared cortex-cerebellum dynamics in the execution and learning of a motor task. *Cell* 177, 669–682. doi: 10.1016/j.cell.2019.02.019

Waxman, S. G., and Bennett, N. (1972). Relative conduction velocities of small myelinated and non-myelinated fibres in the central nervous system. *Nat. New Biol.* 238, 217–219. doi: 10.1038/newbio238217a0

Williams, A. H., and Linderman, S. W. (2021). Statistical neuroscience in the single trial limit. *Curr. Opin. Neurobiol.* 70, 193–205. doi: 10.1016/j.conb.2021.10.008

Willumsen, A., Midtgaard, J., Jespersen, B., Hansen, C. K. K., Lam, S. N., Hansen, S., et al. (2022). Local networks from different parts of the human cerebral cortex generate and share the same population dynamic. *Cereb. Cortex Commun.* 3, 1–19. doi: 10.1093/texcom/tgac040

Wohrer, A., Humphries, M. D., and Machens, C. K. (2013). Population-wide distributions of neural activity during perceptual decision-making. *Prog. Neurobiol.* 103, 156–193. doi: 10.1016/j.pneurobio.2012.09.004

Wu, H., Williams, J., and Nathans, J. (2014). Complete morphologies of basal forebrain cholinergic neurons in the mouse. *eLife* 3:e02444. doi: 10.7554/elife.0244

Xu, W., Huang, X., Takagaki, K., and Wu, J.-Y. (2007). Compression and reflection of visually evoked cortical waves. *Neuron* 55, 119–129. doi: 10.1016/j.neuron.2007.06.016

Yap, M. H. W., Grabowska, M. J., Rohrscheib, C., Jeans, R., Troup, M., Paulk, A. C., et al. (2017). Oscillatory brain activity in spontaneous and induced sleep stages in flies. *Nat. Commun.* 8, 1815. doi: 10.1038/s41467-017-02024-y

Zhu, M. H., Jang, J., Milosevich, M. M., and Antic, S. D. (2021). Population imaging discrepancies between a genetically-encoded calcium indicator (GECI) versus a genetically-encoded voltage indicator (GEVI). *Sci. Rep.* 11, 5295. doi: 10.1038/s41598-021-84651-6

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Updating perspectives on spinal cord function: motor coordination, timing, relational processing, and memory below the brain

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Those studying neural systems within the brain have historically assumed that lower-level processes in the spinal cord act in a mechanical manner, to relay afferent signals and execute motor commands. From this view, abstracting temporal and environmental relations is the province of the brain. Here we review work conducted over the last 50 years that challenges this perspective, demonstrating that mechanisms within the spinal cord can organize coordinated behavior (stepping), induce a lasting change in how pain (nociceptive) signals are processed, abstract stimulus–stimulus (Pavlovian) and response-outcome (instrumental) relations, and infer whether stimuli occur in a random or regular manner. The mechanisms that underlie these processes depend upon signal pathways (e.g., NMDA receptor mediated plasticity) analogous to those implicated in brain-dependent learning and memory. New data show that spinal cord injury (SCI) can enable plasticity within the spinal cord by reducing the inhibitory effect of GABA. It is suggested that the signals relayed to the brain may contain information about environmental relations and that spinal cord systems can coordinate action in response to descending signals from the brain. We further suggest that the study of stimulus processing, learning, memory, and cognitive-like processing in the spinal cord can inform our views of brain function, providing an attractive model system. Most importantly, the work has revealed new avenues of treatment for those that have suffered a SCI.

KEYWORDS

spinal cord injury, recovery, learning, pain, plasticity, metaplasticity, ionic plasticity

Introduction

The study of the vertebrate central nervous system (CNS) has traditionally focused on the brain, with many adopting a systems approach wherein distinct functional capacities are linked to a particular neural structure. In this view, encoding spatial relations is ascribed to the hippocampus, executive function to the prefrontal cortex, and fear to the amygdala. Often implicit is a form of hierarchical control, wherein higher neural systems in the forebrain integrate sensory signals and organize motor commands that are relayed to lower-level processes in the brainstem and spinal cord, which are charged with faithfully executing the orders (Gallistel, 1980). In this scenario, the spinal cord functions as a conduit, relaying neural

impulses to/from the brain, a capacity linked to the outer band of ascending/descending fibers (white matter). Little heed is paid to the inner region of the spinal cord (the central gray), which is seen as a kind of mechanical switchboard, driving ascending fibers and motoneurons in response to afferent sensory signals, modulated by descending fibers. While the central gray is recognized to have some capacity to organize simple (spinal) reflexes, such as withdrawal from a noxious stimulus, complex behavior, learning, and a sense of time are seen as the province of the brain.

Work by the lead author early in his career took a systems approach akin to that outlined above and characterized spinal cord mechanisms as operating in an unconditioned (unlearned) manner (Grau, 1987a,b; Meagher et al., 1989, 1990; McLemore et al., 1999; Crown et al., 2000). His trainees have systematically deconstructed this view, providing evidence that the spinal cord can learn, time, and integrate signals, yielding behavioral outcomes comparable to those taken as evidence of "cognition" in brain-dependent tasks (Allen et al., 2002; Grau, 2002; Grau et al., 2022). While these observations ran counter to prevailing views in psychology, they paralleled discoveries in the area of physiology, where researchers had recognized decades ago that neural circuits within the spinal cord can organize action and rhythmic behavior (Sherrington, 1906; Brown, 1914; Stuart and Hultborn, 2008). Building on this work, researchers showed that the isolated adult spinal cord could be trained to step and that the brain can induce a lasting change in behavior (a kind of memory) by modifying the action of a spinal circuit (Wolpaw and Lee, 1989; Edgerton et al., 1997; Patterson, 2001a). By the late 1990's, a foundation had been laid, leading a group of us (J. W. Grau, M. M. Patterson, V. R. Edgerton, and J.R. Wolpaw) to organize a small conference to bring together the researchers who had questioned the traditional view of spinal cord function. The talks outlined the foundation for a revised view of spinal cord function, one that recognized the computational power of the spinal cord (Patterson, 2001b). From this view, the processing/integration of sensor signal and the execution of organized motor response is distributed across the nervous system, with local systems governing key functions, yielding a structure that is more heterarchical in nature (McCulloch, 1945; Cohen, 1992). In this paper, we will review these discoveries and provide an overview of what has been subsequently learned, referencing current reviews for additional details.

A key feature of the studies we will review is that the results do more than transform our view of CNS function—the results have clinical import, informing treatment for those who have suffered a spinal cord injury (SCI). The traditional view of the spinal cord suggested a bleak future for those with a SCI. If the system is hardwired, and has little capacity to organize behavior, an injury that cuts communication with the brain leaves little hope for recovery. If, in contrast, spinal cord systems can support key behavioral functions (e.g., stepping) with little input from the brain, discovering how to engage these systems offers some hope for recovery. Likewise, if systems within the spinal cord have some capacity for plasticity, this might be harnessed to encourage the adaptive rewiring of surviving circuits in response to neuronal growth and implants designed to span an injury.

In the sections that follow, we introduce key scientific discoveries and how these have impacted clinical treatment. The material is organized into sections, each of which highlights a particular set of findings, with a focus on those that challenge the traditional view of the spinal cord as an immutable relay of neural signals. While we will endeavor to highlight key findings, the scope of work conducted over the last five decades exceeds what can be reviewed here. For that reason, we will present a more personal perspective and refer the reader to other sources for additional details. We also recognize that readers will have varying backgrounds in key areas, with some having little knowledge of how the spinal cord is organized while others have less background on topics related to learning and memory. To address the former, we begin with an overview of the spinal cord and how it is organized. To address the latter, care is taken to unpack key concepts.

Structure of the spinal cord

Anatomy

The soft tissue of the spinal cord is housed within a bony covering that is broken into segments (vertebrae) that are connected by fibrous tissue (ligaments), allowing for some flexibility (Figure 1A). Anatomists have divided the length of the spinal cord into 4 regions (Martin, 1996). The upper (rostral) region (immediately below the skull) is known as the cervical spinal cord, followed by the thoracic, lumbar and sacral. Within each region, the segments are numbered along the rostral to caudal (tail) axis. For example, C1-C7 for the cervical region and T1-T12 for the thoracic. Between the vertebrae, sensory nerves enter the spinal cord on the dorsal (toward the back) side while motor nerves exit from the ventral (toward the abdomen) side.

A cross-section of the spinal cord reveals two distinct regions: an outer ring of myelinated ascending/descending axons (white matter) and an inner region (gray matter) composed of cell bodies, dendrites, interneurons, and glia (Figure 1B). Unlike the brain, which is largely composed of projection neurons, the central gray is predominantly interneuronal, bolstering its integrative capacity (Hochman, 2007).

Regions of the central gray can be differentiated on the basis of the types of neural input they receive, their axonal projections, cell types, and function, yielding a laminae (layered) structure (Kirshblum et al., 2002). Laminae I to IV lie within the dorsal horn and receive input from cutaneous sensory neurons (Figure 1D). Laminae V-VII lie within the intermediate region; V and VI integrate proprioceptive signals related to movement and limb position, while laminae VII acts as a relay between the midbrain and cerebellum. Laminae VIII and IX lie in the ventral horn and coordinate/drive motor output. Additional subdivisions are suggested by research examining gene expression within the interneurons of the central gray (Jessell, 2000; Lee and Pfaff, 2001; Delile et al., 2019), which has revealed a myriad of distinct cell types that may subserve distinct functions.

Development

Development brings an orderly distribution of fibers within the central gray (Figure 1C). For example, in the ventral region motor neurons innervating proximal muscles lie toward the medial (central) region while those deriving distal muscle groups are distributed in the lateral (side) ventral horn (Kirshblum et al., 2002; Grau et al., 2006). In addition, there is a division of labor across segments of the spinal cord. For example, neurons within the caudal (below L3) lumbosacral

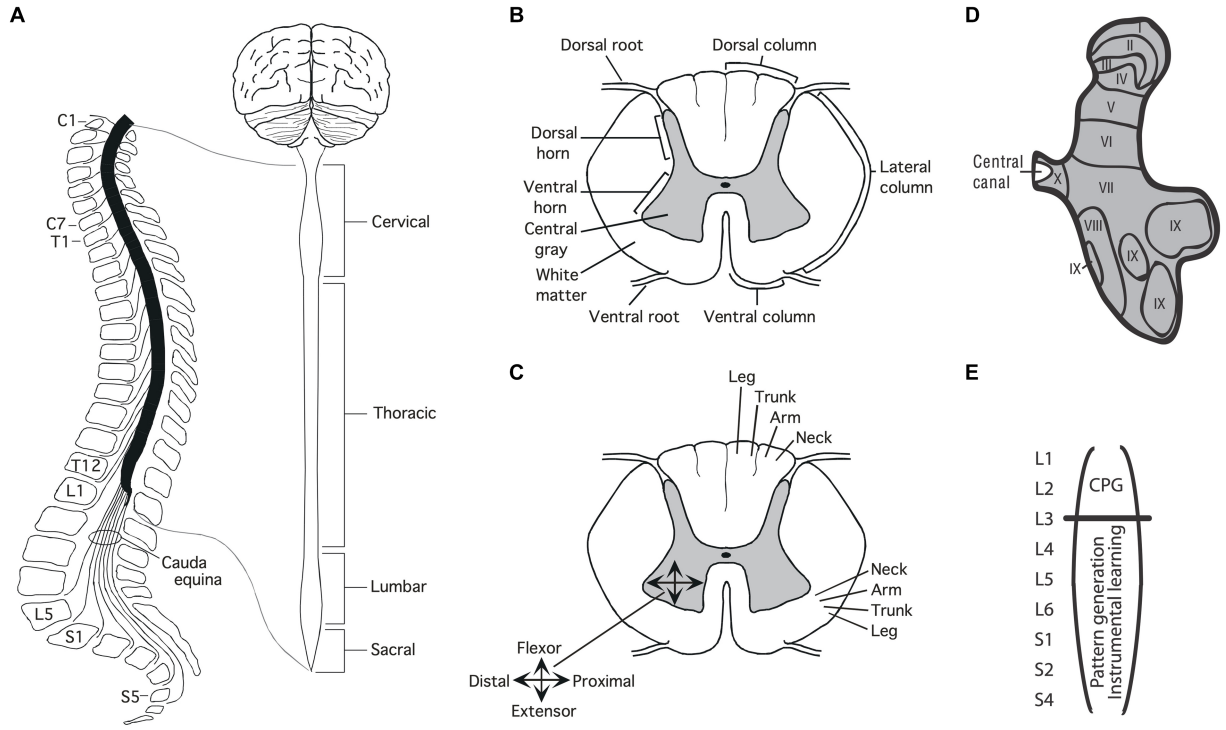

FIGURE 1
Anatomy of the spinal cord. **(A)** Gross anatomy of the spinal cord. Cross-sections of the spinal cord illustrating major structures **(B)**, functional organization **(C)**, and laminae **(D)** Adapted from Grau et al. (2022). **(E)** Research suggests that the central pattern generator (CPG) that drives the rhythm of stepping lies in the rostral lumbar region (L1-L2; Cazalets et al., 1995; Magnuson et al., 1999). The structures needed for instrumental learning, and that underlie the development of a learning deficit after uncontrollable stimulation, lie within the lower lumbosacral (L3-S2) spinal cord (Liu et al., 2005).

region coordinate the motor activity needed to generate lower-limb flexion/extension while neurons in the rostral lumbar (L1-L2) spinal cord contain a neural oscillator [a central pattern generator (CPG)] that drives rhythmic stepping behavior (Grillner and Zangger, 1979; Kiehn and Kjaerulff, 1998; Magnuson et al., 1999; Kiehn, 2006; Pocratsky et al., 2017).

The basic architecture of the spinal cord central gray is laid down early in development, encouraged by diminished gamma-aminobutyric acid (GABA) mediated inhibition (Ben-Ari, 2002, 2014). The neurotransmitter GABA primarily affects neural activity by engaging the ionotropic GABA-A receptor, which allows the anion Cl^- to cross the extracellular membrane (Figure 2). The direction of Cl^- flow depends upon its intracellular concentration, which is regulated by two co-transporters, KCC2 and NKCC1, that control the outward and inward flow of Cl^-, respectively (Kaila et al., 2014; Medina et al., 2014). In the adult CNS, there is a high concentration of membrane-bound KCC2. This moves Cl^- out of the cell, which maintains a low intracellular concentration. Under these conditions, when the GABA-A receptor is engaged, Cl^- flows into the cell, producing a hyperpolarization that inhibits neural firing. But early in development, there is little KCC2 expression, which allows Cl^- to accumulate within the cell. Now, engaging the GABA-A receptor allows Cl^- to flow out of the cell, producing a depolarization that enhances neural excitability. It has been suggested that during early stages of development, this heightened excitation promotes the emergence synaptic circuits (Ben-Ari, 2002, 2014). Later in development, KCC2 expression is up-regulated, which dampens neural excitability, which could help preserve established neural circuits over time. The up-regulation of KCC2 has been linked to the maturation of descending fibers from the brainstem (Viemari et al., 2011).

Neurons within the white matter likewise develop in an orderly manner, laying down ascending/descending fiber tracts that serve distinct functions (Kirshblum et al., 2002). These fibers do more than relay signals to/from the brain; they also relay signals across distinct regions of the spinal cord. For example, the cervical and lumbar regions of the spinal cord are connected by propriospinal neurons that enable the coordination of fore/hind limb movement. Silencing these neurons disrupts left–right limb coupling/coordination (Pocratsky et al., 2020).

Early views of spinal cord function presumed that that axons within the white matter are hardwired in adults with little capacity to change, and unlike peripheral neurons, have little capacity for growth after injury (Patterson, 2001b). Research over the last 25 years has shown that this view is wrong on two counts. First, axons within the white matter demonstrate sprouting in adult animals and can re-innervate the central gray (Fouad et al., 2001; Vavrek et al., 2006). Second, while progress has been slow, researchers have shown that axonal growth can be fostered and produce functional re-innervation (Zheng and Tuszynski, 2023). These studies are complemented by work aiming to replace damaged neurons and glia, to rewire the spinal cord, re-establish the myelin sheath of surviving axons within the

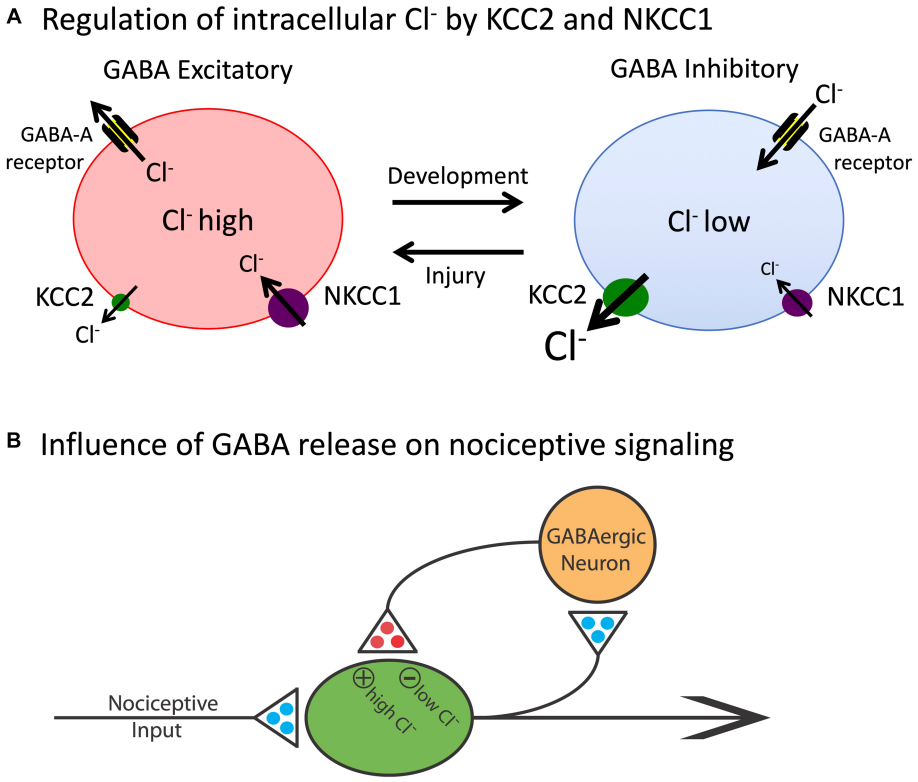

FIGURE 2
The release of GABA can have either an inhibitory (hyperpolarizing) or excitatory (depolarizing) effect depending upon the intracellular concentration of Cl^-. **(A)** The co-transporters KCC2 and NKCC1 regulate the outward and inward flow of Cl^-, respectively. In adult animals (right), the outward flow of Cl^- through the KCC2 channel maintains a low concentration of the anion within the cell. Under these conditions, engaging the GABA-A receptor allows Cl^- to enter the cell, which has a hyperpolarizing effect. Early in development, and after a rostral SCI, the levels of KCC2 are much lower and, as a consequence, there is a rise in the intracellular concentration of Cl^-. Now, engaging the GABA-A receptor allows Cl^- to exit the cell, which has a depolarizing effect. **(B)** Nociceptive stimulation (input) will engage GABAergic neurons within the spinal cord that regulate neural excitability. In adult uninjured animals, the low intracellular concentration of Cl^- will cause GABA to have an inhibitory effect, which will dampen neural excitability. After injury, the reduction in membrane-bound KCC2 would transform how GABA release affects nociceptive circuits, causing it to have a depolarizing [excitatory (+)] effect that could contribute to the development of nociceptive sensitization and spasticity. Excitatory (glutamatergic) transmitters are indicated in blue and inhibitory (GABAergic) transmitters are colored red. Adapted from Grau et al. (2014).

white matter, and use cell implants to replace lost tissue (Fischer et al., 2020).

Peripheral innervation

Peripheral sensory signals are conducted by pseudounipolar neurons that have their cell bodies within the dorsal root ganglia (DRG), with a left/right pair at each vertebral level (Kirshblum et al., 2002). These neurons have two axon-like fibers, one of which projects to the periphery while the other innervates the spinal cord central gray. Myelinated (A) fibers carry signals tied to limb position (proprioception), touch, and fast pain. Unmyelinated (C) fibers transmit signals related to slow, burning, pain. A-fiber function can be further subdivided on the basis of its receptive ending. Sensory neurons can also be distinguished on the basis of chemicals that engage the fiber type. For example, a subset of pain (nociceptive) fibers express the transient receptor potential vanilloid 1 (TRPV1) receptor that is engaged by capsaicin (Willis, 2001), the active ingredient of chili peppers. Research exploring gene expression within sensory neurons has suggested additional subdivisions and provided the methodology needed to selectively engage or inhibit distinct fiber types (Iyer et al., 2016; Cowie et al., 2018; Takeoka and Arber, 2019; Guo et al., 2022; Kupari and Ernfors, 2023).

Skeletal muscles are innervated by motor neurons that have their cell bodies in the ventral horn, with axons that engage muscle contraction through the release of chemical transmitters at the neuromuscular junction (NMJ; Sanes and Lichtman, 2001). Traditionally, the primary transmitter at the NMJ in adult vertebrates has been assumed to be acetylcholine (ACh).

The peripheral nervous system (PNS) also regulates involuntary functions, such as heart rate, blood pressure, and digestion, by innervating smooth muscles and organs. Neurons from the parasympathetic NS, which fosters relaxation after periods of danger, include a number of cranial nerves and projections from the lower (sacral) region of the spinal cord (S2-4; Kirshblum et al., 2002). A state of arousal (fight-or-flight) is driven by the sympathetic component, which projects from the upper thoracic (T1) to the lumbar (L2-L3) segments of the spinal cord to ganglia that form a bilateral sympathetic chain that lies just ventral and lateral to the spinal cord tissue. These ganglia are inter-connected across segments, enabling coordinated output to peripheral processes. Surprisingly little is known about how

signals within the sympathetic chain are coordinated or how they are affected by on-going processes (e.g., injury, inflammation).

Injury

How a physical injury to the spinal cord affects function will depend upon its nature and locus. In the laboratory, researchers often cut (transect) the spinal cord in the upper thoracic (e.g., T2) region to elucidate what lower-level systems within the lumbosacral spinal cord can do minus communication with the brain (Grau et al., 2006). One consequence of a spinal transection is the loss of descending fibers that quell neural excitation, enabling the sensitization of nociceptive activity in the dorsal horn (Sandkuhler and Liu, 1998; Garraway and Hochman, 2001; Gjerstad et al., 2001; Huang et al., 2017; Grau and Huang, 2018). The loss also disrupts the regulation of sympathetic activity, which allows noxious stimulation to drive uncontrolled bouts of sympathetic activity, leading to accelerated heart rate, respiration, and sweating, a phenomenon known as autonomic dysreflexia (Krassioukov et al., 2003; Rabchevsky and Kitzman, 2011; Eldahan and Rabchevsky, 2018). Overtime, this uncontrolled activation of spinal sympathetic circuits worsens, which may be explained in part by the observation that the sympathetic circuity undergoes prolific axonal sprouting and plasticity after SCI (Noble et al., 2018).

While a large proportion of preclinical work is done using rats, key discoveries regarding the organization and function of motor systems have been made with a number of other species, including cats, zebrafish, and the lamprey (Cohen, 1992). In recent years, the development of mice that have distinct genetic anomalies, that enable researchers to selectively disrupt or express particular genes, has fueled the use of this species.

In humans, a complete transection is relatively uncommon, limited to injuries such as gunshot wounds. More commonly, the spinal cord is damaged by a deformation/bruising (contusion injury) that causes an acute tissue loss. The initial damage to the spinal cord initiates a pro-inflammatory cascade (list) that fosters additional tissue loss (secondary injury) over a period of hours to days (Crowe et al., 1997). Naturally, the effect of a contusion injury will depend upon both its severity and locus. A thoracic injury will lead to an insensitivity of stimuli below the waist and an accompanying motor paralysis of the lower limbs (paraplegia). Injuries in the cervical region will disrupt the ability to use the upper limbs, producing a tetraplegia (aka quadriplegia). Because a high-level tetraplegia will affect respiration, individuals may require a ventilator.

Neurons in the spinal cord can coordinate complex behavior

Fifty years ago, most assumed that neural assemblies within the spinal cord can, at most, orchestrate simple reflexive behavior, such as a withdrawal from a noxious stimulus (Ladle et al., 2007). Beyond this, it was known that there was some coordination across limbs. For example, after a thoracic transection, flexion of one hind leg elicits an extension of the contralateral limb (crossed extension reflex; Sherrington, 1906). Likewise, it was known that rhythmic behavior could be elicited by the application of stimuli to the hind limbs in animals that had undergone a rostral transection (Sherrington, 1906). Further analysis showed that alternating flexor-extensor activity can occur without sensory input, implying the existence of a neural oscillator [central pattern generator (CPG)] within the spinal cord (Brown, 1914; Shurrager and Dykman, 1951; Lundberg, 1969). While research in this domain has traditionally characterized CPG activity in terms of a half-center model (Stuart and Hultborn, 2008; Cote et al., 2018), wherein rhythmic behavior is linked to excitatory/inhibitory pools of neurons linked in a reciprocal manner, recent data suggest an alternative view built upon a low-dimensional rotation of neural activity within the spinal cord (Linden et al., 2022).

It was initially assumed that the spinal CPG was a servant of the brain, which regulated its operation through descending fibers. Supporting this, researchers showed that coordinated stepping can be elicited by the local application of a drug (e.g., a noradrenergic agonist) that emulates neural activity in the descending pathway that drives locomotion (Forssberg and Grillner, 1973). From this perspective, while it was acknowledged that the spinal systems organized details of the muscular output, the brain served as the executor. It was within this climate that Rossignol, Edgerton, and their trainees, tried the seemingly impossible—to reestablish the capacity to step in adult spinally transected animals using behavioral training without drug therapy (Forssberg and Grillner, 1973; Grillner and Zangger, 1979; Forssberg et al., 1980; Smith et al., 1983; Edgerton et al., 1992; Hodgson et al., 1994; de Leon and Dy, 2017). Each day, spinally transected cats had their hindlimbs positioned on a treadmill while the upper body was supported. Of course, little hindlimb movement was observed at first, with the hindlegs dragged behind as the treadmill moved beneath. Yet, with some behavioral support (e.g., lifting the hind quarters and/or stimulating the perineum) and weeks of training, the animals slowly recovered the capacity to step. Further, as stepping returned, it adjusted to variation in treadmill speed. Minus input from the brain, or pharmacological intervention, neural systems within the spinal cord could be trained to step. It is presumed here that this training did not "teach" the animals to perform coordinated stepping, but instead reawakened a dormant circuit in the lumbosacral spinal cord.

An interesting feature of the spinal locomotor system is that it can gate afferent stimulation on the basis of step cycle. If the dorsal surface of the hind paw encounters an obstacle as the leg is lifted (swing phase), a flexion is elicited; if the same stimulus is applied while the leg moves rearward (extension), the leg is extended (Forssberg et al., 1977; Forssberg, 1979). And if an obstacle is repeatedly encountered at the same place during the swing phase, the magnitude of the flexion response gets stronger over trials and this effect remains for a number of steps after the obstacle is removed, suggesting a kind of learning (Edgerton et al., 1997, 2004). Such coordinated stepping requires: (1) a CPG with an adjustable frequency; (2) a pattern-formation network to shape the excitatory/inhibitory signals; and (3) the capacity to adapt to a changing environment (Windhorst, 2007). The spinal cord is not a simple reflexive machine.

Subsequent work built on these observations with the hope of fostering the recovery of locomotor performance (de Leon and Dy, 2017). Researchers found that the application of brain-derived neurotrophic factor (BDNF) or serotonin (5HT) to the lumbosacral spinal cord enhances stepping behavior (Rossignol et al., 1998; Lopez-Garcia, 2006; Boyce and Mendell, 2014). So too does electrical stimulation applied to the dorsal (epidural) surface of the spinal cord, an effect that seems related to the activation of afferent neural activity

(Harkema et al., 2011; Angeli et al., 2014; Harkema et al., 2022). Remarkably, epidural stimulation can also enable voluntary movement in humans.

More recent work has revealed that step training can have a therapeutic effect that impacts other pathologies too, for example, counter chronic pain (Cote et al., 2014; Detloff et al., 2014; Tashiro et al., 2015). The benefit of training and exercise has been linked to increased expression of KCC2, which helps re-establish GABA-dependent inhibition. In the dorsal horn, this can counter the sensitization of pain (nociceptive) pathways that drive chronic pain (Huang et al., 2016). In the ventral horn, enhanced inhibition can reduce the over-excitation of motor circuits (spasticity) that often emerges after SCI, which could enable locomotor performance (Boulenguez et al., 2010).

Training can also promote the adaptive rewiring of spinal circuits. A particularly interesting example of this is provided by a paradigm wherein animals receive bilateral hemisections at different regions of the thoracic spinal cord. Each hemisection cuts all ascending/descending fibers for one side of the body; together, all fibers are cut. What is of interest is that an interneuronal bridge can form between the spared fibers from opposite sides, restoring communication across the injury, bringing some recovery of sensory/motor function (Courtine et al., 2008; Courtine and Sofroniew, 2019). The development of this neuronal bridge is encouraged by locomotor training and treatments that help restore GABA-dependent inhibition (Chen et al., 2018).

Brain systems can induce a lasting modification in spinal cord function

It has been known for decades that brain systems can modulate spinal reflexes through descending tracts. This effect can be studied in the laboratory using an electrical analog of the stretch reflex—the Hoffman reflex (H-reflex). Wolpaw and his colleagues trained monkeys to alter the magnitude of the H-reflex by rewarding animals with fruit juice for exhibiting a change (e.g., a stronger) in reflex magnitude (Wolpaw and Lee, 1989; Wolpaw and Carp, 1990). Here, brain-dependent processes encode that there is a relationship between the behavioral response (e.g., exhibiting a stronger H-reflex) and the outcome (fruit juice), a kind of learning known as instrumental conditioning (aka operant learning). With training, they found that animals exhibited a change in H-reflex amplitude, demonstrating regulation of the spinal reflex by brain processes. After extended training, Wolpaw transected the spinal cord rostral to the region that mediates the reflexive response. Remarkably, the alteration in H-reflex magnitude remained, implying that brain-dependent processes can bring about a lasting alteration (memory) in the spinal cord. Interesting, how this spinal memory is laid down appears to depend more on the duration of conditioning than on the number of training trials (Wolpaw, 2018), implying that the modification that underlies the modification of the spinal circuit involves a kind of time-dependent consolidation.

Further evidence that brain systems can induce a lasting modification in spinal cord function comes from work examining the phenomenon of spinal fixation. This was first described by DiGiorgio (1929), who showed that a cerebellar lesion produced a hindlimb postural asymmetry, involving the flexion of one limb and the extension of the other, in anesthetized animals. More interestingly, this brain-injury-induced asymmetry remained after the spinal cord was transected. It was naturally hypothesized that the cerebellar damage induces an alteration in the spinal circuitry through descending fibers. Like other examples of memory, the development of spinal fixation was disrupted by drug treatments that block the NMDA receptor (NMDAR) or protein synthesis (Patterson, 2001b). The NMDA receptor is of interest to those studying learning and memory because activating it requires both presynaptic transmitter release and a strong postsynaptic depolarization (Bliss and Collingridge, 1993; Morris, 2013), providing a form of coincidence detection (a Hebbian synapse). Engaging the NMDAR allows Ca^{++} to flow into the cell, which activates signal pathways that amplify the post-synaptic response to transmitter (glutamate) release (e.g., by trafficking AMPA receptors to the active zone of the synapse; Figure 3). Given many well-studied forms of brain-dependent learning and memory depend upon NMDAR-mediated plasticity, evidence that pretreatment with a NMDAR antagonist blocks the development of spinal fixation suggested a commonality in signal pathways and function—that neurons within the spinal cord are plastic and that this process depends upon neurochemical mechanisms analogous to identified within the brain.

Subsequent work has implicated peripheral processes in the induction of spinal fixation. The first evidence for this came from studies examining the potential role of endogenous opioids. Systemic treatment with drugs that engage the kappa or mu opioid receptor induce a lasting flexion in the left hind leg while administration of a delta opioid agonist produce flexion on the right side (Chazov et al., 1981; Bakalkin, 1989; Bakalkin and Kobylyansky, 1989). Perhaps most surprising, Lukoyanov and colleagues showed that a unilateral brain injury can induce postural asymmetry even when it is preceded by a spinal transection, implying that the alteration in motor behavior does not necessarily depend upon descending fibers (Lukoyanov et al., 2021). They posited that the brain may be impacting spinal cord function by means of a blood borne factor. To explore this possibility, they induced a unilateral brain injury in rats and then collected the animal's serum. When this serum was administered to uninjured rats, it induced a comparable postural asymmetry. An even more remarkable outcome was obtained when pregnant dams were given a unilateral brain injury. Offspring from injured rats exhibited postural asymmetry and this effect too survived a spinal transection (Carvalho et al., 2021). These spinally-mediated alterations have been linked to distinct patterns of gene expression within the spinal cord.

The recognition that spinal circuits are inherently plastic raises a computational problem, because many systems may share a structural component. The hierarchical view of CNS function gains simplicity by assuming lower-level components function in a mechanical manner, assuring that execution of a command reliably elicits a particular motor response. Flexibility in this system was attributed to executive systems within the most rostral regions of the forebrain (e.g., prefrontal cortex). Recognizing that lower-level processes are plastic raises two inter-related problems. First, the higher-level system that evoked the modification would need to adjust the output, to compensate for variation in the vigor of the response elicited by a descending signal. To address this issue, Wolpaw has suggested that behavioral systems seek a form of *negotiated equilibrium* (Wolpaw, 2018). A similar view was suggested by Turvey, who proposed that higher processes "enter into 'negotiations' with lower domains in order

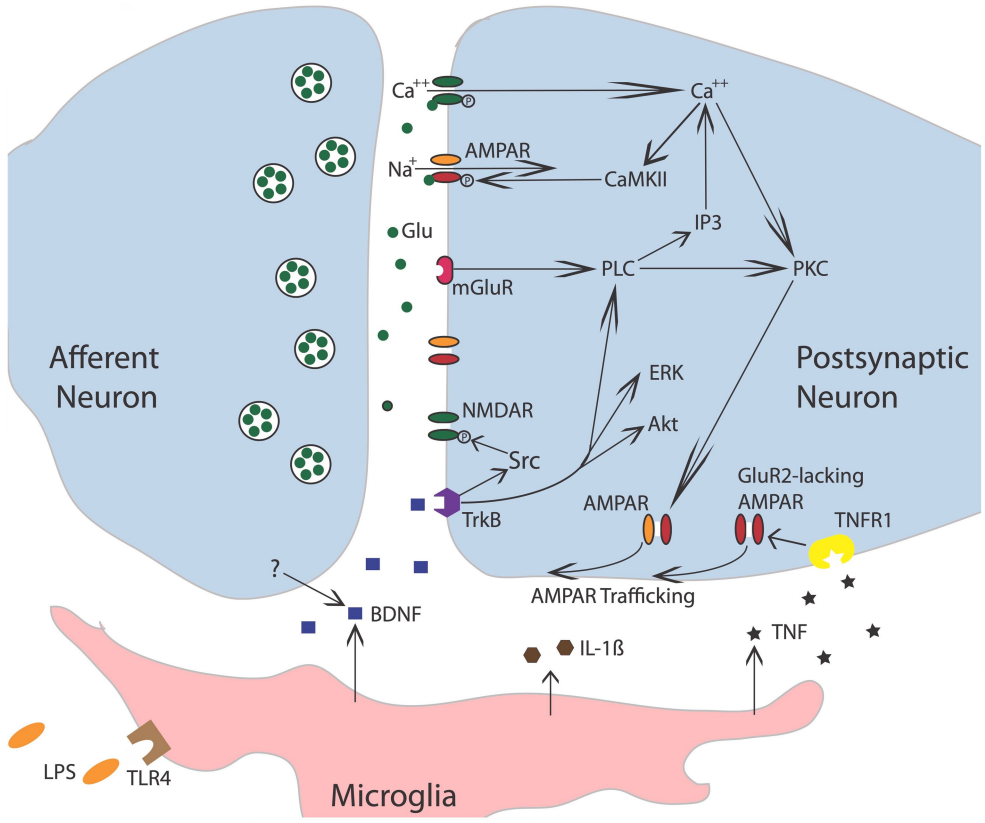

FIGURE 3
Nociceptive stimulation engages neurons within the spinal cord that release the neurotransmitter glutamate (Glu), engaging signal pathways implicated in plasticity. Akt, protein kinase B; AMPAR, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CaMKII, calcium/calmodulin activated protein kinase II; ERK, extracellular signal-regulated kinase; GluR2, glutamate receptor 2; IL-1b, interleukin-1 beta; IP3, inositol 1,4,5-trisphosphate; mGluR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; PKC, protein kinase C; PLC, phospholipase C; TrkB, tropomyosin receptor kinase B; TNF, tumor necrosis factor; TNFR1, TNF receptor 1. Adapted from Grau et al. (2014).

to determine how the higher representation [of an action] shall be stated" (Turvey, 1977; Gallistel, 1980).

The second and more thorny issue stems from the way in which complex behavior is often assembled, with multiple systems sharing common components. Within such a system, a modification that profits the execution of one behavioral process would impact multiple systems, potentially causing a maladaptive consequence. This challenge, together with the recognition that "lower-level" processes may often have considerable computational power, has led some to propose that behavioral processes such as locomotion have an organizational structure that is better described as heterarchical, wherein "each level of the system contributes to the output, and each level helps to shape the final output of the system, and each is shaped in turn by the others" (Cohen, 1992). Here, the structure involves more of a *relative hierarchy* (Gallistel, 1980), wherein the ranking of units is labile rather than fixed, with the order of subordination context dependent.

Building on these views, Wolpaw has suggested the concept of a *heksor*, which he defines as "widely distributed network of neurons and synapses that produces an adaptive behaviour and changes itself as needed in order to maintain the key features of the behaviour" (Wolpaw and Kamesar, 2022). Such a view appears broadly consistent with the behavior systems approach, which is designed to address the flexibility of motivated behavior (Timberlake and Lucas, 1989; Timberlake, 1990; Grau and Joynes, 2001). Timberlake's approach recognizes that aberrant environmental conditions, that enlist incompatible processes, can sometimes cause a kind of mis-behavior to emerge. For example, when a pigeon experiences a colored light paired with grain, conditioning brings about approach to the light. If the light is then presented at a distance from the grain, the pigeon will approach the light even though this has the mal-adaptive consequence of lessening access to grain (Jenkins, 1973). While both Wolpaw and Timberlake assume systems are designed to yield adaptive outcomes, only the behavior systems view recognizes that is not always the case.

Noxious stimulation can sensitize nociceptive fibers in the spinal cord

The prototype of a spinal reflex is the withdrawal response elicited by the application of a noxious stimulus applied to the distal region of an extremity, the *nociceptive withdrawal response* (Ladle et al., 2007). The classic view of this behavior is that it reflects an innate response, that is wired early in development by genetic factors. At a coarse level, this appears to be true, with the expression of trophic factors within the spinal cord guiding the innervation of sensory fibers, so that they connect to the interneurons needed to drive an adaptive withdrawal response (Granmo et al., 2008). However, this early pattern of

innervation reflects a crude/floating somatotopic map, encompassing a diffuse array of connections that has the potential to drive multiple muscles. During early postnatal development (P8-14), the termination pattern is tuned by spontaneous motor activity. This can emerge because spontaneous motor activity produces sensory signals (from skin deformation) that are paired in a Hebbian manner, enabling the selective strengthening of particular sensory-motor connections, a phenomenon known as *somatosensory imprinting* (Petersson et al., 2003; Waldenstrom et al., 2003; Schouenborg, 2008). Interestingly, this tuning can be prevented by pretreatment with a drug that blocks the NMDA receptor (Granmo et al., 2008). Further, in the absence of descending fibers, the tuning is not maintained. Supporting this, a thoracic transection can both prevent and eliminate somatosensory imprinting, increasing the likelihood that a noxious stimulus will elicit an inappropriate approach rather than withdrawal (Schouenborg et al., 1992; Levinsson et al., 1999).

While behavioral studies had shown that stimulus exposure can impact the vigor of a spinal nociceptive reflex, this phenomenon was not extensively studied until the 1990s, when it was recognized that the sensitization of nociceptive pathways in the spinal cord may contribute to the development of chronic pain (Woolf, 1983; Woolf and Thompson, 1991; Willis, 2001; Latremoliere and Woolf, 2009). Nociceptive sensitization develops in response to inflammation or peripheral injury and can bring about an increase in the magnitude of perceived pain (*hyperalgesia*). In addition, there is often an accompanying transformation in the perception of mechanical stimulation, causing a light touch to elicit pain (*allodynia*). These phenomena can be studied in an animal model by applying an irritant (e.g., capsaicin) to one hind paw. To assess the development of an allodynic-like response, plastic monofilaments that vary in thickness/force (von Frey stimuli) are applied to the planter surface of the paw and the stimulus force that engages a withdrawal response is recorded. What is typically found is that treatment with capsaicin enhances reactivity to mechanical stimulation, causing animals to exhibit a withdrawal response to filaments that induce a weak deformation of the skin, below the threshold for engaging nociceptive fibers. Importantly, the amplification of reflexive withdrawal is often accompanied by an enhancement in brain-dependent measures of pain [e.g., a stimulus-elicited vocalization or aversion to an environment (context) that has been paired with mechanical stimulation] (Huang and Grau, 2018). What is remarkable is that the amplification of mechanical reactivity, as measured by a withdrawal response to non-noxious stimulation, is observed in animals that have undergone a rostral spinal transection (Huang et al., 2016), implying that the alteration is due, at least in part, to an intra-spinal modification. Notice here that a change in pain perception arises due to a phenotypic shift in sensory function, that causes signals that normally generate mechanical sensations to elicit pain (Neumann et al., 1996). Contrary to what is sometimes assumed, afferent sensory function is not fixed.

The idea that modifications outside the brain can impact pain processing is supported by electrophysiological studies. Early work had shown that electrical stimulation of sensory fibers at an intensity that engages unmyelinated nociceptive (C) fibers causes a progressive increase in the duration of discharge that fades over the course of minutes (windup; Mendell and Wall, 1965). Subsequent research revealed that a prolonged activation of C-fibers, induced by the application of the TRPV1 agonist capsaicin, inflammation, or nerve injury, can induce a lasting increase in neural excitability (central sensitization) within the spinal cord dorsal horn (Woolf, 1983; Woolf and Thompson, 1991; Willis, 2001; Latremoliere and Woolf, 2009). Subsequent cellular work linked the modification of nociceptive circuits in the dorsal horn to neurochemical systems analogous to those known to underlie learning and memory in the brain (Ji et al., 2003; Figure 3). For example, inducing a lasting modification depends upon the NMDA receptor and an increase in AMPA receptor-mediated excitation. At a cellular level, the neural over-excitation is accompanied by enhanced expression of the immediate early gene *c-fos* and the activation (phosphorylation) of extracellular signal-regulated kinase (ERK). And like many examples of brain-dependent synaptic plasticity, the development of nociceptive sensitization is regulated by BDNF (Pezet et al., 2002; Merighi et al., 2008; Smith, 2014; Huang et al., 2017). Further parallels have been identified by Sandkuhler and his colleagues, who showed that electrical stimulation of nociceptive fibers can induce a form of long-term potentiation (LTP), and that this effect too is blocked by pretreatment with an NMDAR receptor antagonist (Liu and Sandkuhler, 1997; Liu et al., 1998; Sandkuhler and Liu, 1998; Sandkuhler, 2000).

Further work has shown that neural excitability within the dorsal horn is regulated by serotonergic fibers that descend through the dorsolateral funiculus (DLF), which dampen neural excitability by engaging the 5HT-1A receptor, inhibiting the development of nociceptive sensitization and spinally-mediated LTP (Gjerstad et al., 1996; Liu and Sandkuhler, 1997; Sandkuhler and Liu, 1998; Crown and Grau, 2005). Supporting this, bilaterally cutting fibers in the DLF at the thoracic level fosters the development of enhanced mechanical reactivity after capsaicin treatment and increases the expression of cellular indices of nociceptive sensitization in the dorsal horn (e.g., c-fos and pERK; Ji et al., 1999, 2003; Latremoliere and Woolf, 2009). Clinically, the observations imply that a SCI that damages these descending fibers would foster nociceptive sensitization and the development of chronic pain.

More recent work has revealed that SCI enables the development of nociceptive sensitization within the spinal cord by reducing GABAergic inhibition (Huang et al., 2016). As noted above, SCI reduces the expression of the co-transporter KCC2 caudal to injury. This reduces the intracellular Cl^- concentration, which attenuates the hyperpolarizing (inhibitory) effect of GABA, removing a brake on neural activity that fosters neural excitation. This alteration in GABA function can be countered by pharmacological treatments that lower the intracellular concentration of $Cl^-$and by application of drugs that engage the 5HT-1A receptor, which up-regulates the expression of KCC2 (Huang and Grau, 2018). Likewise, as noted above, training and exercise can up-regulate KCC2 expression, which counters the development of chronic pain after SCI (Cote et al., 2014; Tashiro et al., 2015).

Interestingly, in the absence of SCI, local inflammation within the spinal cord can also induce a depolarizing shift in GABA that fosters nociceptive processing. This effect appears linked to the activation of microglia and the release of BDNF, which reduces KCC2 expression in uninjured animals (Coull et al., 2005; Lu et al., 2009; Beggs and Salter, 2013). Here the effect of BDNF is opposite to what has been reported after SCI, where BDNF has been shown to increase KCC2 expression caudal to injury and counter the development of nociceptive sensitization (Huang et al., 2017). These divergent effects have been linked to the activation of the TrkB receptor by BDNF and

the downstream engagement of Shc, which can impact KCC2 expression in opposite ways depending on levels of phospholipase C-γ (PLC-γ; Rivera et al., 2004, 2005). When PLC-γ is present, Shc down-regulates KCC2. However, in the absence of PLC-γ, engaging Shc increases KCC2 expression. Because PLC-γ levels are high in uninjured adult animals, BDNF-induced Shc signaling will cause a reduction in KCC2 expression, bringing an increase in neural excitability that would foster nociceptive sensitization. SCI reduces PLC-γ, which would transform how BDNF affects KCC2 expression. Now, engaging Shc signaling would up-regulate KCC2 expression, re-establishing GABA-dependent inhibition and quelling neural excitation. Interestingly, locomotor training may re-establish GABAergic inhibition because it increases the expression of PLC-γ (Tashiro et al., 2015).

Just as those studying the brain have often assumed that systems within the spinal cord are fixed, those exploring spinal cord plasticity have sometimes assumed sensory fibers behave in a mechanical manner, with the afferent input reliably tied to the extent of injury. Recent findings suggest that this view too needs to be updated—that nociceptive sensitization after SCI may be attributable, in part, to the sensitization of afferent nociceptive neurons (Yang et al., 2014; Walters et al., 2023). As noted above, the cell bodies of afferent neurons are contained within the DRG, which lie proximal to the spinal cord tissue within the epidural space. Under natural conditions, the sensory fibers designed to detect tissue damage/injury would only be engaged by peripheral events—because damage to the spinal cord would be lethal. SCI sets up a non-natural situation wherein the central projections innervate damaged tissue, which can engage retrograde signals that activate the sensory neuron, causing these neurons to exhibit on-going spontaneous activity (at about 1 Hz). This aberrant activity could drive pain circuits in the spinal cord in the absence of peripheral damage, to foster neuropathic pain (Bedi et al., 2010; Yang et al., 2014; Walters, 2018; Walters et al., 2023). The activity could also fuel the development of LTP, amplifying the elicited response. These changes have been shown to be persistent, with on-going activity observed in TRPV1 sensitive neurons weeks after SCI. Further, because the extracellular signals related to injury are diffusely distributed, aberrant activity may arise in adjoining regions, fostering both above-level and below-level pain. Support for this general view comes from studies demonstrating that the development of spontaneous activity within DRG nociceptive neurons is correlated with behavioral indices of neuropathic pain (Bedi et al., 2010). More importantly, silencing a voltage gated Na^+ channel (Nav1.8) that is exclusively expressed on nociceptive afferents attenuates both the development of spontaneous activity and behavioral signs of neuropathic pain after SCI (Yang et al., 2014).

Neurons within the spinal cord are sensitive to stimulus–stimulus relations

The findings reviewed above show that engaging nociceptive fibers can sensitize neural excitability within the spinal cord, a modification that enhances behavioral reactivity and pain signaling. Because noxious stimulation has a lasting effect, and is attributable to a single event, it constitutes an example of single stimulus (non-associative) learning (Grau, 2014; Grau et al., 2020). Bolstered by data demonstrating that this effect is mediated by signal pathways implicated in brain-dependent memory (Ji et al., 2003), the phenomenon is widely accepted and recognized to have implications for the treatment of chronic pain (Latremoliere and Woolf, 2009). What has proven more controversial is whether the spinal cord can encode an environmental relation, either between two stimulus events (*Pavlovian conditioning*) or a response and an outcome (*instrumental conditioning*). As we will see, this controversy arose in large measure because learning has been historically couched in associative terms, a process most assume requires a brain (Grau et al., 2022).

Prior to initiating his classic studies detailing the role of the cerebellum in learning (Thompson, 1986), the neurobiologist Richard Thompson and his students explored whether neural processes within the spinal cord could support a simple form of Pavlovian conditioning (Thompson, 2001). With P. Groves, Thompson had previously detailed the circumstances under which stimulation causes a spinal reflex to decline (habituate) or grow stronger (sensitize), laying the foundation for the dual process model of these phenomena (Groves et al., 1969; Groves and Thompson, 1970; Patterson, 2001a; Thompson, 2001). To examine whether spinal neurons are sensitive to stimulus–stimulus (S-S) relations, stimuli were applied below the waist in animals that had undergone a thoracic transection. Weak stimulation to the saphenous nerve was used for the to-be-trained cue [the conditioned stimulus (CS)], which initially generated a weak flexion response (Figure 4A). This CS was paired with more intense stimulation of the peroneal nerve, which generated a robust unconditioned (unlearned) flexion response prior to training and served as the unconditioned stimulus (US). They found that pairing the events endowed the CS with the capacity to elicit a stronger flexion response [the conditioned response (CR)], relative to animals that experienced the CS and US in an explicitly unpaired manner. Importantly, the training had a lasting effect and group differences were evident when animals were tested under common conditions, demonstrating that mechanisms caudal to the spinal transection are sensitive to S-S relations. Further work showed that learning depends upon the temporal order in which the stimuli were presented, with a forward CS→US relation yielding learning while a backward (US→CS) relation did not, and that presentation of the trained CS alone causes the learned response (CR) to wane (extinction; Durkovic, 2001). And here too, pretreatment with a NMDA receptor antagonist disrupts learning (Durkovic and Prokowich, 1998).

Subsequent studies showed that introducing a S-S relation also affects how spinal neurons process nociceptive signals. In uninjured animals, a cue (the CS+) that has been paired with a noxious shock (the US) produces an inhibition of nociceptive processing (an antinociception) relative to a cue (the CS-) that was never paired with the US (Fanselow, 1986). In intact animals, this conditioned antinociception is mediated by brain processes, which can inhibit nociceptive processing within the spinal cord through descending pathways (McNally et al., 2011). This conditioned antinociception is often assessed by recording the latency to exhibit a spinal nociceptive reflex, tail withdrawal from a thermal stimulus (the tail-flick test). Using this test, we examined whether a conditioned antinociception could be established without input from the brain, in rats that had undergone a thoracic (T2) transection (Joynes and Grau, 1996). Weak stimulation to one hind leg, at an intensity that induced a moderate antinociception, served as the CS and was paired with an intense tail-shock (the US). After 30 trials of training, the paired CS (CS+) elicited antinociception relative to a cue that was presented an equal number

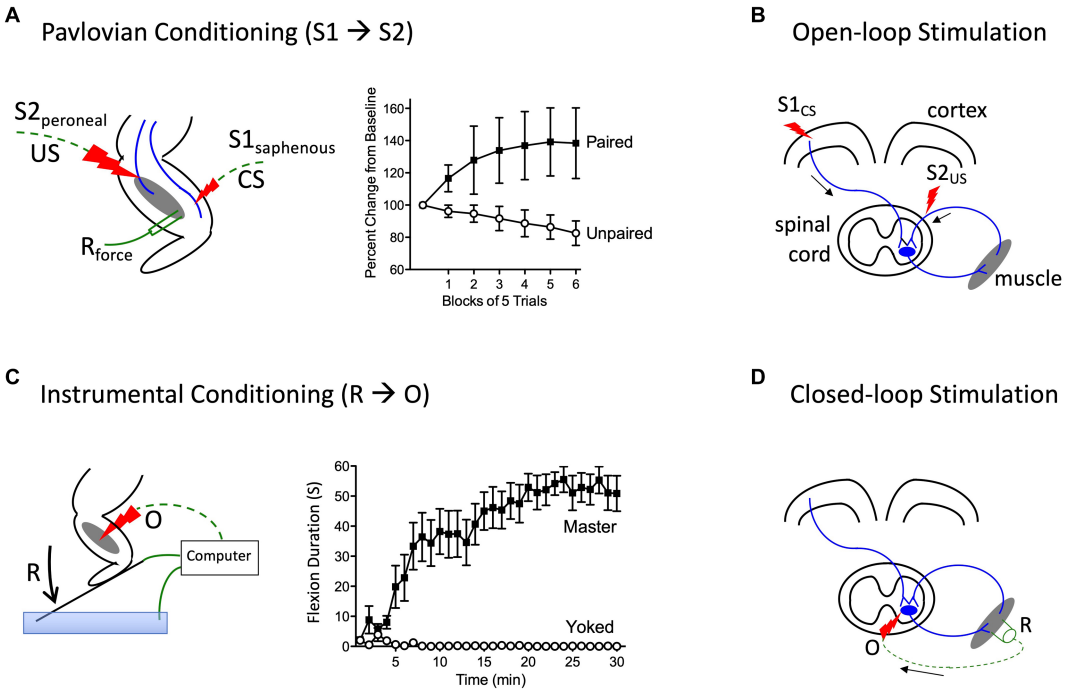

FIGURE 4
Methods for instituting a Pavlovian (S1→S2) and instrumental (R→O) relation. **(A)** In rats that have received a rostral (T2) transection, pairing electrical stimulation of the peroneal nerve [S2; the unconditioned stimulus (US)] with weak stimulation of the saphenous nerve [S1; the conditioned stimulus (CS)] amplifies the response elicited by S1 relative to animals that experience S1 and S2 in an unpaired manner (Durkovic, 2001). **(B)** Electrical stimulation of the motor cortex (S1) can engage surviving descending (corticospinal) fibers after SCI. Pairing S1 with epidural stimulation, which engages sensory afferents, in a Pavlovian manner (open-loop stimulation) enhances motor performance after SCI (Harel and Carmel, 2016). **(C)** Spinally transected rats (Master) that receive noxious electrical stimulation of the tibialis anterior muscle [the outcome (O)] whenever the leg is extended [the response (R)] exhibit a progressive increase in flexion duration that reduces net exposure to the noxious stimulus. Animals that receive stimulation independent of leg position (Yoked) do not exhibit a change in flexion duration (Grau et al., 1998). **(D)** An instrumental (R-O) relation can also be established using electrophysiological methods (closed-loop stimulation). For example, after SCI, surviving corticospinal neurons can evoke a small evoked (electrical) muscular response (the R). Stimulating the motor neurons (the O) when a R is detected can strengthen motor performance after SCI (McPherson et al., 2015). Error bars indicate the standard error of the mean.

of times in an explicitly unpaired manner (the CS−), providing further evidence that neurons within the spinal cord are sensitive to S-S (Pavlovian) relations.

We then went on to explore whether the system could support a number of phenomena traditionally accounted for in terms of attention. For example, it is known that pre-exposure to the CS alone prior to training undermines the development of a conditioned response, a phenomenon known as *latent inhibition* (Lubow, 1973). Likewise, when animals experience a stimulus compound composed of cues that differ in noticeability (salience), learning about the more salient cue typically *overshadows* learning about the weaker stimulus (Pavlov, 1927). We found that presenting a CS alone prior to training, or in compound with a more salient cue, attenuated conditioning in spinally transected rats, providing evidence for both latent inhibition and overshadowing (Grau et al., 1990).

More recent work has used a form of stimulus–stimulus learning to promote motor performance after SCI by pairing epidural stimulation with activity in descending motor pathways (Figure 4B). In rats this can be achieved by applying electrical stimulation over the cervical dorsal root entry zone at an intensity that is subthreshold for eliciting a forelimb response (Mishra et al., 2017). Descending fibers can be engaged by electrically stimulating the cortex at a site that elicits a motor evoked potential (MEP) within the bicep. Instituting this S-S (Pavlovian) relation, which engineers refer to as *open loop* stimulation, amplifies the MEP. Importantly, the effect becomes stronger with repeated pairing and has a lasting effect. It was posited that pairing mattered because it engages a form of *spike-timing dependent plasticity* within the spinal cord (Dan and Poo, 2004). An analogous effect has been induced in humans by activating descending fibers in the corticospinal pathway using transcranial magnetic stimulation (TMS) to engage the cortical region that innervates the leg (Urbin et al., 2017). When TMS was paired with activity in the common peroneal nerve, it amplified the MEP elicited by cortical stimulation. Interestingly, evidence suggests that this example of S-S learning also depends upon a form of NMDAR-mediated plasticity (Donges et al., 2018).

Neurons in the spinal cord are sensitive to response-outcome relations

Other studies have provided evidence that neural systems within the spinal cord are sensitive to response-outcome (R-O) relations (Grau et al., 1998). This was shown using rats that had undergone a thoracic (T2) transection. Electrical stimulation (shock) was then

applied to the tibialis anterior muscle at an intensity that elicited a flexion response (the R). Animals in one group (master) received shock (the O) whenever the leg was extended (Figure 4C). Animals in a second group were experimentally coupled (yoked) to rats in the master condition and received stimulation at the same time, but unrelated to limb position (uncontrollable shock). Application of *response-contingent* (controllable) shock to master rats caused a gradual increase in flexion duration. Animals in the yoked condition exhibited a mechanical response to shock, but did not exhibit an increase in response duration—the index of learning. Importantly, training with controllable shock induced a lasting increase in flexion duration that was evident when animals were tested under common conditions. Further analysis revealed that the change in flexion duration was reinforced by the onset of shock, not its offset (Grau et al., 1998).

The key difference between the master and yoked animals is that the former receives shock when the leg reaches a particular position. The fact that only response contingent shock produces a change in response duration implies that the consequence of shock is modulated by cues related to limb position—proprioceptive cues that indicate either the leg angle (muscle length) or a vector that describes the momentary change in limb position at the time of shock onset (Grau et al., 2012). In either case, learning (the increase in response duration) emerges when the noxious stimulus occurs in a regular (the same) proprioceptive context. As we have noted elsewhere (Grau et al., 2012, 2022), an implication of this analysis is that a response-outcome relation (limb position at the time of shock onset) can be inferred from sensory cues, allowing the organism to *directly perceive* the relation between proprioceptive cues indicative of body location (the response) and the onset of noxious stimulation (the outcome; Gibson, 1979). To appreciate this, consider the feedback associated with tapping one's finger against a table. The outcome (mechanical feedback related to hitting the table) occurs in a regular proprioceptive context (the downward movement of the finger), allowing the immediate perception of the relation. This account contrasts with a more cognitive view that presumes that the events (the R and the O) that underlie instrumental learning are independently transmitted to the brain, which then derives the underlying (R-O) relation.

At a neurochemical level, spinally-mediated instrumental learning depends upon a form of NMDAR-mediated plasticity, which is modulated by BDNF (Allen et al., 2002; Joynes et al., 2004; Gomez-Pinilla et al., 2007). Further, the strength of the learned response is positively correlated with cellular indices of synaptic plasticity (e.g., CaMKII, CREB, and synapsin I expression).

Above, we described how a form of Pavlovian conditioning (open-loop stimulation) can be used to promote rehabilitation after SCI. An alternative procedure (*closed-loop stimulation*) builds on a form of instrumental conditioning by instituting a R-O relation (Figure 4D). For example, McPherson assessed whether this type of training would benefit recovery of forelimb function in rats that had received a cervical injury (McPherson et al., 2015). A tractable R was obtained by monitoring electromyographic (EMG) activity within a muscle of the impaired limb. When EMG activity (the R) was detected, an electrical pulse (the O) was applied to the cervical spinal cord at a site that drove motor behavior. This R-O training fostered behavioral recovery and had a lasting effect that was evident weeks after training was terminated. Again, the learning was related to a form of spike-timing-dependent plasticity that fostered synaptic connectivity between surviving corticospinal fibers and motoneurons.

A neurofunctionalist account of learning

Evidence that neural systems within the spinal cord can encode environmental relations was met by researchers within the field of learning with some skepticism, forcing those studying spinal cord plasticity to lay out the defining criteria for learning and address alternative interpretations of the results (Joynes and Grau, 1996; Grau et al., 1998; Grau and Joynes, 2001; Grau, 2014). Two issues proved central: (1) does the experience (training) have a lasting effect; and (2) are the consequences of training evident when animals are tested under common conditions? For both Pavlovian and instrumental learning, these criteria have been met (Grau, 2014; Grau et al., 2020, 2022).

Those seeking to preserve a brain-centric view of learning may acknowledge spinal cord systems are sensitive to environmental relations, but deny that this reflects a form of associative learning, suggesting instead that the learning involves a modification of a pre-existing response tendency rather than a *de novo* association (Grau et al., 2022). The implicit claim is that *true learning* is associative in nature. From this perspective, simple invertebrates and neurons in the spinal cord may be sensitive to Pavlovian and instrumental relations, but this learning depends upon simpler processes that are built upon pre-existing response tendencies. The conclusion is that these examples of learning do not represent a challenge to the traditional view that associative learning requires a brain.

While there are a number of issues lurking here, the core complaint is tied to the formation of a *de novo* link (Gormezano and Kehoe, 1975). From this view, associative learning enables organisms to build a storehouse of knowledge encoding new environmental relations—to build a model of the world. To study this process, researchers have sought paradigms wherein the events have no pre-existing tendency to elicit the to-be-trained behavior. For example, an auditory cue (a tone) may be paired with an air-puff to one eye, establishing a conditioned response (eyeblink) to the tone. Here it is suggested that the tone had no discernable behavioral effect prior to training, implying the learning involved the formation of a new link. As detailed elsewhere (Grau et al., 2022), a problem with this approach is that further probing routinely reveals that the presumably "neutral" CS has some capacity to elicit the to-be-trained response. Indeed, current neurobiological accounts of eyeblink conditioning, the prototype of *associative* learning, assume that the CS-US link is biologically prepared (by a pre-existing connection within the cerebellum; Thompson, 1986).

Likewise, while learning to press a bar (the R) for food (the O) may appear an arbitrary relation for a rat, further analysis has revealed that this example of instrumental learning is built upon pre-existing response tendencies (Timberlake and Lucas, 1989; Timberlake, 1990). Observations such as these suggest that the ideals of associative learning may be seldom achieved in studies of animal learning. Of course, there is considerable variation in the extent to which biological preparedness constrains learning and it is true that learning within the spinal cord is highly prepared. Conversely, forms of learning mediated by the hippocampus, which

can encode relations across gaps in time, a spatial map, and what, when, and where an event occurred (episodic memory), are much less constrained. But none of this necessarily implies a qualitative change in the underlying processes. Indeed, at a neurochemical level, commonality appears the rule (Ji et al., 2003; Latremoliere and Woolf, 2009).

While common neurobiological processes may be involved, how the consequent circuits support learning can differ. The assumption here is that the same environmental puzzle (e.g., encoding a stimulus–stimulus relation) may be solved in multiple ways, by systems that have distinct functional properties (Grau and Joynes, 2005a,b). For example, pairing a CS with a US can alter a CS elicited response by slowing the rate of habituation to the CS (protection from habituation), enhancing a pre-existing CS-elicited response (pairing-specific enhanced sensitization), or build upon a new neuronal connection (associative learning; Figure 5). While each mechanism may be governed by some common rules (e.g., a dependence on contiguity, stimulus competition), the underlying processes can be distinguished at a functional level (e.g., by comparing the magnitude of the CR elicited by the trained CS to a cue that is novel). Likewise, there is considerable evidence that R-O relations can be encoded in multiple ways, with learning in some situations reflecting the modification of a pre-existing stimulus–response (S-R) habit and in others a goal directed response that depends upon the current value of the outcome (Domjan, 2015). We have suggested that this diversity in process is best handled by first recognizing that Pavlovian and instrumental conditioning reference the environmental relations that support the learning and that, at a functional level, these relations can be encoded in multiple ways. Here it is assumed that no process is superior to the rest, a view that runs counter to the notion that *true* learning is associative in nature. At a neurobiological level, the processes may often share common elements, but their relative contribution and how they are assembled is assumed to vary. In some cases, the development of a CR may be largely accounted for by an increase in transmitter release from the presynaptic neuron whereas in others, an enhancement in the post-synaptic response could underlie the learning. By identifying how the CNS encodes the events at a functional level, we gain additional insight into how the process operates. By recognizing that the same relation can be encoded in multiple ways, this *neurofunctionalist* approach embraces the diversity of biological solutions (Grau and Joynes, 2005a,b).

Learning can induce a peripheral memory

We noted above that early work on nociceptive sensitization focused on the enhancement of neural excitability within the dorsal horn and that more recent work has challenged this view by showing that peripheral alterations within the DRG contribute to the increase in neural excitability. Likewise, new findings suggest that researchers may have underestimated the peripheral contribution to some examples of motor learning. Here, the usual assumption was that training alters the efferent motor output from neurons in the ventral dorsal horn. From this view, the application of response-contingent (controllable) shock to a hind leg of a spinally transected rat produces an increase in flexion duration because it increases the efferent drive from motor neurons. Here it was implicitly assumed that peripheral changes contribute little to the behavioral modification. This fits with the general assumption that the elicitation of a muscle response at the NMJ is over-determined, to assure a behavioral response is reliably triggered given motoneuron activity. Building on these assumptions, we sought to identify the intraspinal processes that maintain a prolonged flexion (Hoy et al., 2020). Preliminary work revealed that the application of drugs targeting signal pathways implicated in memory had surprisingly little effect. Given this, we decided to verify our method for applying a drug to the spinal cord through an intrathecal (i.t.) catheter was effective. To confirm this, we administered an anesthetic, the Na^+ channel blocker lidocaine. We had previously shown that pretreatment with lidocaine blocks the acquisition of a spinally-mediated instrumental response (Crown et al., 2002a), which is not surprising given the drug disrupts the performance of a spinal reflex (e.g., tail withdrawal from radiant heat) within minutes of application (Hoy et al., 2020). But when the drug was applied after 30 min of instrumental training, it had no discernable effect on the maintenance of the behavioral response. Likewise, cutting efferent fibers to the muscle, by transecting the sciatic nerve, blocked learning but not the maintenance of the behavioral response. Even removing the region of the spinal cord between L3 and S3, which has been shown to mediate instrumental learning (Liu et al., 2005), had no effect on the maintenance of the behavioral response. Together, the results suggested that motor output from the spinal cord contributed little to the maintenance of the flexion response.

Neurochemical transmission at the NMJ depends upon acetylcholine (ACh; Sanes and Lichtman, 1999, 2001). To verify that

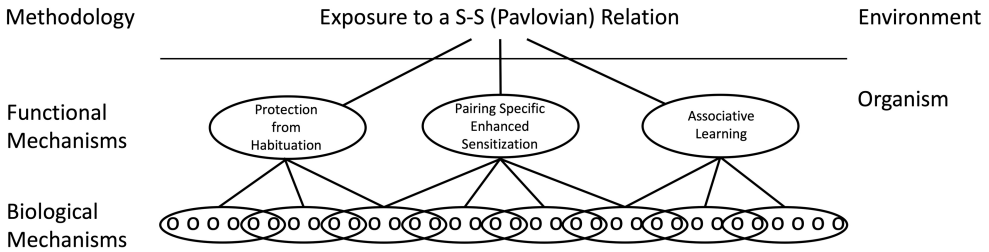

FIGURE 5
A neural-functionalist perspective on Pavlovian conditioning. It is assumed that environmental relations can be encoded by multiple mechanisms within the organism, which can be distinguished by their functional properties. It is likewise assumed that a functional mechanism can be neurally encoded in multiple ways and that a particular biological mechanism (e.g., NMDA receptor-mediated plasticity) can be enlisted by multiple processes. Adapted from Grau and Joynes (2005a).

the maintenance of the behavioral response depended upon ACh release, rather than a tonic intramuscular process (latch) that maintained contraction, spinally transected rats were trained for 30 min and then the ACh receptor antagonist curare was applied to the muscle (Hoy et al., 2020). Curare caused the behavioral response to quickly wane, implying a dependence upon ACh release. Further work showed that the learning increased the evoked electrical (electromyography [EMG]) response within the tibialis anterior and that this effect survived a sciatic cut. Confocal microscopy revealed that training increased fluorescent labeling of the ACh receptor, implying an up-regulation that would amplify the elicited response.

We posited that efferent motoneuron output during training, in conjunction with electrical stimulation of the muscle, may strengthen synaptic efficacy at the NMJ in a Hebbian (pairing based) manner. Supporting this, paired stimulation of the efferent nerve and muscle induced an increase in flexion duration without input from the spinal cord (Hoy et al., 2020). Other work suggests that the release of glutamate may also contribute to depolarization at the NMJ. Using immunohistochemical techniques, both vesicular glutamate transporters and the NMDAR have been shown to be present at the NMJ in adult vertebrate skeletal muscles (Mays et al., 2009; Malomouzh et al., 2011). Given this, we examined the effect of applying the NMDAR antagonist MK-801 to the muscle. We found that the drug disrupted both the acquisition and the maintenance of the behavioral response, implying that NMDAR-mediated plasticity plays a role (Hoy et al., 2020).

These results are consistent with a growing body of work that over-turns some long held views regarding NMJ function in adult vertebrates. One is that muscle memory is a myth—that training does not affect the strength of the synaptic connection at the NMJ, which is designed to function well above threshold to assure a muscular response is reliably elicited. While this may be generally true, it does not mean that plastic potential disappears after the system matures. Prolonged execution of a specific response can increase synaptic efficacy enabling contraction with lower transmitter release. In many regards, this conclusion is not surprising, given that the selection of NMJ's during development depends upon a competitive process linked to coordinated activity (Personius and Balice-Gordon, 2000). Secondly, the work calls into question the standard view of neurochemical communication at the NMJ in a mature vertebrate, which was assumed to depend upon ACh alone. Early in development, and in invertebrates, glutamate plays a pivotal role at the NMJ (Personius et al., 2016). Given this, it should not be surprising that glutamate continues to play a functional role in adult vertebrates.

Engaging plasticity impacts plastic potential (metaplasticity) within the spinal cord

To demonstrate learning, it is important to show that training has a lasting effect, that is evident when animals are tested under common conditions (Rescorla, 1988). To address this issue in our instrumental learning paradigm, we tested spinally transected rats that had received either controllable (master) or uncontrollable (yoked) stimulation for 30 min with response contingent shock (Grau et al., 1998). We also included a group that had been set-up in the same manner, but never received stimulation (unshocked). We found that animals that had received controllable stimulation re-acquired the behavioral response faster than the naïve group, demonstrating a savings effect indicative of learning. Our assumption was that the yoked animals would show no evidence of savings and learn at a rate comparable to the previously unshocked group. Contrary to our expectations, animals that had received uncontrollable shock exhibited a shock-elicited flexion, but not an increase in flexion duration—our index of learning. It appears that prior exposure uncontrollable shock induced a learning impairment, an effect reminiscent of the phenomenon of learned helplessness (Maier and Seligman, 2016).

Further work showed that a relatively brief period of uncontrollable stimulation (6 min of intermittent shock provided on a variable schedule) has a lasting effect that blocks learning when animals are tested with response-contingent shock 24 h later (Crown et al., 2002b). Further, the deficit reflects a general effect on plastic potential, impairing the capacity to learn after uncontrollable stimulation is applied to the opposite leg or even the tail. We posited that uncontrollable stimulation might impair learning because it sensitizes nociceptive circuits in the dorsal horn, producing a diffuse state of over-excitation that saturates plasticity. Supporting this, treatments that induce nociceptive sensitization (e.g., peripheral treatment with capsaicin) produce a learning impairment (Ferguson et al., 2006). Further, like capsaicin, uncontrollable shock enhances reactivity to mechanical stimulation applied to the hind paws. This over-excitation has been linked to the expression of the pro-inflammatory cytokine tumor necrosis factor (TNF) and an upregulation of Ca^{++} permeable AMPA receptors (Huie et al., 2012a, 2015). The long-term effect of uncontrollable stimulation depends upon protein synthesis and NMDAR-mediated plasticity (Patton et al., 2004; Ferguson et al., 2006). Interestingly, like the learning impairment observed after uncontrollable stimulation in intact rats, the spinally-mediated deficit is reversed (temporarily) by administration of the opioid antagonist naltrexone (Joynes and Grau, 2004; Washburn et al., 2008). We have also recently discovered that the adverse effect of noxious stimulation is gated by limb position; noxious shock and capsaicin induce a learning impairment if given while the hind legs are extended, but not if the legs are maintained in flexed (protective) position (Hudson et al., 2022). It appears that the proprioceptive context modulates how noxious stimulation affects spinal cord function.

If spinally transected rats are given controllable shock prior to uncontrollable stimulation, no learning impairment is observed (Crown and Grau, 2001). Conversely, administration of controllable shock (in compound with an opioid antagonist) eliminates the learning impairment. Exposure to controllable stimulation also counters the learning impairment and enhanced mechanical reactivity produced by peripheral application of capsaicin (Hook et al., 2008). These restorative effects have been linked to the expression of BDNF (Huie et al., 2012b).

Taken together, the results imply that controllable and uncontrollable stimulation have opposing effects on spinal cord plasticity, the former enables learning while the latter disables it. In both cases, learning affects future plastic potential, a kind of plasticity of plasticity (metaplasticity; Abraham and Bear, 1996; Abraham, 2008; Grau et al., 2014; Grau and Huang, 2018).

Spinal cord neurons have a sense of time

Having shown that exposure to uncontrollable intermittent stimulation impairs spinal cord plasticity, we sought to identify the circumstances under which this effect develops. When we compared intermittent stimulation to continuous, we found that only the former induced a learning impairment (Crown et al., 2002b). Indeed, concurrent exposure to continuous stimulation has a protective effect that blocks the induction of the learning impairment by intermittent stimulation. Given the stimulation must be intermittent, we then set out to elucidate the stimulus frequency and intensity that has an adverse effect. We found that the deficit emerges at an intensity that engages unmyelinated pain (C) fibers (Baumbauer et al., 2008). To explore the effective frequency range, we modified the computer program used to generate uncontrollable stimulation. Our usual procedure applied brief (100 msec) shocks on a variable time (VT, 0.2–3.8″) schedule, with shocks spaced an average of 2 s apart (0.5 Hz). Recognizing that it would be easier to manipulate stimulus frequency if the interval between the stimuli was fixed, we examined the effect of administering intermittent shock for 6 min (180 shocks) in a regular (fixed time [FT]) or variable time (VT) fashion. As expected, both shock schedules produced a lasting learning impairment (Figure 6A). This made sense given the large literature on timing, which has linked the capacity to discriminate alternative temporal schedules to neural systems in the brain (Mauk and Buonomano, 2004). From this view, there was little reason to expect that neurons within the spinal cord could discriminate FT and VT stimulation.

In a subsequent experiment, we assessed the impact of increasing the duration of stimulus exposure 5-fold, giving animals 900 shocks on either a VT or FT schedule. To our surprise, only VT stimulation induced a learning impairment (Baumbauer et al., 2008, 2009). Given that fewer FT shocks (180) impaired learning, but 900 did not, the results suggested that continued exposure to FT stimulation (540–720 more shocks) has a restorative effect. Further work showed that an extended exposure to FT stimulation blocks the induction of a learning impairment when animals are given VT stimulation 24 h later. The induction of this protective effect was prevented by pharmacological treatments that block protein synthesis or the NMDA receptor. Taken together, the results imply that continued exposure to regular (FT) stimulation has a protective/restorative (metaplastic) effect analogous to that produced by training with controllable stimulation (Baumbauer and Grau, 2011), and here too, the beneficial effect of training was linked to the expression of BDNF (Baumbauer et al., 2009).

What makes these findings especially remarkable is that they imply that the spinal cord can discriminate whether stimuli occur at random or fixed intervals, suggesting that neural systems within the spinal cord can abstract how stimuli are distributed over time. We posited that the capacity to detect the regularity of stimulation may be linked to the engagement of an internal oscillator, possibly the CPG that drives stepping (Baumbauer et al., 2009; Lee et al., 2015, 2016). Consistent with this, the restorative effects of regular stimulation emerge within the frequency range of stepping (de Leon et al., 1994; Cha et al., 2007). If regular stimulation has a special effect because it engages an internal (central) oscillator, it could potentially abstract regularity when stimuli are presented to distinct regions of the body (across sensory dermatomes). Supporting this, we showed that an extended exposure to regular stimulation induces a restorative effect when half of the shocks are applied to the leg while the other half are presented to the tail (Figure 6B), and that this is true independent of whether the locus of stimulation varies in a regular or random manner (Figure 6D).

If an internal oscillator is engaged by regular stimulation, and has some momentum, the system should be able to derive regularity when some of the stimuli are omitted (Figure 6E). As predicted, we found that randomly omitting half the shocks had no effect on the development of restorative effect (Lee et al., 2016). Finally, if an internal oscillator effectively predicts the occurrence of the next shock, based upon a constant period, stimuli would have to remain in phase. As hypothesized, a restorative effect does not emerge if regular stimulation is given across dermatomes at different frequencies (Figure 6C). Likewise, when shocks are randomly omitted, a protective effect only emerges if the shocks remain in phase (Figure 6E).

The fact that randomly omitting half the shocks given on a FT schedule does not affect the emergence of the restorative effect has implications for the conditions that engage this process. As noted earlier, when no shocks are omitted, a restorative effect emerges after 540 shocks—360 is not sufficient. But when 720 shocks are given, and half are omitted, the restorative effect is observed (Lee et al., 2015). This implies that it is not the number of shocks that is critical. Rather, what appears critical is how long the CPG is engaged. This is consistent with other work demonstrating a form of savings across days. Animals given a single bout of 360 FT shocks exhibit a learning impairment. If they receive two bouts of 360 FT shocks, 24 h apart, the capacity for learning is restored. Importantly, the two bouts do not have to be the same frequency. What appears to be summated across days is a marker linked to the duration of regular stimulation, not the specific frequency.

Evidence that the detection of regularity is linked to the CPG that underlies stepping was obtained using a surgical manipulation. Prior work has shown that spinally-mediated instrumental learning depends upon neurons within the lower lumbosacral spinal cord, between L3 and S2 (Figure 1E) (Liu et al., 2005). Interestingly, the neural circuit that mediates the CPG used for stepping appears to lie in a more rostral region, L1-L2 (Cazalets et al., 1995; Magnuson et al., 1999). Given this, we should be able to surgically disconnect the circuit needed for instrumental learning from the CPG by transecting the spinal cord at L3. Minus access to the CPG, FT stimulation should not have a restorative effect, and instead produce a learning impairment, which is what we found (Lee et al., 2016).

The results are consistent with other work demonstrating that regular movement, induced by passively moving the hind limbs over an extended period of time or training animals to step on a treadmill, has a restorative effect (Alluin et al., 2011; Rossignol, 2017). Further, regular stimulation of the perineum, which is often used to encourage stepping on a treadmill, may promote behavior because it engages the CPG. Interestingly, studies examining the consequences of step training have shown that animals trained at one stepping rate exhibit improved performance when tested at different treadmill speeds (Edgerton et al., 1997, 2004). Again, what may be critical is engagement of the CPG for an extended period of time, not the particular frequency used in each bout of training.

Regular stimulation can also impact neuronal function in the cervical spinal cord, which regulates breathing. Mitchell and his colleagues have shown that intermittent bouts of hypoxia can enhance activity in the (phrenic) nerve that drives respiration, inducing a lasting effect [phrenic long-term facilitation (pLTF)] that has been

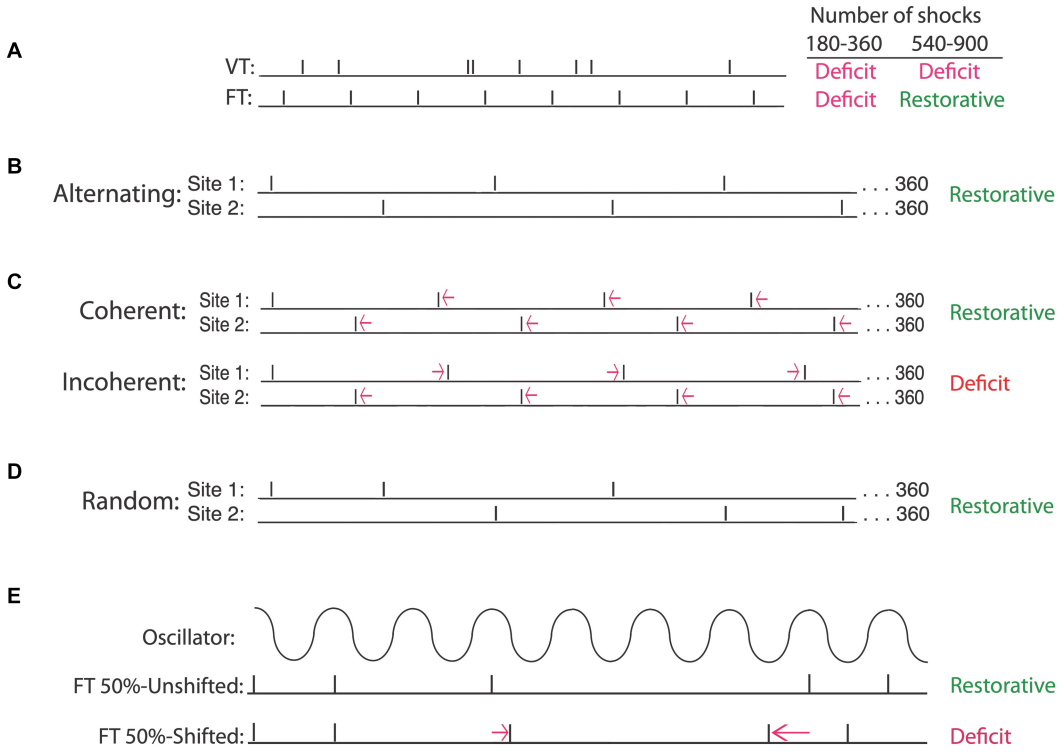

FIGURE 6
Intermittent stimulation can have distinct effects on spinal cord plasticity depending upon the underlying temporal relation. **(A)** When the interval between stimuli is randomly varied [variable time (VT)], a learning impairment is observed when animals are tested after 180–900 stimuli (Deficit). If stimuli occur in a regular manner [fixed time (FT)], a learning deficit is observed when animals are exposed to 180–360 stimuli. Exposure to additional stimulation (540–900) has a restorative effect that counters the learning deficit. **(B)** A restorative effect emerges when the locus of FT stimulation is alternated across regions of the body (e.g., hind leg and tail). **(C)** Temporally displacing alternating stimuli by a small amount preserves the regularity of stimuli applied at each site. Displacing the stimuli in opposite directions introduces an irregular relation (incoherent) across sites and produces a learning deficit. If the stimuli are displaced in the same direction (coherent), a regular pattern can be abstracted across sites and a restorative effect emerges. Regularity can also be abstracted when the site of stimulation is randomly varied across sites **(D)** and when half of the stimuli are randomly omitted **(E)**, provided the stimuli remain in phase (FT 50%-Unshifted). Shifting the phase relation after a stimulus is omitted (FT 50%-Shifted) disrupts the abstraction of regularity, causing the same number of stimuli to induce a learning deficit. Adapted from Lee et al. (2015), Lee et al. (2016), and Grau et al. (2022).

linked to increased expression of BDNF (Baker-Herman et al., 2004; Dale-Nagle et al., 2010; Fields and Mitchell, 2015; Fuller and Mitchell, 2017). While a continuous period of hypoxia can enhance the rate of respiration, it does not induce pLTF or impact BDNF expression. In rats, daily intermittent hypoxia promotes the recovery of breathing capacity after SCI and in combination with ladder walking, promotes the restoration of forelimb function. In humans, daily intermittent hypoxia combined with walking practice increased endurance by 38% (Hayes et al., 2014; Navarrete-Opazo et al., 2017).

Our work on timing within the spinal cord was originally motivated by a simple question—what type of process allows neurons within the spinal cord to discriminate (and provide distinct physiological consequences) whether the stimuli occur in a random or regular (predictable) manner? Our experiments explored whether this might be linked to a kind of neurochemical/physiological hourglass or an internal oscillator (Boulos and Terman, 1980). As we have seen, our results suggest that regularity is tied to an oscillator, which we linked to the CPG that drives the rhythmicity of stepping. What is especially surprising is the system can abstract regularity when stimuli are randomly omitted or when the locus of stimulation is varied. Here the computational capacity of the system goes well beyond an elicited reflex, demonstrating a cognitive-like ability to abstract relations to modulate performance and plastic potential.

Spinal cord injury removes the GABA-dependent brake on neural excitability (ionic plasticity)

We noted earlier that SCI brings about a depolarizing shift in GABA (ionic plasticity), which removes a brake on neural excitability (Viemari et al., 2011). Evidence suggests that this enables the development of nociceptive sensitization, which we have argued underlies the learning impairment observed after uncontrollable shock (Ferguson et al., 2012). These observations suggest that drug treatments that restore the inhibitory effect of GABA should attenuate both the enhanced mechanical reactivity and learning impairment induced by uncontrollable shock in spinally transected rats, and recent findings are consistent with this prediction (Huang et al., 2016; Grau et al., 2022; Hudson and Grau, 2022). In addition, a depolarizing shift in GABA action, which accompanies spinal cord transection, appears necessary for spinally-mediated instrumental learning. If the hyperpolarizing

effect of GABA is re-established in spinally transected rats, by lowering the inward flow of $Cl^-$with the NKCC1 blocker bumetanide, spinally transected rats fail to learn. Taken together, the results imply that ionic plasticity enables learning within the spinal cord.

These observations suggest that the adult spinal cord, minus injury or inflammation, may indeed be relatively immutable, with the inhibition action of GABA maintaining circuits laid down early in development (Ben-Ari, 2002, 2014). Some may take this as evidence for the traditional view. We take an alternative position (Grau et al., 2022), because other work has shown that these observations are not unique to the spinal cord (Hudson and Grau, 2022). A depolarizing shift in the action of GABA has been shown to contribute to a variety of brain-dependent pathologies linked to neural over-excitation (e.g., epilepsy, addiction, Rett syndrome). Moreover, dampening the inhibitory effect of GABA may be a prerequisite to plasticity, LTP, and learning within the brain. Across the CNS, GABA may function to maintain neural circuits laid down by development and learning.

Noxious stimulation impairs recovery and fosters the development of chronic pain after SCI

Given noxious stimulation induces a form of maladaptive plasticity in spinally transected animals, we hypothesized that it could adversely affect recovery after a contusion injury (Grau et al., 2004). This is clinically important because many SCIs are accompanied by other tissue damage (polytrauma). To examine whether pain after SCI affects injury-related processes, rats were given a moderate contusion injury to the lower thoracic spinal cord. The next day, nociceptive fibers were engaged by exposing animals to 6 min of uncontrollable tail-shock or applying capsaicin to one hind paw. Both treatments disrupted long-term behavioral recovery, producing a drop in locomotor performance that was evident 6 weeks later (Grau et al., 2004; Turtle et al., 2018). Noxious stimulation soon after injury (within the first 4 days) also fostered the development of spasticity and increased tissue loss at the site of injury. Importantly, the adverse effect of intermittent shock was only observed if the stimulation was given in an uncontrollable manner; an equal number of controllable shocks had no effect. Further, engaging pain fibers soon after injury fostered the development of chronic pain (Grau et al., 2004; Garraway et al., 2014). Other studies have shown that noxious stimulation during the chronic phase of injury can adversely affect performance, but does not have a lasting effect (Bouffard et al., 2014; Caudle et al., 2015).

A physical blow to the spinal cord produces an immediate (*primary*) injury. As described above, this injury then engages processes that drive cell death and fuel inflammation (Beattie and Bresnahan, 2000), producing a pro-inflammatory storm that expands the area of tissue loss (*secondary* injury). We posited that noxious stimulation after injury has an adverse effect because it fuels secondary processes. To explore this possibility, we collected the injured spinal cord soon after animals received noxious stimulation. We found that nociceptive stimulation amplified the expression of pro-inflammatory cytokines (IL-1, IL-18, TNF) and signals (e.g., caspase 1, 3, 8) that drive cell death (Garraway et al., 2014; Turtle et al., 2018).

In the course of doing these experiments, we noticed that the protein samples were color coded—those from rats that had received noxious stimulation were tinted red (Turtle et al., 2019). Spectrophotometry showed increased absorbance at the wavelength (420 nm) associated with hemoglobin. Cellular assays for hemoglobin confirmed that nociceptive stimulation increased blood content, implying an infiltration of blood (hemorrhage) at the site of injury. Because some blood components are neurotoxic (Regan and Guo, 1998; Losey et al., 2014), this would expand the area of tissue loss.

As noted earlier, descending fibers normally quell nociceptive activity in the spinal cord (Fauss et al., 2021). Given this, we hypothesized that cutting communication with the brain would amplify nociception-induced hemorrhage in contused rats. Contrary to our expectations, the transection had the opposite effect—it blocked nociception-induced hemorrhage (Reynolds et al., 2019). A rostral transection also blocked the up-regulation of pro-inflammatory cytokines and signals indicative of cell death. The surprising implication is that rostral (brain) systems can drive tissue loss after SCI. We presumed that these brain systems were driven by surviving ascending fibers. If this is true, reversibly blocking communication with the brain using lidocaine applied at T2 should prevent nociception-induced hemorrhage, which it did (Davis et al., 2020). Lidocaine treatment also blocked the adverse effect noxious stimulation has on long-term recovery. These observations led us to hypothesize that treatments that diminish brain activity (e.g., general anesthesia) should have a protective effect, and that too is true (Davis et al., 2023). These findings have important clinical implications, suggesting that inhibiting cellular activity within the spinal cord (using a local anesthetic) or inducing a coma-like state (using a general anesthetic) could reduce tissue loss after SCI.

We have shown that engaging sensory fibers that drive a conscious state of pain soon after injury promotes tissue loss and impairs recovery. Given this, we naturally hypothesized that administration of an analgesic, such as morphine, would lessen the adverse effect of noxious stimulation. Surprisingly, administration of morphine at a dose that blocks behavioral reactivity to noxious stimulation does not attenuate secondary tissue loss or the impairment in long-term recovery (Hook et al., 2007, 2009; Turtle et al., 2017). What was especially concerning is that morphine treated rats exhibited greater tissue loss and increased mortality, raising concerns regarding the clinical use of opiate analgesic soon after injury (Hook et al., 2007, 2017).

Our results suggest that the adverse effect of noxious stimulation after injury is due, in part, to a brain-dependent process that fosters the infiltration of blood (hemorrhage) at the site of injury. We assume that this effect depends upon both local (at the site of injury) and systemic processes. Engaging nociceptive (C) sensory fibers can initiate the expression of proinflammatory cytokines at the site of injury and weaken the blood spinal cord barrier (Steinhoff et al., 2014). At the same time, surviving ascending nociceptive fibers could engage a fight-or-flight response that drives a burst of sympathetic activity, bringing a rise in heart rate and blood pressure, Given the weakened state of the blood spinal cord barrier at the site of injury, the rise blood pressure could fuel hemorrhage. Recent work has confirmed that noxious electrical stimulation produces a surge in blood pressure and blood flow (Strain et al., 2021). Further, pharmacologically attenuating the rise in blood pressure, by administering the alpha-1 adrenergic receptor inverse agonist prazosin attenuated the rise in blood pressure, hemorrhage, and the adverse effect noxious stimulation has on long-term recovery. Conversely, pharmacologically inducing a rise in blood pressure, by administering adrenergic agonist norepinephrine a day after injury, impaired recovery and increased tissue loss. These observations are consistent with other work showing that hypertension at the time of injury is associated with a decrement in recovery (Nielson et al., 2015).

The findings outlined above are consistent with other studies demonstrating that SCI can engage systemic processes that can impact tissue loss, recovery, and wellbeing. Of course, SCI recruits both local and systemic components of the immune system, which can have opposing effects on long-term recovery (Popovich, 2014; Schwab et al., 2014); bringing a benefit through the clearance of cellular debris, but limiting re-innervation through the production of a fibrotic (glial) scar (Yang et al., 2020). Beyond this, there is a loss of descending regulatory control over components of the sympathetic nervous system innervated by fiber pathways below the injury (DiSabato et al., 2023). The consequent dysregulation causes systemic immune and metabolic dysfunction that can impact multiple major organ systems, including the liver, lungs, gut, and urinary tract, increasing susceptibility to urinary and lung infections, gut dysbiosis, and a disruption in lipid metabolism (metabolic syndrome; Kopp et al., 2017; Holmes and Blanke, 2019; Kigerl et al., 2020; Rodgers et al., 2022). Pneumonia and urinary tract infections are among the leading causes of mortality after SCI (Schwab et al., 2014; DiSabato et al., 2023; Michel-Flutot et al., 2023). Further, immune dysregulation and an increase in circulating pro-inflammatory cytokines can promote depression and pain (Maier and Watkins, 1998; Slavich and Irwin, 2014; Lees et al., 2015). Finally, these processes can negatively impact tissue sparing and adaptive plasticity at the site of injury. Indeed, preclinical research has shown that liver dysfunction undermines long-term recovery (Failli et al., 2012; Goodus et al., 2021).

Conclusion

Historically, many have seen the spinal cord as a conduit for neural impulses to/from the brain with a limited capacity to organize some simple reflexive responses. From this perspective, the orchestration of complex behavior, the recognition of response-outcome relations, pain modulation, timing, learning, and memory are the province of the brain. The work we have reviewed supports an alternative position, that recognizes the computational power of neural assemblies within the spinal cord. We align with Windhorst (2007) who argued:

> "Those who believed the spinal cord and peripheral motor plant to be well-understood and thus turned their attentions to higher centers of motor planning and coordination (e.g., cerebral cortex and cerebellum) now find that their edifices are built upon 'the shifting sands of spinal segmental circuitry.'"

As we have seen, neural machinery within the spinal cord can organize coordinated stepping and modify its execution in response to changing environmental demands (e.g., an obstacle; Edgerton et al., 2004; Rossignol and Frigon, 2011; de Leon and Dy, 2017). Noxious stimulation can sensitize nociceptive circuits in the dorsal horn and this effect is mediated by signal pathways analogous to those identified in the study of brain-dependent learning and memory (Sandkuhler, 2000; Ji et al., 2003). At a functional level, neural systems in the spinal cord are sensitive to Pavlovian (stimulus–stimulus) and instrumental (response-outcome) relations and have the capacity to abstract regularity (Grau, 2014; Grau et al., 2022). Further, engaging these processes can influence the capacity to learn, demonstrating a form of metaplasticity (Abraham and Bear, 1996; Abraham, 2008; Grau et al., 2014; Grau and Huang, 2018). And these insights have been shown to impact recovery after SCI (Grau et al., 2004; Edgerton et al., 2008; Garraway et al., 2011, 2014; McPherson et al., 2015; Turtle et al., 2017; Courtine and Sofroniew, 2019; Davis et al., 2020, 2023; Jo and Perez, 2020; Mitchell and Baker, 2022) fueling an optimism that, by harnessing the inherent capacity of the spinal cord, rehabilitation can restore function and counter the development of chronic pain and spasticity.

Researchers exploring motor performance have long recognized the complexity of spinal circuits, which handle the coordination of motor commands, drive rhythmic behavior, and can adapt to perturbations (Edgerton et al., 2004; Rossignol and Frigon, 2011). From this perspective, the execution of locomotor performance occurs within an organizational structure that is not strictly hierarchical, but instead occurs within an interactive network that enables a form of shared governance [a heterarchy; (McCulloch, 1945; Cohen, 1992)]. Our work suggests that the same is true for the regulation of pain, with nociceptive signals regulated by neural mechanisms within the spinal cord (Figure 7)—a computational system that is capable of abstracting response-outcome and temporal relations (Grau, 2002). Further, experience can have a lasting impact on how these systems operate, to mute or amplify motor responses and the signal relayed to the brain.

Just as brain-centric researchers have underestimated the processing power of the spinal cord, those wedded to the central nervous system have sometimes underestimated the role of peripheral processes. Recent findings show that exposure to a noxious stimulus can induce a state of hyperexcitability in afferent sensory neurons that can foster the development of chronic pain and that prolonged execution of a behavioral response can engage alterations at the NMJ that enhance its efficacy, providing evidence for a kind of muscle memory (Bedi et al., 2010; Hoy et al., 2020; Walters et al., 2023). And we should not forget that, while much has been learned about the capacities of spinal circuits isolated from the brain, those exploring spinal cord systems must take into account how these processes are impacted by, and interact with, brain systems (Wolpaw, 2018; Wolpaw and Kamesar, 2022).

While much of our review has focused on the plastic potential of circuits within the spinal cord, we have acknowledged that GABAergic inhibition will limit neural excitability/plasticity within the uninjured adult spinal cord, a hyperpolarizing effect that we assume helps to maintain circuits laid down early in development. In this way, the adult spinal cord may appear hardwired (Grau et al., 2022). Likewise, we have noted how learning in the spinal cord builds upon pre-existing circuits—that it is biologically prepared by genetic and developmental processes. Here, one might attempt to save the traditional view by arguing the brain is a flexible system, adaptable and unconstrained. We instead suggest the opposite, that GABA-dependent inhibition preserves neural circuits laid down by development and learning throughout the CNS and that learning in both the spinal cord and brain is constrained by our evolutionary past. From this view, the spinal cord is governed by analogous rules and at a neurochemical level, employs the same signal pathways. There are no obvious qualitative differences.

Work over the last 50 years suggests the neural systems within the spinal cord play an integral role in registering, modulating, and elaborating sensory/motor signals. It is basic component of the CNS and can serve as an ideal model system for exploring the processing capacity and limits of neural circuits. And while it is often difficult to link neurobiological modifications in discrete brain regions to behavior, at the level of the spinal cord, just a few synapses may intervene, simplifying the application of our linking hypotheses. Moreover, unpacking how the spinal cord functions often has important clinical implications. Beyond this, those seeking to understand how the brain processes information need to know the types of information contained within the signal from

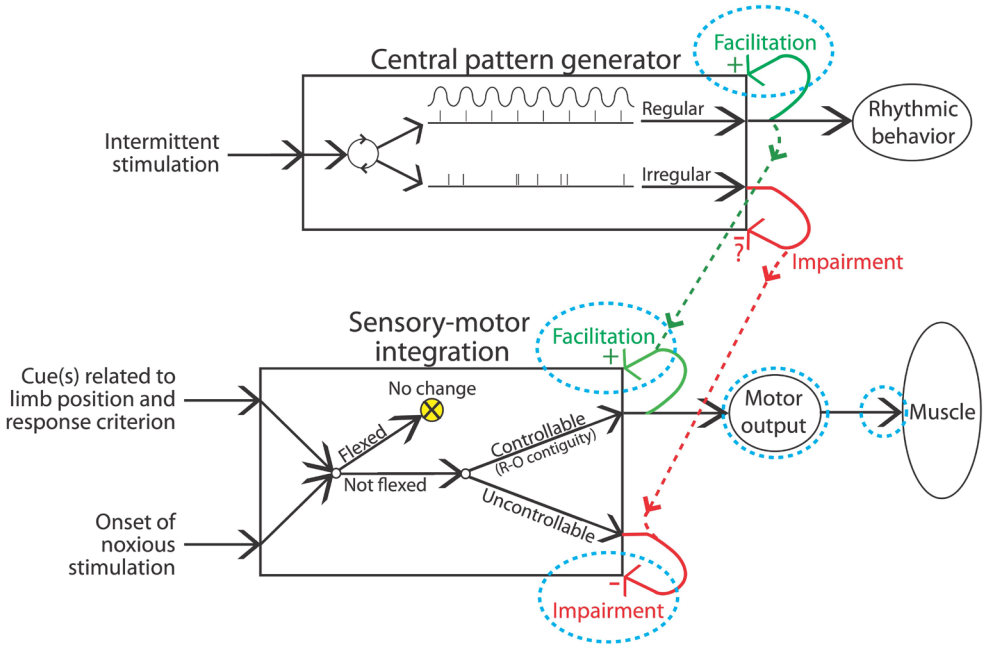

FIGURE 7
A schematic illustrating the intra-spinal processes that mediate instrumental conditioning, timing, and the consequences of uncontrollable stimulation. Evidence suggests that neural processes within the caudal lumbosacral (L3-S2) spinal cord enable sensory-motor integration (lower box). The effect of noxious stimulation appears to be gated by proprioceptive cues related to limb position; if the leg(s) is flexed, stimulation has no impact on spinal function (blue circle). If the leg is not flexed, a biologically prepared circuit enables the rapid detection of a relationship between the current limb position (the R) and the onset of noxious stimulation (the O). If there is a R-O relation, the stimulation is classified as controllable, which fosters the performance of a motor response that reduces net exposure to noxious stimulation. In the absence of a R-O relation (uncontrollable stimulation), a state of over-excitation is induced that enhances reactivity to mechanical stimulation and induces a lasting impairment in relational learning. Conversely, exposure to controllable stimulation has a restorative effect that fosters learning and counters the adverse effect of uncontrollable stimulation. Other work indicates that a central pattern generator exists in the rostral (L1-L2) spinal cord (upper box) that can be entrained by regular stimulation. Evidence suggests that regularity can be abstracted when stimulation is applied to different regions of the lower body and when some stimuli are randomly omitted. Periods of regular stimulation can foster rhythmic behavior, the abstraction of regularity across days (savings), and counter the adverse effects of uncontrollable stimulation (green lines). Exposure to stimuli that occur in a variable (irregular) manner impairs instrumental learning. Further work is needed to determine whether irregular stimulation also interferes with the abstraction of regularity (red?). Research is also needed to determine how sensory-motor integration impacts the central pattern generator. Evidence suggests that noxious stimulation can interfere with CPG function and the generation of rhythmic behavior (Bouffard et al., 2014; Caudle et al., 2015), implying that the dashed red line reflects a bi-directional process. It is not known whether exposure to controllable stimulation fosters the engagement of the CPG. Note that a '+' and '−'indicate how processes affect function, not the nature of neural communication (i.e., whether an excitatory or inhibitory process underlies the effects). The consequences of training that have been shown to have a lasting effect (implying a form of memory) are enclosed with dashed circles. Adapted from Grau et al. (2022).

the spinal cord. As we have outlined, relations presumed to be abstracted by the brain may have already been derived by processes within the spinal cord. Conversely, an understanding of how neural circuits within the spinal cord can orchestrate behavioral action will inform our views of the motor commands needed to drive behavior, with evidence suggesting that the structure of behavior is often organized by local circuits.

Author contributions

JG wrote the first draft of this manuscript, integrating components provided by KH, DJ, and SP. The final draft was edited by JG. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Abraham, W. C. (2008). Metaplasticity: tuning synapses and networks for plasticity. *Nat. Rev. Neurosci.* 9, 387–399. doi: 10.1038/nrn2356

Abraham, W. C., and Bear, M. F. (1996). Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci.* 19, 126–130. doi: 10.1016/S0166-2236(96)80018-X

Allen, C., Grau, J. W., and Meagher, M. W. (2002). "The lower bounds of cognition: what do spinal cords reveal?" in *The Oxford handbook of philosophy of neuroscience*. ed. J. Bickle (Oxford: Oxford Press), 129–142.

Alluin, O., Karimi-Abdolrezaee, S., Delivet-Mongrain, H., Leblond, H., Fehlings, M. G., and Rossignol, S. (2011). Kinematic study of locomotor recovery after spinal cord clip compression injury in rats. *J. Neurotrauma* 28, 1963–1981. doi: 10.1089/neu.2011.1840

Angeli, C. A., Edgerton, V. R., Gerasimenko, Y. P., and Harkema, S. J. (2014). Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 137, 1394–1409. doi: 10.1093/brain/awu038

Bakalkin, G. (1989). Neuropeptides induce directional asymmetry in brain and spinal cord: facts and hypotheses. *Int. J. Neurosci.* 48, 105–124. doi: 10.3109/00207458909002155

Bakalkin, G., and Kobylyansky, A. G. (1989). Opioids induce postural asymmetry in spinal rat: the side of the flexed limb depends upon the type of opioid agonist. *Brain Res.* 480, 277–289. doi: 10.1016/0006-8993(89)90193-5

Baker-Herman, T. L., Fuller, D. D., Bavis, R. W., Zabka, A. G., Golder, F. J., Doperalski, N. J., et al. (2004). BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat. Neurosci.* 7, 48–55. doi: 10.1038/nn1166

Baumbauer, K. M., and Grau, J. W. (2011). Timing in the absence of supraspinal input iii: regularly spaced cutaneous stimulation prevents and reverses the spinal learning deficit produced by peripheral inflammation. *Behav. Neurosci.* 125, 37–45. doi: 10.1037/a0022009

Baumbauer, K. M., Hoy, K. C., Huie, J. R., Hughes, A. J., Woller, S. A., Puga, D. A., et al. (2008). Timing in the absence of supraspinal input I: variable, but not fixed, spaced stimulation of the sciatic nerve undermines spinally-mediated instrumental learning. *Neuroscience* 155, 1030–1047. doi: 10.1016/j.neuroscience.2008.07.003

Baumbauer, K. M., Huie, J. R., Hughes, A. J., and Grau, J. W. (2009). Timing in the absence of supraspinal input ii: regularly spaced stimulation induces a lasting alteration in spinal function that depends on the nmda receptor, bdnf release, and protein synthesis. *J. Neurosci.* 29, 14383–14393. doi: 10.1523/JNEUROSCI.3583-09.2009

Beattie, M. S., and Bresnahan, J. C. (2000). "Cell death, repair, and recovery of function after spinal cord contusion injuries in rats" in *Neurobiology of spinal cord injury*. eds. R. G. Kalb and S. M. Strittmatter (Totowa, NJ: Humana Press), 1–21.

Bedi, S. S., Yang, Q., Crook, R. J., Du, J., Wu, Z., Fishman, H. M., et al. (2010). Chronic spontaneous activity generated in the somata of primary nociceptors is associated with pain-related behavior after spinal cord injury. *J. Neurosci.* 30, 14870–14882. doi: 10.1523/JNEUROSCI.2428-10.2010

Beggs, S., and Salter, M. W. (2013). The known knowns of microglia-neuronal signalling in neuropathic pain. *Neurosci. Lett.* 557, 37–42. doi: 10.1016/j.neulet.2013.08.037

Ben-Ari, Y. (2002). Excitatory actions of GABA during development: the nature of the nurture. *Nat. Rev. Neurosci.* 3, 728–739. doi: 10.1038/nrn920

Ben-Ari, Y. (2014). The GABA excitatory/inhibitory developmental sequence: a personal journey. *Neuroscience* 279, 187–219. doi: 10.1016/j.neuroscience.2014.08.001

Bliss, T. V., and Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 361, 31–39. doi: 10.1038/361031a0

Bouffard, J., Bouyer, L. J., Roy, J. S., and Mercier, C. (2014). Tonic pain experienced during locomotor training impairs retention despite normal performance during acquisition. *J. Neurosci.* 34, 9190–9195. doi: 10.1523/JNEUROSCI.5303-13.2014

Boulenguez, P., Liabeuf, S., Bos, R., Bras, H., Jean-Xavier, C., Brocard, C., et al. (2010). Down-regulation of the potassium-chloride cotransporter KCC2 contributes to spasticity after spinal cord injury. *Nat. Med.* 16, 302–307. doi: 10.1038/nm.2107

Boulos, Z., and Terman, M. (1980). Food availability and daily biological rhythms. *Neurosci. Biobehav. Rev.* 4, 119–131. doi: 10.1016/0149-7634(80)90010-x

Boyce, V. S., and Mendell, L. M. (2014). Neurotrophins and spinal circuit function. *Front Neural Circuits* 8:59. doi: 10.3389/fncir.2014.00059

Brown, T. G. (1914). On the nature of the fundamental activity of the nervous centres; together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J. Physiol.* 48, 18–46. doi: 10.1113/jphysiol.1914.sp001646

Carvalho, L. S., Brito, H. M., Lukoyanova, E. A., Maia, G. H., Sarkisyan, D., Nosova, O., et al. (2021). Unilateral brain injury to pregnant rats induces asymmetric neurological deficits in the offspring. *Eur. J. Neurosci.* 53, 3621–3633. doi: 10.1111/ejn.15243

Caudle, K. L., Atkinson, D. A., Brown, E. H., Donaldson, K., Seibt, E., Chea, T., et al. (2015). Hindlimb stretching alters locomotor function after spinal cord injury in the adult rat. *Neurorehabil. Neural Repair* 29, 268–277. doi: 10.1177/1545968314543500

Cazalets, J. R., Borde, M., and Clarac, F. (1995). Localization and organization of the central pattern generator for hindlimb locomotion in newborn rat. *J. Neurosci.* 15, 4943–4951. doi: 10.1523/JNEUROSCI.15-07-04943.1995

Cha, J., Heng, C., Reinkensmeyer, D. J., Roy, R. R., Edgerton, V. R., and De Leon, R. D. (2007). Locomotor ability in spinal rats is dependent on the amount of activity imposed on the hindlimbs during treadmill training. *J. Neurotrauma* 24, 1000–1012. doi: 10.1089/neu.2006.0233

Chazov, E. I., Bakalkin, G., Yarigin, K. N., Trushina, E. D., Titov, M. I., and Smirnov, V. N. (1981). Enkephalins induce asymmetrical effects on posture in the rat. *Experientia* 37, 887–889. doi: 10.1007/BF01985696

Chen, B., Li, Y., Yu, B., Zhang, Z., Brommer, B., Williams, P. R., et al. (2018). Reactivation of dormant relay pathways in injured spinal cord by KCC2 manipulations. *Cell* 174:1599. doi: 10.1016/j.cell.2018.08.050

Cohen, A. H. (1992). The role of heterarchical control in the evolution of central pattern generators. *Brain Behav. Evol.* 40, 112–124. doi: 10.1159/000113907

Cote, M. P., Gandhi, S., Zambrotta, M., and Houle, J. D. (2014). Exercise modulates chloride homeostasis after spinal cord injury. *J. Neurosci.* 34, 8976–8987. doi: 10.1523/jneurosci.0678-14.2014

Cote, M. P., Murray, L. M., and Knikou, M. (2018). Spinal control of locomotion: individual neurons, their circuits and functions. *Front. Physiol.* 9:784. doi: 10.3389/fphys.2018.00784

Coull, J. A., Beggs, S., Boudreau, D., Boivin, D., Tsuda, M., Inoue, K., et al. (2005). BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 438, 1017–1021. doi: 10.1038/nature04223

Courtine, G., and Sofroniew, M. V. (2019). Spinal cord repair: advances in biology and technology. *Nat. Med.* 25, 898–908. doi: 10.1038/s41591-019-0475-6

Courtine, G., Song, B., Roy, R. R., Zhong, H., Herrmann, J. E., Ao, Y., et al. (2008). Recovery of supraspinal control of stepping via indirect propriospinal relay connections after spinal cord injury. *Nat. Med.* 14, 69–74. doi: 10.1038/nm1682

Cowie, A. M., Moehring, F., O'Hara, C., and Stucky, C. L. (2018). Optogenetic inhibition of CGRPalpha sensory neurons reveals their distinct roles in neuropathic and incisional pain. *J. Neurosci.* 38, 5807–5825. doi: 10.1523/JNEUROSCI.3565-17.2018

Crowe, M. J., Bresnahan, J. C., Shuman, S. L., Masters, J. N., and Beattie, M. S. (1997). Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. *Nat. Med.* 3, 73–76. doi: 10.1038/nm0197-73

Crown, E. D., Ferguson, A. R., Joynes, R. L., and Grau, J. W. (2002a). Instrumental learning within the spinal cord II. Evidence for central mediation. *Physiol. Behav.* 77, 259–267. doi: 10.1016/S0031-9384(02)00859-4

Crown, E. D., Ferguson, A. R., Joynes, R. L., and Grau, J. W. (2002b). Instrumental learning within the spinal cord: IV. Induction and retention of the behavioral deficit observed after noncontingent shock. *Behav. Neurosci.* 116, 1032–1051. doi: 10.1037/0735-7044.116.6.1032

Crown, E. D., and Grau, J. W. (2005). Evidence that descending serotonergic systems protect spinal cord plasticity against the disruptive effect of uncontrollable stimulation. *Exp. Neurol.* 196, 164–176. doi: 10.1016/j.expneurol.2005.07.016

Crown, E. D., and Grau, J. W. (2001). Preserving and restoring behavioral potential within the spinal cord using an instrumental training paradigm. *J. Neurophysiol.* 86, 845–855. doi: 10.1152/jn.2001.86.2.845

Crown, E. D., King, T. E., Meagher, M. W., and Grau, J. W. (2000). Shock-induced hyperalgesia: III. Role of the bed nucleus of the stria terminalis and amygdaloid nuclei. *Behav. Neurosci.* 114, 561–573. doi: 10.1037/0735-7044.114.3.561

Dale-Nagle, E. A., Hoffman, M. S., Mac Farlane, P. M., Satriotomo, I., Lovett-Barr, M. R., Vinit, S., et al. (2010). Spinal plasticity following intermittent hypoxia: implications for spinal injury. *Ann. N. Y. Acad. Sci.* 1198, 252–259. doi: 10.1111/j.1749-6632.2010.05499.x

Dan, Y., and Poo, M. M. (2004). Spike timing-dependent plasticity of neural circuits. *Neuron* 44, 23–30. doi: 10.1016/j.neuron.2004.09.007

Davis, J. A., Bopp, A. C., Henwood, M. K., Baine, R. E., Cox, C. C., and Grau, J. W. (2020). Pharmacological transection of brain-spinal cord communication blocks pain-

induced hemorrhage and locomotor deficits after spinal cord injury in rats. *J. Neurotrauma* 37, 1729–1739. doi: 10.1089/neu.2019.6973

Davis, J. A., Bopp, A. C., Henwood, M. K., Baine, R. E., Grau, J. W., and Bean, P. (2023). General anesthesia blocks pain-induced hemorrhage and locomotor deficits after spinal cord injury in rats. *J. Neurotrauma* 40, 2552–2565. doi: 10.1089/neu.2022.0449

de Leon, R. D., and Dy, C. J. (2017). What did we learn from the animal studies of body weight-supported treadmill training and where do we go from Here? *J. Neurotrauma* 34, 1744–1750. doi: 10.1089/neu.2016.4561

de Leon, R., Hodgson, J. A., Roy, R. R., and Edgerton, V. R. (1994). Extensor-and flexor-like modulation within motor pools of the rat hindlimb during treadmill locomotion and swimming. *Brain Res.* 654, 241–250. doi: 10.1016/0006-8993(94)90485-5

Delile, J., Rayon, T., Melchionda, M., Edwards, A., Briscoe, J., and Sagner, A. (2019). Single cell transcriptomics reveals spatial and temporal dynamics of gene expression in the developing mouse spinal cord. *Development* 146:807. doi: 10.1242/dev.173807

Detloff, M. R., Smith, E. J., Quiros Molina, D., Ganzer, P. D., and Houle, J. D. (2014). Acute exercise prevents the development of neuropathic pain and the sprouting of non-peptidergic (GDNF-and artemin-responsive) c-fibers after spinal cord injury. *Exp. Neurol.* 255, 38–48. doi: 10.1016/j.expneurol.2014.02.013

DiGiorgio, A. M. (1929). Persistenza nell'animale spinale, di asimmetrie osturali e motorie di origine cerebellare [Persistence of postural and motor asymmetries in spinal animals of cerebellar orgin]. *Arch. Fisiol.* 27, 518–580.

DiSabato, D. J., Marion, C. M., Mifflin, K. A., Alfredo, A. N., Rodgers, K. A., Kigerl, K. A., et al. (2023). System failure: systemic inflammation following spinal cord injury. *Eur. J. Immunol.* 54:e2250274. doi: 10.1002/eji.202250274

Domjan, M. (2015). *Principles of learning and behavior*. Stamford, CT: Cengage.

Donges, S. C., D'Amico, J. M., Butler, J. E., and Taylor, J. L. (2018). Involvement of N-methyl-d-aspartate receptors in plasticity induced by paired corticospinal-motoneuronal stimulation in humans. *J. Neurophysiol.* 119, 652–661. doi: 10.1152/jn.00457.2017

Durkovic, R. G. (2001). "Pavlovian conditioning of flexion reflex potentiation in spinal cat: temporal effects following spinal transection" in *Spinal cord plasticity: Alterations in reflex function*. eds. M. M. Patterson and J. W. Grau (Boston: Kluwer Academic Publishers), 55–75.

Durkovic, R. G., and Prokowich, L. J. (1998). D-2-Amino-5-phosphonovalerate, an NMDA receptor antagonist, blocks induction of associative long-term potentiation of the flexion reflex in spinal cat. *Neurosci. Lett.* 257, 162–164. doi: 10.1016/s0304-3940(98)00820-9

Edgerton, V. R., Courtine, G., Gerasimenko, Y. P., Lavrov, I., Ichiyama, R. M., Fong, A. J., et al. (2008). Training locomotor networks. *Brain Res. Rev.* 57, 241–254. doi: 10.1016/j.brainresrev.2007.09.002

Edgerton, V. R., Roy, R. R., DeLeon, R., Tillakaratne, N., and Hodgson, J. A. (1997). Does motor learning occur in the spinal cord? *Neuroscientist* 3, 287–294. doi: 10.1177/107385849700300510

Edgerton, V. R., Roy, R. R., Hodgson, J. A., Prober, R. J., de Guzman, C. P., and de Leon, R. (1992). Potential of adult mammalian lumbosacral spinal cord to execute and acquire improved locomotion in the absence of supraspinal input. *J. Neurotrauma* 9, S119–S128.

Edgerton, V. R., Tillakaratne, N. J. K., Bigbee, A. J., de Leon, R. D., and Roy, R. R. (2004). Plasticity of the spinal neural circuitry after injury. *Annu. Rev. Neurosci.* 27, 145–167. doi: 10.1146/annurev.neuro.27.070203.144308

Eldahan, K. C., and Rabchevsky, A. G. (2018). Autonomic dysreflexia after spinal cord injury: systemic pathophysiology and methods of management. *Auton. Neurosci.* 209, 59–70. doi: 10.1016/j.autneu.2017.05.002

Failli, V., Kopp, M. A., Gericke, C., Martus, P., Klingbeil, S., Brommer, B., et al. (2012). Functional neurological recovery after spinal cord injury is impaired in patients with infections. *Brain* 135, 3238–3250. doi: 10.1093/brain/aws267

Fanselow, M. S. (1986). Conditioned fear-induced opiate analgesia: a competing motivational state theory of stress analgesia. *Ann. N. Y. Acad. Sci.* 467, 40–54. doi: 10.1111/j.1749-6632.1986.tb14617.x

Fauss, G. N. K., Strain, M. M., Huang, Y. J., Reynolds, J. A., Davis, J. A., Henwood, M. K., et al. (2021). Contribution of brain processes to tissue loss after spinal cord injury: does a pain-induced rise in blood pressure fuel hemorrhage? *Front. Syst. Neurosci.* 15:733056. doi: 10.3389/fnsys.2021.733056

Ferguson, A. R., Crown, E. D., and Grau, J. W. (2006). Nociceptive plasticity inhibits adaptive learning in the spinal cord. *Neuroscience* 141, 421–431. doi: 10.1016/j.neuroscience.2006.03.029

Ferguson, A. R., Huie, J. R., Crown, E. D., Baumbauer, K. M., Hook, M. A., Garraway, S. M., et al. (2012). Maladaptive spinal plasticity opposes spinal learning and recovery in spinal cord injury. *Front. Physiol.* 3:399. doi: 10.3389/fphys.2012.00399

Fields, D. P., and Mitchell, G. S. (2015). Spinal metaplasticity in respiratory motor control. *Front Neural Circuits* 9:2. doi: 10.3389/fncir.2015.00002

Fischer, I., Dulin, J. N., and Lane, M. A. (2020). Transplanting neural progenitor cells to restore connectivity after spinal cord injury. *Nat. Rev. Neurosci.* 21, 366–383. doi: 10.1038/s41583-020-0314-2

Forssberg, H. (1979). Stumbling corrective reaction: a phase-dependent compensatory reaction during locomotion. *J. Neurophysiol.* 42, 936–953. doi: 10.1152/jn.1979.42.4.936

Forssberg, H., and Grillner, S. (1973). The locomotion of the acute spinal cat injected with clonidine i. v. *Brain Res.* 50, 184–186. doi: 10.1016/0006-8993(73)90606-9

Forssberg, H., Grillner, S., and Halbertsma, J. (1980). The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiol. Scand.* 108, 269–281. doi: 10.1111/j.1748-1716.1980.tb06533.x

Forssberg, H., Grillner, S., and Rossignol, S. (1977). Phasic gain control of reflexes from the dorsum of the paw during spinal locomotion. *Brain Res.* 132, 121–139. doi: 10.1016/0006-8993(77)90710-7

Fouad, K., Pedersen, V., Schwab, M. E., and Brosamle, C. (2001). Cervical sprouting of corticospinal fibers after thoracic spinal cord injury accompanies shifts in evoked motor responses. *Curr. Biol.* 11, 1766–1770. doi: 10.1016/s0960-9822(01)00535-8

Fuller, D. D., and Mitchell, G. S. (2017). Respiratory neuroplasticity—overview, significance and future directions. *Exp. Neurol.* 287, 144–152. doi: 10.1016/j.expneurol.2016.05.022

Gallistel, C. R. (1980). *The organization of action: A new synthesis*. Hillsdale, NJ: Erlbaum.

Garraway, S. M., and Hochman, S. (2001). Serotonin increases the incidence of primary afferent-evoked long-term depression in rat deep dorsal horn neurons. *J. Neurophysiol.* 85, 1864–1872. doi: 10.1152/jn.2001.85.5.1864

Garraway, S. M., Turtle, J. D., Huie, J. R., Lee, K. H., Hook, M. A., Woller, S. A., et al. (2011). Intermittent noxious stimulation following spinal cord contusion injury impairs locomotor recovery and reduces spinal brain-derived neurotrophic factor-tropomyosin-receptor kinase signaling in adult rats. *Neuroscience* 199, 86–102. doi: 10.1016/j.neuroscience.2011.10.007

Garraway, S. M., Woller, S. A., Huie, J. R., Hartman, J. J., Hook, M. A., Miranda, R. C., et al. (2014). Peripheral noxious stimulation reduces withdrawal threshold to mechanical stimuli after spinal cord injury: role of tumor necrosis factor alpha and apoptosis. *Pain* 155, 2344–2359. doi: 10.1016/j.pain.2014.08.034

Gibson, J. J. (1979). *The ecological approach to visual perception*. Boston, MA: Houghton Mifflin.

Gjerstad, J., Tjolsen, A., and Hole, K. (1996). The effect of 5-HT1A receptor stimulation on nociceptive dorsal horn neurones in rats. *Eur. J. Pharmacol.* 318, 315–321. doi: 10.1016/s0014-2999(96)00819-9

Gjerstad, J., Tjolsen, A., and Hole, K. (2001). Induction of long-term potentiation of single wide dynamic range neurones in the dorsal horn is inhibited by descending pathways. *Pain* 91, 263–268. doi: 10.1016/s0304-3959(00)00448-6

Gomez-Pinilla, F., Huie, J. R., Ying, Z., Ferguson, A. R., Crown, E. D., Baumbauer, K. M., et al. (2007). BDNF and learning: evidence that instrumental training promotes learning within the spinal cord by up-regulating BDNF expression. *Neuroscience* 148, 893–906. doi: 10.1016/j.neuroscience.2007.05.051

Goodus, M. T., Carson, K. E., Sauerbeck, A. D., Dey, P., Alfredo, A. N., Popovich, P. G., et al. (2021). Liver inflammation at the time of spinal cord injury enhances intraspinal pathology, liver injury, metabolic syndrome and locomotor deficits. *Exp. Neurol.* 342:113725. doi: 10.1016/j.expneurol.2021.113725

Gormezano, I., and Kehoe, E. J. (1975). "Classical conditioning: some methodological-conceptual issues" in *Handbook of learning and cognitive processes*. ed. W. K. Estes (Hillsdale, NJ: Erlbaum), 143–179.

Granmo, M., Petersson, P., and Schouenborg, J. (2008). Action-based body maps in the spinal cord emerge from a transitory floating organization. *J. Neurosci.* 28, 5494–5503. doi: 10.1523/JNEUROSCI.0651-08.2008

Grau, J. W. (1987a). Activation of the opioid and nonopioid analgesic systems-evidence for a memory hypothesis and against the Coulometric hypothesis. *J. Exp. Psychol. Anim. Behav. Process.* 13, 215–225. doi: 10.1037/0097-7403.13.3.215

Grau, J. W. (1987b). The central representation of an aversive event maintains the opioid and nonopioid forms of analgesia. *Behav. Neurosci.* 101, 272–288. doi: 10.1037/0735-7044.101.2.272

Grau, J. W. (2002). "Learning and memory without a brain" in *The cognitive animal*. eds. C. Bekoff, C. Allen and G. Burghardt (Cambridge, Mass: MIT Press)

Grau, J. W. (2014). Learning from the spinal cord: how the study of spinal cord plasticity informs our view of learning. *Neurobiol. Learn. Mem.* 108, 155–171. doi: 10.1016/j.nlm.2013.08.003

Grau, J. W., Baine, R. E., Bean, P. A., Davis, J. A., Fauss, G. N. K., Henwood, M. K., et al. (2020). Learning to promote recovery after spinal cord injury. *Exp. Neurol.* 330, 113334–113320. doi: 10.1016/j.expneurol.2020.113334

Grau, J. W., Barstow, D. G., and Joynes, R. L. (1998). Instrumental learning within the spinal cord: I Behavioral properties. *Behav. Neurosci.* 112, 1366–1386. doi: 10.1037/0735-7044.112.6.1366

Grau, J. W., Crown, E. D., Ferguson, A. R., Washburn, S. N., Hook, M. A., and Miranda, R. C. (2006). Instrumental learning within the spinal cord: underlying mechanisms and implications for recovery after injury. *Behav. Cogn. Neurosci. Rev.* 5, 191–239. doi: 10.1177/1534582306289738

Grau, J. W., and Huang, Y. J. (2018). Metaplasticity within the spinal cord: evidence brain-derived neurotrophic factor (BDNF), tumor necrosis factor (TNF), and alterations in GABA function (ionic plasticity) modulate pain and the capacity to learn. *Neurobiol. Learn. Mem.* 154, 121–135. doi: 10.1016/j.nlm.2018.04.007

Grau, J. W., Hudson, K. E., Tarbet, M. M., and Strain, M. M. (2022). Behavioral studies of spinal conditioning: the spinal cord is smarter than you think it is. *J Exp Psychol Anim Learn Cogn* 48, 435–457. doi: 10.1037/xan0000332

Grau, J. W., Huie, J. R., Garraway, S. M., Hook, M. A., Crown, E. D., Baumbauer, K. M., et al. (2012). Impact of behavioral control on the processing of nociceptive stimulation. *Front. Physiol.* 3:262. doi: 10.3389/fphys.2012.00262

Grau, J. W., Huie, J. R., Lee, K. H., Hoy, K. C., Huang, Y. J., Turtle, J. D., et al. (2014). Metaplasticity and behavior: how training and inflammation affect plastic potential within the spinal cord and recovery after injury. *Front Neural Circuits* 8:100. doi: 10.3389/fncir.2014.00100

Grau, J. W., and Joynes, R. L. (2001). "Pavlovian and instrumental conditioning within the spinal cord: methodological issues" in *Spinal cord plasticity: Alterations in reflex function*. eds. M. M. Patterson and J. W. Grau (Boston: Kluwer Academic Publishers), 13–54.

Grau, J. W., and Joynes, R. L. (2005a). A neural-functionalist approach to learning. *Int. J. Comp. Psychol.* 18, 1–22. doi: 10.46867/IJCP.2005.18.01.09

Grau, J. W., and Joynes, R. L. (2005b). Neurofunctionalism revisited: learning is more than you think it is. *Int. J. Comp. Psychol.* 18, 46–59.

Grau, J. W., Salinas, J. A., Illich, P. A., and Meagher, M. W. (1990). Associative learning and memory for an antinociceptive response in the spinalized rat. *Behav. Neurosci.* 104, 489–494. doi: 10.1037/0735-7044.104.3.489

Grau, J. W., Washburn, S. N., Hook, M. A., Ferguson, A. R., Crown, E. D., Garcia, G., et al. (2004). Uncontrollable stimulation undermines recovery after spinal cord injury. *J. Neurotrauma* 21, 1795–1817. doi: 10.1089/neu.2004.21.1795

Grillner, S., and Zangger, P. (1979). Central generation of locomotion in the low spinal cat. *Exp. Brain Res.* 34, 241–261. doi: 10.1007/BF00235671

Groves, P. M., De Marco, R., and Thompson, R. F. (1969). Habituation and sensitization of spinal interneuron activity in acute spinal cat. *Brain Res.* 14, 521–525. doi: 10.1016/0006-8993(69)90129-2

Groves, P. M., and Thompson, R. F. (1970). Habituation a dual process theory. *Psychol. Rev.* 77, 419–450. doi: 10.1037/h0029810

Guo, F., Du, Y., Qu, F. H., Lin, S. D., Chen, Z., and Zhang, S. H. (2022). Dissecting the neural circuitry for pain modulation and chronic pain: insights from Optogenetics. *Neurosci. Bull.* 38, 440–452. doi: 10.1007/s12264-022-00835-8

Harel, N. Y., and Carmel, J. B. (2016). Paired stimulation to promote lasting augmentation of corticospinal circuits. *Neural Plast.* 2016, 1–11. doi: 10.1155/2016/7043767

Harkema, S., Angeli, C., and Gerasimenko, Y. (2022). Historical development and contemporary use of neuromodulation in human spinal cord injury. *Curr. Opin. Neurol.* 35, 536–543. doi: 10.1097/WCO.0000000000001080

Harkema, S., Gerasimenko, Y., Hodes, J., Burdick, J., Angeli, C., Chen, Y., et al. (2011). Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet* 377, 1938–1947. doi: 10.1016/s0140-6736(11)60547-3

Hayes, H. B., Jayaraman, A., Herrmann, M., Mitchell, G. S., Rymer, W. Z., and Trumbower, R. D. (2014). Daily intermittent hypoxia enhances walking after chronic spinal cord injury: a randomized trial. *Neurology* 82, 104–113. doi: 10.1212/01.WNL.0000437416.34298.43

Hochman, S. (2007). Spinal cord. *Curr. Biol.* 17, R950–R955. doi: 10.1016/j.cub.2007.10.014

Hodgson, J. A., Roy, R. R., de Leon, R., Dobkin, B., and Edgerton, V. R. (1994). Can the mammalian lumbar spinal cord learn a motor task? *Med. Sci. Sports Exerc.* 26, 1491–1497.

Holmes, G. M., and Blanke, E. N. (2019). Gastrointestinal dysfunction after spinal cord injury. *Exp. Neurol.* 320:113009. doi: 10.1016/j.expneurol.2019.113009

Hook, M. A., Huie, J. R., and Grau, J. W. (2008). Peripheral inflammation undermines the plasticity of the isolated spinal cord. *Behav. Neurosci.* 122, 233–249. doi: 10.1037/0735-7044.122.1.233

Hook, M. A., Liu, G. T., Washburn, S. N., Ferguson, A. R., Bopp, A. C., Huie, J. R., et al. (2007). The impact of morphine after a spinal cord injury. *Behav. Brain Res.* 179, 281–293. doi: 10.1016/j.bbr.2007.02.035

Hook, M. A., Moreno, G., Woller, S., Puga, D., Hoy, K., Balden, R., et al. (2009). Intrathecal morphine attenuates recovery of function after a spinal cord injury. *J. Neurotrauma* 26, 741–752. doi: 10.1089/neu.2008.0710

Hook, M. A., Woller, S. A., Bancroft, E., Aceves, M., Funk, M. K., Hartman, J., et al. (2017). Neurobiological effects of morphine after spinal cord injury. *J. Neurotrauma* 34, 632–644. doi: 10.1089/neu.2016.4507

Hoy, K. C., Strain, M. M., Turtle, J. D., Lee, K. H., Huie, J. R., Hartman, J. J., et al. (2020). Evidence that the central nervous system can induce a modification at the neuromuscular junction that contributes to the maintenance of a behavioral response. *J. Neurosci.* 40, 9186–9209. doi: 10.1523/JNEUROSCI.2683-19.2020

Huang, Y. J., and Grau, J. W. (2018). Ionic plasticity and pain: the loss of descending serotonergic fibers after spinal cord injury transforms how GABA affects pain. *Exp. Neurol.* 306, 105–116. doi: 10.1016/j.expneurol.2018.05.002

Huang, Y. J., Lee, K. H., and Grau, J. W. (2017). Complete spinal cord injury (SCI) transforms how brain derived neurotrophic factor (BDNF) affects nociceptive sensitization. *Exp. Neurol.* 288, 38–50. doi: 10.1016/j.expneurol.2016.11.001

Huang, Y.-J., Lee, K. H., Murphy, L., Garraway, S. M., and Grau, J. W. (2016). Spinal cord injury (SCI) transforms how GABA affects nociceptive plasticity. *Exp. Neurol.* 285, 82–95. doi: 10.1016/j.expneurol.2016.09.005

Hudson, K. E., and Grau, J. W. (2022). Ionic plasticity: common mechanistic underpinnings of pathology in spinal cord injury and the brain. *Cell* 11:2910. doi: 10.3390/cells11182910

Hudson, K. E., Tarbet, M. M., and Grau, J. W. (2022). Proprioceptive gating of nociceptive signaling: Positioning to minimize maladaptive plasticity after spinal cord injury. *National Neurotrauma Symposium*. Atlanta, GA. J.: Neurotrauma. 39:A31. doi: 10.1089/neu.2022.29126.abstracts

Huie, J. R., Baumbauer, K. M., Lee, K. H., Bresnahan, J. C., Beattie, M. S., Ferguson, A. R., et al. (2012a). Glial tumor necrosis factor alpha (TNF alpha) generates metaplastic inhibition of spinal learning. *PLoS One* 7:e39751. doi: 10.1371/journal.pone.0039751

Huie, J. R., Garraway, S. M., Baumbauer, K. M., Hoy, K. C., Beas, B. S., Montgomery, K. S., et al. (2012b). Brain-derived neurotrophic factor promotes adaptive plasticity within the spinal cord and mediates the beneficial effects of controllable stimulation. *Neuroscience* 200, 74–90. doi: 10.1016/j.neuroscience.2011.10.028

Huie, J. R., Stuck, E. D., Lee, K. H., Irvine, K. A., Beattie, M. S., Bresnahan, J. C., et al. (2015). AMPA receptor phosphorylation and synaptic co-localization on motor neurons drive maladaptive plasticity below complete spinal cord injury. *eNeuro* 2:eneuro.0091-15.2015. doi: 10.1523/eneuro.0091-15.2015

Iyer, S. M., Vesuna, S., Ramakrishnan, C., Huynh, K., Young, S., Berndt, A., et al. (2016). Optogenetic and chemogenetic strategies for sustained inhibition of pain. *Sci. Rep.* 6:30570. doi: 10.1038/srep30570

Jenkins, H. M. (1973). "Effects of the stimulus-reinforcer relation on selected and unselected responses" in *Constraints on learning*. eds. R. A. Hinde and J. S. Hinde (New York: Academic Press)

Jessell, T. M. (2000). Neuronal specification in the spinal cord: inductive signals and transcriptional codes. *Nat. Rev. Genet.* 1, 20–29. doi: 10.1038/35049541

Ji, R. R., Baba, H., Brenner, G. J., and Woolf, C. J. (1999). Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity. *Nat. Neurosci.* 2, 1114–1119. doi: 10.1038/16040

Ji, R. R., Kohno, T., Moore, K. A., and Woolf, C. J. (2003). Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends Neurosci.* 26, 696–705. doi: 10.1016/j.tins.2003.09.017

Jo, H. J., and Perez, M. A. (2020). Corticospinal-motor neuronal plasticity promotes exercise-mediated recovery in humans with spinal cord injury. *Brain J. Neurol.* 143, 1368–1382. doi: 10.1093/brain/awaa052

Joynes, R. L., and Grau, J. W. (1996). Mechanisms of pavlovian conditioning: role of protection from habituation in spinal conditioning. *Behav. Neurosci.* 110, 1375–1387. doi: 10.1037/0735-7044.110.6.1375

Joynes, R. L., and Grau, J. W. (2004). Instrumental learning within the spinal cord: III. Prior exposure to noncontingent shock induces a behavioral deficit that is blocked by an opioid antagonist. *Neurobiol. Learn. Mem.* 82, 35–51. doi: 10.1016/j.nlm.2004.04.001

Joynes, R. L., Janjua, K., and Grau, J. W. (2004). Instrumental learning within the spinal cord: VI the NMDA receptor antagonist, AP5, disrupts the acquisition and maintenance of an acquired flexion response. *Behav. Brain Res.* 154, 431–438. doi: 10.1016/j.bbr.2004.03.030

Kaila, K., Price, T. J., Payne, J. A., Puskarjov, M., and Voipio, J. (2014). Cation-chloride cotransporters in neuronal development, plasticity and disease. *Nat. Rev. Neurosci.* 15, 637–654. doi: 10.1038/nrn3819

Kiehn, O. (2006). Locomotor circuits in the mammalian spinal cord. *Annu. Rev. Neurosci.* 29, 279–306. doi: 10.1146/annurev.neuro.29.051605.112910

Kiehn, O., and Kjaerulff, O. (1998). Distribution of central pattern generators for rhythmic motor outputs in the spinal cord of limbed vertebrates. *Ann. N. Y. Acad. Sci.* 860, 110–129. doi: 10.1111/j.1749-6632.1998.tb09043.x

Kigerl, K. A., Zane, K., Adams, K., Sullivan, M. B., and Popovich, P. G. (2020). The spinal cord-gut-immune axis as a master regulator of health and neurological function after spinal cord injury. *Exp. Neurol.* 323:113085. doi: 10.1016/j.expneurol.2019.113085

Kirshblum, S., Campagnolo, D. I., and DeLisa, J. A. (2002). *Spinal cord medicine*. Philadelphia, PA: Lippincott Williams & Williams.

Kopp, M. A., Watzlawick, R., Martus, P., Failli, V., Finkenstaedt, F. W., Chen, Y., et al. (2017). Long-term functional outcome in patients with acquired infections after acute spinal cord injury. *Neurology* 88, 892–900. doi: 10.1212/WNL.0000000000003652

Krassioukov, A. V., Furlan, J. C., and Fehlings, M. G. (2003). Autonomic dysreflexia in acute spinal cord injury: an under-recognized clinical entity. *J. Neurotrauma* 20, 707–716. doi: 10.1089/089771503767869944

Kupari, J., and Ernfors, P. (2023). Molecular taxonomy of nociceptors and pruriceptors. *Pain* 164, 1245–1257. doi: 10.1097/j.pain.0000000000002831

Ladle, D. R., Pecho-Vrieseling, E., and Arber, S. (2007). Assembly of motor circuits in the spinal cord: driven to function by genetic and experience-dependent mechanisms. *Neuron* 56, 270–283. doi: 10.1016/j.neuron.2007.09.026

Latremoliere, A., and Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J. Pain* 10, 895–926. doi: 10.1016/j.jpain.2009.06.012

Lee, K. H., Huang, Y. J., and Grau, J. W. (2016). Learning about time within the spinal cord II: evidence that temporal regularity is encoded by a spinal oscillator. *Front. Behav. Neurosci.* 10:14. doi: 10.3389/fnbeh.2016.00014

Lee, S. K., and Pfaff, S. L. (2001). Transcriptional networks regulating neuronal identity in the developing spinal cord. *Nat. Neurosci.* 4, 1183–1191. doi: 10.1038/nn750

Lee, K. H., Turtle, J. D., Strain, M. M., Huang, Y.-J., Baumbauer, K. M., and Grau, J. W. (2015). Learning about time within the spinal cord: evidence that spinal neurons can abstract and store an index of regularity. *Front. Behav. Neurosci.* 9:274. doi: 10.3389/fnbeh.2015.00274

Lees, J. G., Fivelman, B., Duffy, S. S., Makker, P. G., Perera, C. J., and Moalem-Taylor, G. (2015). Cytokines in neuropathic pain and associated depression. *Modern Trends Pharmacopsych* 30, 51–66. doi: 10.1159/000435932

Levinsson, A., Luo, X. L., Holmberg, H., and Schouenborg, J. (1999). Developmental tuning in a spinal nociceptive system: effects of neonatal spinalization. *J. Neurosci.* 19, 10397–10403. doi: 10.1523/JNEUROSCI.19-23-10397.1999

Linden, H., Petersen, P. C., Vestergaard, M., and Berg, R. W. (2022). Movement is governed by rotational neural dynamics in spinal motor networks. *Nature* 610, 526–531. doi: 10.1038/s41586-022-05293-w

Liu, G. T., Ferguson, A. R., Crown, E. D., Bopp, A. C., Miranda, R. C., and Grau, J. W. (2005). Instrumental learning within the rat spinal cord: localization of the essential neural circuit. *Behav. Neurosci.* 119, 538–547. doi: 10.1037/0735-7044.119.2.538

Liu, X. G., Morton, C. R., Azkue, J. J., Zimmermann, M., and Sandkuhler, J. (1998). Long-term depression of C-fibre-evoked spinal field potentials by stimulation of primary afferent a delta-fibres in the adult rat. *Eur. J. Neurosci.* 10, 3069–3075. doi: 10.1046/j.1460-9568.1998.00310.x

Liu, X., and Sandkuhler, J. (1997). Characterization of long-term potentiation of C-fiber-evoked potentials in spinal dorsal horn of adult rat: essential role of NK1 and NK2 receptors. *J. Neurophysiol.* 78, 1973–1982. doi: 10.1152/jn.1997.78.4.1973

Lopez-Garcia, J. A. (2006). Serotonergic modulation of spinal sensory circuits. *Curr. Top. Med. Chem.* 6, 1987–1996. doi: 10.2174/156802606778522159

Losey, P., Young, C., Krimholtz, E., Bordet, R., and Anthony, D. C. (2014). The role of hemorrhage following spinal-cord injury. *Brain Res.* 1569, 9–18. doi: 10.1016/j.brainres.2014.04.033

Lu, V. B., Biggs, J. E., Stebbing, M. J., Balasubramanyan, S., Todd, K. G., Lai, A. Y., et al. (2009). Brain-derived neurotrophic factor drives the changes in excitatory synaptic transmission in the rat superficial dorsal horn that follow sciatic nerve injury. *J. Physiol.* 587, 1013–1032. doi: 10.1113/jphysiol.2008.166306

Lubow, R. E. (1973). Latent inhibition as a means of behavior prophylaxis. *Psychol. Rep.* 32, 1247–1252. doi: 10.2466/pr0.1973.32.3c.1247

Lukoyanov, N., Watanabe, H., Carvalho, L. S., Kononenko, O., Sarkisyan, D., Zhang, M., et al. (2021). Left-right side-specific endocrine signaling complements neural pathways to mediate acute asymmetric effects of brain injury. *Elife* 10:247. doi: 10.7554/eLife.65247

Lundberg, A. (1969). Convergence of excitatory and inhibitory action on interneurones in the spinal cord. *UCLA Forum Med. Sci.* 11, 231–265.

Magnuson, D. S., Trinder, T. C., Zhang, Y. P., Burke, D., Morassutti, D. J., and Shields, C. B. (1999). Comparing deficits following excitotoxic and contusion injuries in the thoracic and lumbar spinal cord of the adult rat. *Exp. Neurol.* 156, 191–204. doi: 10.1006/exnr.1999.7016

Maier, S. F., and Seligman, M. E. (2016). Learned helplessness at fifty: insights from neuroscience. *Psychol. Rev.* 123, 349–367. doi: 10.1037/rev0000033

Maier, S. F., and Watkins, L. R. (1998). Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol. Rev.* 105, 83–107. doi: 10.1037/0033-295x.105.1.83

Malomouzh, A. I., Nurullin, L. F., Arkhipova, S. S., and Nikolsky, E. E. (2011). NMDA receptors at the endplate of rat skeletal muscles: precise postsynaptic localization. *Muscle Nerve* 44, 987–989. doi: 10.1002/mus.22250

Martin, J. H. (1996). *Neuroanatomy: Text and atlas*. Stamford, CT: Appleton & Lange.

Mauk, M. D., and Buonomano, D. V. (2004). The neural basis of temporal processing. *Annu. Rev. Neurosci.* 27, 307–340. doi: 10.1146/annurev.neuro.27.070203.144247

Mays, T. A., Sanford, J. L., Hanada, T., Chishti, A. H., and Rafael-Fortney, J. A. (2009). Glutamate receptors localize postsynaptically at neuromuscular junctions in mice. *Muscle Nerve* 39, 343–349. doi: 10.1002/mus.21099

McCulloch, W. (1945). The heterarchy of values determined by the topology of nervous nets. *Bull. Math. Biophys.* 7:227. doi: 10.1007/BF02478429

McLemore, S., Crown, E. D., Meagher, M. W., and Grau, J. W. (1999). Shock-induced hyperalgesia: II. Role of the dorsolateral periaqueductal gray. *Behav. Neurosci.* 113, 539–549. doi: 10.1037/0735-7044.113.3.539

McNally, G. P., Johansen, J. P., and Blair, H. T. (2011). Placing prediction into the fear circuit. *Trends Neurosci.* 34, 283–292. doi: 10.1016/j.tins.2011.03.005

McPherson, J. G., Miller, R. R., and Perlmutter, S. I. (2015). Targeted, activity-dependent spinal stimulation produces long-lasting motor recovery in chronic cervical spinal cord injury. *Proc. Natl. Acad. Sci. U. S. A.* 112, 12193–12198. doi: 10.1073/pnas.1505383112

Meagher, M. W., Grau, J. W., and King, R. A. (1989). Frontal-cortex lesions block the opioid and nonopioid Hypoalgesia elicited by brief shocks but not the nonopioid Hypoalgesia elicited by long shocks. *Behav. Neurosci.* 103, 1366–1371. doi: 10.1037/0735-7044.103.6.1366

Meagher, M. W., Grau, J. W., and King, R. A. (1990). Role of supraspinal systems in environmentally induced antinociception—effect of spinalization and decerebration on brief shock-induced and long shock-induced antinociception. *Behav. Neurosci.* 104, 328–338. doi: 10.1037/0735-7044.104.2.328

Medina, I., Friedel, P., Rivera, C., Kahle, K. T., Kourdougli, N., Uvarov, P., et al. (2014). Current view on the functional regulation of the neuronal K+-Cl^- cotransporter KCC2. *Front. Cell. Neurosci.* 8:18. doi: 10.3389/fncel.2014.00027

Mendell, L. M., and Wall, P. D. (1965). Responses of single dorsal cord cells to peripheral cutaneous unmyelinated fibres. *Nature* 206, 97–99. doi: 10.1038/206097a0

Merighi, A., Salio, C., Ghirri, A., Lossi, L., Ferrini, F., Betelli, C., et al. (2008). BDNF as a pain modulator. *Prog. Neurobiol.* 85, 297–317. doi: 10.1016/j.pneurobio.2008.04.004

Michel-Flutot, P., Lane, M. A., Lepore, A. C., and Vinit, S. (2023). Therapeutic strategies targeting respiratory recovery after spinal cord injury: from preclinical development to clinical translation. *Cell* 12:519. doi: 10.3390/cells12111519

Mishra, A. M., Pal, A., Gupta, D., and Carmel, J. B. (2017). Paired motor cortex and cervical epidural electrical stimulation timed to converge in the spinal cord promotes lasting increases in motor responses. *J. Physiol.* 595, 6953–6968. doi: 10.1113/JP274663

Mitchell, G. S., and Baker, T. L. (2022). Respiratory neuroplasticity: mechanisms and translational implications of phrenic motor plasticity. *Handb. Clin. Neurol.* 188, 409–432. doi: 10.1016/B978-0-323-91534-2.00016-3

Morris, R. G. (2013). NMDA receptors and memory encoding. *Neuropharmacology* 74, 32–40. doi: 10.1016/j.neuropharm.2013.04.014

Navarrete-Opazo, A., Alcayaga, J., Sepulveda, O., Rojas, E., and Astudillo, C. (2017). Repetitive intermittent hypoxia and locomotor training enhances walking function in incomplete spinal cord injury subjects: a randomized, triple-blind, Placebo-Controlled Clinical Trial. *J. Neurotrauma* 34, 1803–1812. doi: 10.1089/neu.2016.4478

Neumann, S., Doubell, T. P., Leslie, T., and Woolf, C. J. (1996). Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature* 384, 360–364. doi: 10.1038/384360a0

Nielson, J. L., Paquette, J., Liu, A. W., Guandique, C. F., Tovar, C. A., Inoue, T., et al. (2015). Topological data analysis for discovery in preclinical spinal cord injury and traumatic brain injury. *Nat. Commun.* 6:8581. doi: 10.1038/ncomms9581

Noble, B. T., Brennan, F. H., and Popovich, P. G. (2018). The spleen as a neuroimmune interface after spinal cord injury. *J. Neuroimmunol.* 321, 1–11. doi: 10.1016/j.jneuroim.2018.05.007

Patterson, M. M. (2001a). Classical conditioning of spinal reflexes: the first seventy years. In: *Model Systems and the Neurobiology of Associative Learning: A Festschrift in Honor of Richard F. Thompson*. eds. J. E. Steinmetz, M. A. Gluck and P. R. Solomon Mahwah, NJ: Lawrence Erlbaum Associates. 1–22.

Patterson, M. M. (2001b). "Spinal fixation: long-term alterations in spinal reflex excitability with altered or sustained sensory inputs" in *Spinal cord plasticity: Alterations in reflex function*. eds. M. M. Patterson and J. W. Grau (Norwell, MA: Kluwer Academic Publishers), 77–100.

Patton, B. C., Hook, M. A., Ferguson, A. R., Crown, E. D., and Grau, J. W. (2004). The behavioral deficit observed following noncontingent shock in spinalized rats is prevented by the protein synthesis inhibitor cycloheximide. *Behav. Neurosci.* 118, 653–658. doi: 10.1037/0735-7044.118.3.653

Pavlov, I. P. (1927). *Conditioned reflexes*. [AnrepG. V., trans.] London: Oxforad University Press.

Personius, K. E., and Balice-Gordon, R. J. (2000). Activity-dependent editing of neuromuscular synaptic connections. *Brain Res. Bull.* 53, 513–522. doi: 10.1016/s0361-9230(00)00384-1

Personius, K. E., Slusher, B. S., and Udin, S. B. (2016). Neuromuscular NMDA Receptors Modulate Developmental Synapse Elimination. *J. Neurosci.* 36, 8783–8789. doi: 10.1523/jneurosci.1181-16.2016

Petersson, P., Waldenstrom, A., Fahraeus, C., and Schouenborg, J. (2003). Spontaneous muscle twitches during sleep guide spinal self-organization. *Nature* 424, 72–75. doi: 10.1038/nature01719

Pezet, S., Malcangio, M., and McMahon, S. B. (2002). BDNF: a neuromodulator in nociceptive pathways? *Brain Res. Rev.* 40, 240–249. doi: 10.1016/S0165-0173(02)00206-0

Pocratsky, A. M., Burke, D. A., Morehouse, J. R., Beare, J. E., Riegler, A. S., Tsoulfas, P., et al. (2017). Reversible silencing of lumbar spinal interneurons unmasks a task-specific network for securing hindlimb alternation. *Nat. Commun.* 8:1963. doi: 10.1038/s41467-017-02033-x

Pocratsky, A. M. S. C. T., Morehouse, J. R., Burke, D. A., Riegler, A. S., Hardin, J. T., Beare, J. E., et al. (2020). Long ascending propriospinal neurons provide flexible, context-specific control of interlimb coordination. *Elife* 9:565. doi: 10.7554/eLife.53565

Popovich, P. G. (2014). Neuroimmunology of traumatic spinal cord injury: a brief history and overview. *Exp. Neurol.* 258, 1–4. doi: 10.1016/j.expneurol.2014.05.001

Rabchevsky, A. G., and Kitzman, P. H. (2011). Latest approaches for the treatment of spasticity and autonomic dysreflexia in chronic spinal cord injury. *Neurotherapeutics* 8, 274–282. doi: 10.1007/s13311-011-0025-5

Regan, R. F., and Guo, Y. (1998). Toxic effect of hemoglobin on spinal cord neurons in culture. *J. Neurotrauma* 15, 645–653. doi: 10.1089/neu.1998.15.645

Rescorla, R. A. (1988). Pavlovian conditioning: It's not what you think it is. *Am. Psychol.* 43, 151–160. doi: 10.1037/0003-066X.43.3.151

Reynolds, J. A., Henwood, M. K., Turtle, J. D., Baine, R. E., Johnston, D. T., and Grau, J. W. (2019). Brain-dependent processes fuel pain-induced hemorrhage after spinal cord injury. *Front. Syst. Neurosci.* 13:44. doi: 10.3389/fnsys.2019.00044

Rivera, C., Voipio, J., and Kaila, K. (2005). Two developmental switches in GABAergic signalling: the K+Cl$^-$ cotransporter KCC2 and carbonic anhydrase CAVII. *J. Physiol.* 562, 27–36. doi: 10.1113/jphysiol.2004.077495

Rivera, C., Voipio, J., Thomas-Crusells, J., Li, H., Emri, Z., Sipila, S., et al. (2004). Mechanism of activity-dependent downregulation of the neuron-specific K-cl cotransporter KCC2. *J. Neurosci.* 24, 4683–4691. doi: 10.1523/JNEUROSCI.5265-03.2004

Rodgers, K. A., Kigerl, K. A., Schwab, J. M., and Popovich, P. G. (2022). Immune dysfunction after spinal cord injury—a review of autonomic and neuroendocrine mechanisms. *Curr. Opin. Pharmacol.* 64:102230. doi: 10.1016/j.coph.2022.102230

Rossignol, S. (2017). "Plasticity of stepping in rhythms in the intact and injured mammalian spinal cord" in *Oxford research encyclopedia of neuroscience*. ed. M. Sherman (New York: Oxford University Press)

Rossignol, S., Chau, C., Brustein, E., Giroux, N., Bouyer, L., Barbeau, H., et al. (1998). Pharmacological activation and modulation of the central pattern generator for locomotion in the cat. *Ann. N. Y. Acad. Sci.* 860, 346–359. doi: 10.1111/j.1749-6632.1998.tb09061.x

Rossignol, S., and Frigon, A. (2011). Recovery of locomotion after spinal cord injury: some facts and mechanisms. *Annu. Rev. Neurosci.* 34, 413–440. doi: 10.1146/annurev-neuro-061010-113746

Sandkuhler, J. (2000). Learning and memory in pain pathways. *Pain* 88, 113–118. doi: 10.1016/s0304-3959(00)00424-3

Sandkuhler, J., and Liu, X. G. (1998). Induction of long-term potentiation at spinal synapses by noxious stimulation or nerve injury. *Eur. J. Neurosci.* 10, 2476–2480. doi: 10.1046/j.1460-9568.1998.00278.x

Sanes, J. R., and Lichtman, J. W. (1999). Development of the vertebrate neuromuscular junction. *Annu. Rev. Neurosci.* 22, 389–442. doi: 10.1146/annurev.neuro.22.1.389

Sanes, J. R., and Lichtman, J. W. (2001). Induction, assembly, maturation and maintenance of a postsynaptic apparatus. *Nat. Rev. Neurosci.* 2, 791–805. doi: 10.1038/35097557

Schouenborg, J. (2008). Action-based sensory encoding in spinal sensorimotor circuits. *Brain Res. Rev.* 57, 111–117. doi: 10.1016/j.brainresrev.2007.08.007

Schouenborg, J., Holmberg, H., and Weng, H. R. (1992). Functional organization of the nociceptive withdrawal reflexes. II. Changes of excitability and receptive fields after spinalization in the rat. *Exp. Brain Res.* 90, 469–478. doi: 10.1007/BF00230929

Schwab, J. M., Zhang, Y., Kopp, M. A., Brommer, B., and Popovich, P. G. (2014). The paradox of chronic neuroinflammation, systemic immune suppression, autoimmunity after traumatic chronic spinal cord injury. *Exp. Neurol.* 258, 121–129. doi: 10.1016/j.expneurol.2014.04.023

Sherrington, C. S. (1906). *The integrative action of the nervous system*. New Haven, CT: Yale University Press.

Shurrager, P. S., and Dykman, R. A. (1951). Walking spinal carnivores. *J. Comp. Physiol. Psychol.* 44, 252–262. doi: 10.1037/h0059889

Slavich, G. M., and Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol. Bull.* 140, 774–815. doi: 10.1037/a0035302

Smith, P. A. (2014). BDNF: NO GAIN WITHOUT PAIN? *Neuroscience* 283, 107–123. doi: 10.1016/j.neuroscience.2014.05.044

Smith, J. L., Edgerton, V. R., Eldred, E., and Zernicke, R. F. (1983). The chronic spinalized cat: a model for neuromuscular plasticity. *Birth Defects Orig. Artic. Ser.* 19, 357–373.

Steinhoff, M. S., von Mentzer, B., Geppetti, P., Pothoulakis, C., and Bunnett, N. W. (2014). Tachykinins and their receptors: contributions to physiological control and the mechanisms of disease. *Physiol. Rev.* 94, 265–301. doi: 10.1152/physrev.00031.2013

Strain, M. M., Johnston, D. T., Baine, R. E., Reynolds, J. A., Huang, Y. J., Henwood, M. K., et al. (2021). Hemorrhage and locomotor deficits induced by pain input after spinal cord injury are partially mediated by changes in hemodynamics. *J. Neurotrauma* 38, 3406–3430. doi: 10.1089/neu.2021.0219

Stuart, D. G., and Hultborn, H. (2008). Thomas Graham Brown (1882--1965), Anders Lundberg (1920-), and the neural control of stepping. *Brain Res. Rev.* 59, 74–95. doi: 10.1016/j.brainresrev.2008.06.001

Takeoka, A., and Arber, S. (2019). Functional local proprioceptive feedback circuits initiate and maintain locomotor recovery after spinal cord injury. *Cell Rep.* 27, 71–85.e3. doi: 10.1016/j.celrep.2019.03.010

Tashiro, S., Shinozaki, M., Mukaino, M., Renault-Mihara, F., Toyama, Y., Liu, M., et al. (2015). BDNF induced by treadmill training contributes to the suppression of spasticity and allodynia after spinal cord injury via upregulation of KCC2. *Neurorehabil. Neural Repair* 29, 677–689. doi: 10.1177/1545968314562110

Thompson, R. F. (1986). The neurobiology of learning and memory. *Science* 233, 941–947. doi: 10.1126/science.3738519

Thompson, R. F. (2001). *"spinal plasticity," in spinal cord plasticity: Alterations in reflex function*. Norwell, MA: Klower Academic Publishers, 1–12.

Timberlake, W. (1990). "Biological behaviorism" in *Handbook of behaviorism*. eds. W. O'Donohuse and R. Kitchener (New York: Academic Press), 244–286.

Timberlake, W., and Lucas, G. A. (1989). "Behavior systems and learning: from misbehavior to general principles" in *Contemporary learning theory: Instrumental conditioning and the impact of biological constraints on learning*. eds. S. B. Klein and R. R. Mowrer (Hillsdale, NJ: Lawrence Erlbaum), 237–275.

Turtle, J. D., Henwood, M. K., Strain, M. M., Huang, Y. J., Miranda, R. C., and Grau, J. W. (2019). Engaging pain fibers after a spinal cord injury fosters hemorrhage and expands the area of secondary injury. *Exp. Neurol.* 311, 115–124. doi: 10.1016/j.expneurol.2018.09.018

Turtle, J. D., Strain, M. M., Aceves, M., Huang, Y. J., Reynolds, J. A., Hook, M. A., et al. (2017). Pain input impairs recovery after spinal cord injury: treatment with lidocaine. *J. Neurotrauma* 34, 1200–1208. doi: 10.1089/neu.2016.4778

Turtle, J. D., Strain, M. M., Reynolds, J. A., Huang, Y. J., Lee, K. H., Henwood, M. K., et al. (2018). Pain input after spinal cord injury (SCI) undermines long-term recovery and engages signal pathways that promote cell death. *Front. Syst. Neurosci.* 12:27. doi: 10.3389/fnsys.2018.00027

Turvey, M. T. (1977). "Preliminaries to a theory of action with reference to vision" in *Perceiving, acting, and knowing*. eds. R. Shaw and J. Branford (New Jersey: Lawrence Erlbaum Associates)

Urbin, M. A., Ozdemir, R. A., Tazoe, T., and Perez, M. A. (2017). Spike-timing-dependent plasticity in lower-limb motoneurons after human spinal cord injury. *J. Neurophysiol.* 118, 2171–2180. doi: 10.1152/jn.00111.2017

Vavrek, R., Girgis, J., Tetzlaff, W., Hiebert, G. W., and Fouad, K. (2006). BDNF promotes connections of corticospinal neurons onto spared descending interneurons in spinal cord injured rats. *Brain* 129, 1534–1545. doi: 10.1093/brain/awl087

Viemari, J. C., Bos, R., Boulenguez, P., Brocard, C., Brocard, F., Bras, H., et al. (2011). "Importance of chloride homeostasis in the operation of rhythmic motor networks" in *Breathe, walk and chew: The neural challenge: Part ii*. eds. J. P. Gossard, R. Dubuc and A. Kolta (Amsterdam: Elsevier Science Bv), 3–14.

Waldenstrom, A., Thelin, J., Thimansson, E., Levinsson, A., and Schouenborg, J. (2003). Developmental learning in a pain-related system: evidence for a cross-modality mechanism. *J. Neurosci.* 23, 7719–7725. doi: 10.1523/JNEUROSCI.23-20-07719.2003

Walters, E. T. (2018). How is chronic pain related to sympathetic dysfunction and autonomic dysreflexia following spinal cord injury? *Auton. Neurosci.* 209, 79–89. doi: 10.1016/j.autneu.2017.01.006

Walters, E. T., Crook, R. J., Neely, G. G., Price, T. J., and Smith, E. S. J. (2023). Persistent nociceptor hyperactivity as a painful evolutionary adaptation. *Trends Neurosci.* 46, 211–227. doi: 10.1016/j.tins.2022.12.007

Washburn, S. N., Maultsby, M. L., Puga, D. A., and Grau, J. W. (2008). Opioid regulation of spinal cord plasticity: evidence the kappa-2 opioid receptor agonist GR89696 inhibits learning within the rat spinal cord. *Neurobiol. Learn. Mem.* 89, 1–16. doi: 10.1016/j.nlm.2007.09.009

Willis, W. D. (2001). "Mechanisms of central sensitization of nociceptive dorsal horn neurons" in *Spinal cord plasticity: Alterations in reflex function*. eds. M. M. Patterson and J. W. Grau (Boston: Kluwer Academic Publishers), 127–161.

Windhorst, U. (2007). Muscle proprioceptive feedback and spinal networks. *Brain Res. Bull.* 73, 155–202. doi: 10.1016/j.brainresbull.2007.03.010

Wolpaw, J. R. (2018). The negotiated equilibrium model of spinal cord function. *J. Physiol.* 596, 3469–3491. doi: 10.1113/JP275532

Wolpaw, J. R., and Carp, J. S. (1990). Memory traces in spinal-cord. *Trends Neurosci.* 13, 137–142. doi: 10.1016/0166-2236(90)90005-u

Wolpaw, J. R., and Kamesar, A. (2022). Heksor: the central nervous system substrate of an adaptive behaviour. *J. Physiol.* 600, 3423–3452. doi: 10.1113/JP283291

Wolpaw, J. R., and Lee, C. L. (1989). Memory traces in primate spinal cord produced by operant conditioning of H-reflex. *J. Neurophysiol.* 61, 563–572. doi: 10.1152/jn.1989.61.3.563

Woolf, C. J. (1983). Evidence for a central component of post-injury pain hypersensitivity. *Nature* 306, 686–688. doi: 10.1038/306686a0

Woolf, C. J., and Thompson, S. W. N. (1991). The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation—implications for the treatment of postinjury pain hypersensitivity states. *Pain* 44, 293–299. doi: 10.1016/0304-3959(91)90100-c

Yang, T., Dai, Y. J., Chen, G., and Cui, S. S. (2020). Dissecting the dual role of the glial scar and scar-forming astrocytes in spinal cord injury. *Front. Cell. Neurosci.* 14:78. doi: 10.3389/fncel.2020.00078

Yang, Q., Wu, Z., Hadden, J. K., Odem, M. A., Zuo, Y., Crook, R. J., et al. (2014). Persistent pain after spinal cord injury is maintained by primary afferent activity. *J. Neurosci.* 34, 10765–10769. doi: 10.1523/JNEUROSCI.5316-13.2014

Zheng, B., and Tuszynski, M. H. (2023). Regulation of axonal regeneration after mammalian spinal cord injury. *Nat. Rev. Mol. Cell Biol.* 24, 396–413. doi: 10.1038/s41580-022-00562-y

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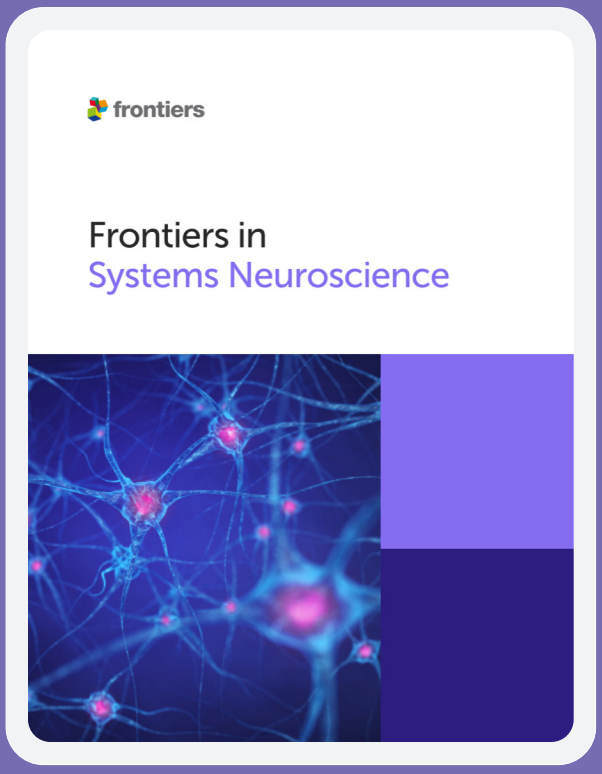

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