

Sleep as a window on the sensorimotor foundations of the developing hippocampus

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Abstract

The hippocampal formation plays established roles in learning, memory, and related cognitive functions. Recent findings also suggest that the hippocampus integrates sensory feedback from self-generated movements to modulate ongoing motor responses in a changing environment. Such findings support the view of Bland and Oddie (Behavioural Brain Research, 2001, 127, 119–136) that the hippocampus is a site of sensorimotor integration. In further support of this view, we review neurophysiological evidence in developing rats that hippocampal function is built on a sensorimotor foundation and that this foundation is especially evident early in development. Moreover, at those ages when the hippocampus is first establishing functional connectivity with distant sensory and motor structures, that connectivity is preferentially expressed during periods of active (or REM) sleep. These findings reinforce the notion that sleep, as the predominant state of early infancy, provides a critical context for sensorimotor development, including development of the hippocampus and its associated network.

KEYWORDS

development, functional connectivity, myoclonic twitching, red nucleus, REM sleep, somatosensory cortex

1 | INTRODUCTION

The hippocampal formation is implicated in a variety of behavioral and cognitive functions, most notably declarative and working memory (Bird & Burgess, 2008), spatial navigation (Igarashi, Lu, Colgin, Moser, & Moser, 2014; Pereira et al., 2007) novelty detection (Berke, Hetrick, Breck, & Greene, 2008; França et al., 2014), and perception (Ekstrom & Ranganath, 2018; Lee, Yeung, & Barense, 2012; Schiller et al., 2015). To support these functions, hippocampal neurons must process sensory information arising from internal and external stimuli. In effect, the hippocampal neural network comprises a hub for sensory information arising from sources throughout the nervous system (Martin, Beshel, & Kay, 2007; Mohedano-Moriano et al., 2008; Pereira et al., 2007). It is not yet clear, however, how the hippocampus integrates information from different sensory modalities to adaptively modulate the organisms' response to a changing environment.

Here, we review the functional features of hippocampal activity in newborn rodents and show how developmental analysis helps to reveal that structure's sensorimotor foundations. In addition, by considering the role of behavioral state in shaping activity in the developing hippocampus, it has become clear that active (or REM) sleep provides a critical context for its activity-dependent development and formation of functional connections with other related structures.

2 | BEYOND THE ROLE OF THE HIPPOCAMPUS IN LEARNING AND MEMORY

The early seminal discovery that episodic memory is compromised in patients with hippocampal damage (Scoville & Milner, 1957) inspired decades of research on the mechanisms underlying hippocampal-dependent memory consolidation (Bird & Burgess, 2008; Eichenbaum, 2017; Klinzing, Niethard, & Born, 2019). In time, it

became clear that the hippocampus serves a myriad of other cognitive functions. Many of these functions, such as spatial navigation and novelty detection, inherently rely on the processing of internal and external sensory cues. Accordingly, hippocampal neurons must process multimodal sensory information. Indeed, stimulus-evoked hippocampal activity has been documented in adult rodents for olfactory (Li et al., 2017), auditory (Itskov, Vinnik, Honey, Schnupp, & Diamond, 2012), and visual (Sakurai, 1996; Zhao, Wang, Spruston, & Magee, 2020) cues.

In the sensorimotor system, whisker-related sensory feedback from external stimulation (*exafference*) and self-generated movement (*reafference*) reliably drives single-unit and field activity in hippocampal CA1 (Grion, Akrami, Zuo, Stella, & Diamond, 2016; Pereira et al., 2007). Moreover, electrical stimulation of the infraorbital nerve, which conveys sensory input from the whiskers, triggers spiking activity in CA1 neurons; this evoked activity is suppressed by pharmacological inactivation of the ventral posteromedial nucleus of the thalamus or primary somatosensory cortex (S1), indicating that sensory information from the whiskers reaches the hippocampus through primary sensory pathways (Pereira et al., 2007). Other experiments in adult rats have demonstrated that somatosensory cortical inputs to the hippocampus arrive via the entorhinal cortex (Bellistri, Aguilar, Brotons-Mas, Foffani, & de la Prida, 2013). Finally, hippocampal neurons form and maintain detailed sensory representations to modulate motor output (Bender et al., 2015; Bland & Oddie, 2001), goal- and reward-oriented behavior (Crochet, Lee, & Petersen, 2019; Itskov, Vinnik, & Diamond, 2011), and spatial navigation (Moser, Kropff, & Moser, 2008; Moser, Moser, & McNaughton, 2017).

3 | THE SENSORIMOTOR NATURE OF THE HIPPOCAMPAL FORMATION

Bland and Oddie (2001) proposed a model in which the hippocampal formation processes sensory information to adapt ongoing motor responses in the context of a dynamic environment. They argued that this process—known as sensorimotor integration—is supported by cortical and subcortical structures involved in the production and synchrony of neural oscillatory activity in the theta band (4–10 Hz; Bland & Oddie, 2001). Theta oscillations coordinate neural activity and modulate synaptic plasticity throughout hippocampus-related neuronal networks (Buzsáki, 2002). Importantly, early studies of hippocampal theta in rats established a clear association with locomotor activities (Vanderwolf, 1969).

Along with the aforementioned primary sensory networks, Bland and Oddie's model posited that the ascending pathways that drive theta also convey sensorimotor information to the hippocampus. These pathways originate in such brainstem nuclei as the reticularis pontis oralis and the pedunculo-pontine tegmental nucleus and ascend through the posterior hypothalamus and medial forebrain bundle to reach the medial septum and, then, the hippocampal formation. According to the model, hippocampal neurons integrate the sensory information and convey it to motor regions to modulate their output.

This model introduced a novel sensorimotor function for the hippocampus, whereby it processes internal cues signaling movement initiation and modulation. As demonstrated in subsequent experiments, this model requires that the hippocampus have functional connections with brain areas involved in motor control (Bast & Feldon, 2003; Bender et al., 2015; Dypvik & Bland, 2004). Also, communication among sensory, motor, and hippocampal subsystems partly relies on synchronized theta activity (Dypvik & Bland, 2004; Grion et al., 2016; Hallworth & Bland, 2004). In the next section, we summarize evidence in infant rodents that supports Bland and Oddie's sensorimotor model of hippocampal function.

4 | THE EMERGENCE OF HIPPOCAMPAL ACTIVITY IS TIED TO SLEEP AND SENSORY EXPERIENCE

Before the development of the adult pattern of continuous brain activity, the activity in cortical and subcortical areas is characterized by brief bursts of single-unit and oscillatory activity interposed with relatively longer periods of silence (Colonnese & Phillips, 2018; Khazipov & Luhmann, 2006; Vanhatalo & Kaila, 2006). This *discontinuous* pattern of activity is a distinct feature of the developing brain in humans and neonatal rodents and appears to contribute to the activity-dependent development of the nervous system, including such processes as synapse formation, neuronal differentiation and migration, programmed cell death (apoptosis), and formation and refinement of topographic maps (Blanquie et al., 2017a, 2017b; Hanganu-Opatz, 2010; Khazipov & Luhmann, 2006; Lebedeva et al., 2017; Yang, Reyes-Puerta, Kilb, & Luhmann, 2016). In addition, the temporal coupling or coactivation of these discrete oscillatory events is thought to denote emerging connectivity across functionally related networks (Ahlbeck, Song, Chini, Bitzenhofer, & Hanganu-Opatz, 2018; Bitzenhofer et al., 2017; Bitzenhofer, Sieben, Siebert, Spehr, & Hanganu-Opatz, 2015; Brockmann, Pöschel, Cichon, & Hanganu-Opatz, 2011; Del Rio-Bermudez & Blumberg, 2018; Del Rio-Bermudez, Kim, Sokoloff, & Blumberg, 2020; Uhlhaas & Singer, 2011; Valeeva et al., 2019).

Many investigations of early brain activity and its associated molecular mechanisms were performed using *in vitro* preparations or under experimental conditions *in vivo* that block the normal expression of sleep–wake cycles (i.e., anesthesia). Under such conditions, hippocampal activity during the first postnatal week is characterized by seemingly random periodic bursts of oscillations with rhythmic components in the theta, alpha (8–13 Hz), beta (14–30 Hz), and gamma (30–50 Hz) domains; these oscillations are also associated with multiunit discharge (Brockmann et al., 2011).

In contrast, when neural activity is recorded in behaving pups, it is evident that hippocampal activity is both sensory- and state-dependent. For example, recording from the dorsal CA1 of week-old rats, we recently demonstrated that both spiking and oscillatory activity are markedly increased during active sleep, as compared with periods of wakefulness or behavioral quiescence (Del Rio-Bermudez

et al., 2020). In line with a previous study (Mohns & Blumberg, 2008, 2010), this increased hippocampal activity during active sleep was often coupled with the occurrence of self-generated myoclonic twitches, characteristic of this behavioral state. Unlike twitches, wake-related movements elicited relatively little CA1 activity, further indicating that active sleep provides a unique context for the sensory-related activation of developing hippocampal networks (for reviews of sleep-related twitching in early development, see Blumberg, Marques, & Iida, 2013; Blumberg, 2015a; Del Rio-Bermudez & Blumberg, 2018). The mechanisms underlying the modulation of sensory feedback from wake-related movements in sensory areas such as the hippocampus (Del Rio-Bermudez, Kim, Sokoloff, & Blumberg, 2017; Mohns & Blumberg, 2010), thalamus (Tiriac, Uitermarkt, Fanning, Sokoloff, & Blumberg, 2012), and sensorimotor cortex (Dooley & Blumberg, 2018; Dooley, Glanz, Sokoloff, & Blumberg, 2020; Tiriac et al., 2012; Tiriac, Del Rio-Bermudez, & Blumberg, 2014) of neonatal rats are complex. However, evidence in week-old rats indicates that sensory gating occurs at the earliest stages of sensory processing and that this gating largely disappears by the end of the second postnatal week (Dooley & Blumberg, 2018; Tiriac & Blumberg, 2016).

Regarding efference, we and others have also shown that passive movement of the whiskers reliably trigger activity in the hippocampus of neonatal rats (Del Rio-Bermudez et al., 2020; Valeeva et al., 2019). Thus, sensory input arising from both self- and other-generated movements likely contributes to the activity-dependent development of hippocampal circuits.

The contribution of sensory stimulation to hippocampal development is also revealed by studies that employ early sensory deprivation. For instance, long-term deprivation of whisker-related tactile input in developing mice depressed activity in CA3 pyramidal neurons, increased the fraction of silent synapses, and reduced the NMDA-to-AMPA ratio at CA3-CA1 synapses (Milshtein-Parush et al., 2017). Given such findings, it appears that sensory experience sculpts key plastic processes important for the proper functioning of the hippocampus later in life, as extensively demonstrated in the barrel cortex (Crocker-Buque, Brown, Kind, Isaac, & Daw, 2015; Fox, 1992; Simons & Land, 1987).

5 | ACTIVE SLEEP PROMOTES THE EARLY ORCHESTRATION OF HIPPOCAMPAL SENSORIMOTOR NETWORKS

In infants and adults, synchronized oscillatory activity across neuronal structures provides evidence of functional connectivity (Brockmann et al., 2011; Buzsáki & Draguhn, 2004; Del Rio-Bermudez et al., 2017; Karalis et al., 2016; Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). As discussed above, because active sleep and twitches facilitate the expression of neonatal hippocampal oscillations, we hypothesized that they are key contributors to the emergence of connectivity in hippocampus-related sensorimotor networks. We have tested this hypothesis by assessing hippocampal connectivity in cortical and brainstem structures.

5.1 | Cortico-hippocampal network

To characterize the contribution of active sleep and sleep-related twitches to the oscillatory coupling between hippocampus and S1, we simultaneously recorded neural activity from dorsal CA1 and barrel cortex of P8 rats while monitoring whisker movements across behavioral states (Del Rio-Bermudez et al., 2020). The expression of coherent (i.e., temporally coupled) oscillations in this network was strongly modulated across the sleep-wake cycle: Unlike periods of active wakefulness or behavioral quiescence, we observed significantly enhanced coherence in the beta2 domain (20–30 Hz) during active sleep (Figure 1). Moreover, beta2 oscillations were triggered by sleep-related whisker twitches in both S1 and CA1; assessment of peak latencies from twitch onset suggested that twitch-related sensory feedback was conveyed sequentially from cortex to hippocampus. Crucially, disrupting whisker-related sensory feedback by transecting the infraorbital nerve specifically suppressed beta2 oscillatory coherence in the vicinity of twitches as well as during active sleep more generally. These results indicated that sensory experience and sleep shape the earliest expression of coupled beta2 activity in the cortico-hippocampal system.

These findings in infant rats are informed by what is known about beta2 activity in adults. For example, in adults, cortical beta2 activity occurs in response to sensory stimulation (Hamada, Miyashita, & Tanaka, 1999; Martin et al., 2007) and is thought to support cortico-muscular coherence and sensorimotor integration (Baker, 2007); in the hippocampus, these oscillations may assist in the encoding and representation of novel environments (Berke et al., 2008; França et al., 2014; Grossberg, 2009; Igarashi et al., 2014; Vinck et al., 2016).

Movement-related sensory feedback reaches the infant rat's hippocampus via the medial entorhinal cortex (MEC; Del Rio-Bermudez et al., 2020; Mohns & Blumberg, 2010; Valeeva et al., 2019). At the molecular level, the consecutive activation of neural networks along the MEC-CA3-CA1-DG-subiculum pathway appears necessary for the anatomical and functional development of these structures (Donato, Jacobsen, Moser, & Moser, 2017). Given that sleep is the predominant behavioral state in the perinatal period in rats (Gramsbergen, Schwartz, & Precht, 1970; Jouvet-Mounier, Astic, & Lacote, 1969), twitching may be a key contributor to the activity-dependent development of the cortico-hippocampal sensory network.

5.2 | Rubro-hippocampal network

As described above, the sensorimotor integration model of hippocampal function (Bland & Oddie, 2001) posits that the hippocampus tunes behavior via functional connections with subcortical motor structures. To test this hypothesis in early development, we focused on the network comprising the hippocampus and the red nucleus (RN; Del Rio-Bermudez et al., 2017), a subcortical structure that is important for motor control of the limbs (Hermer-Vazquez et al., 2004; Mil-eykovskiy, Kiyashchenko, & Siegel, 2002; Morris, Vallester, Newton, Kearsley, & Whishaw, 2015; Muir & Whishaw, 2000). We targeted

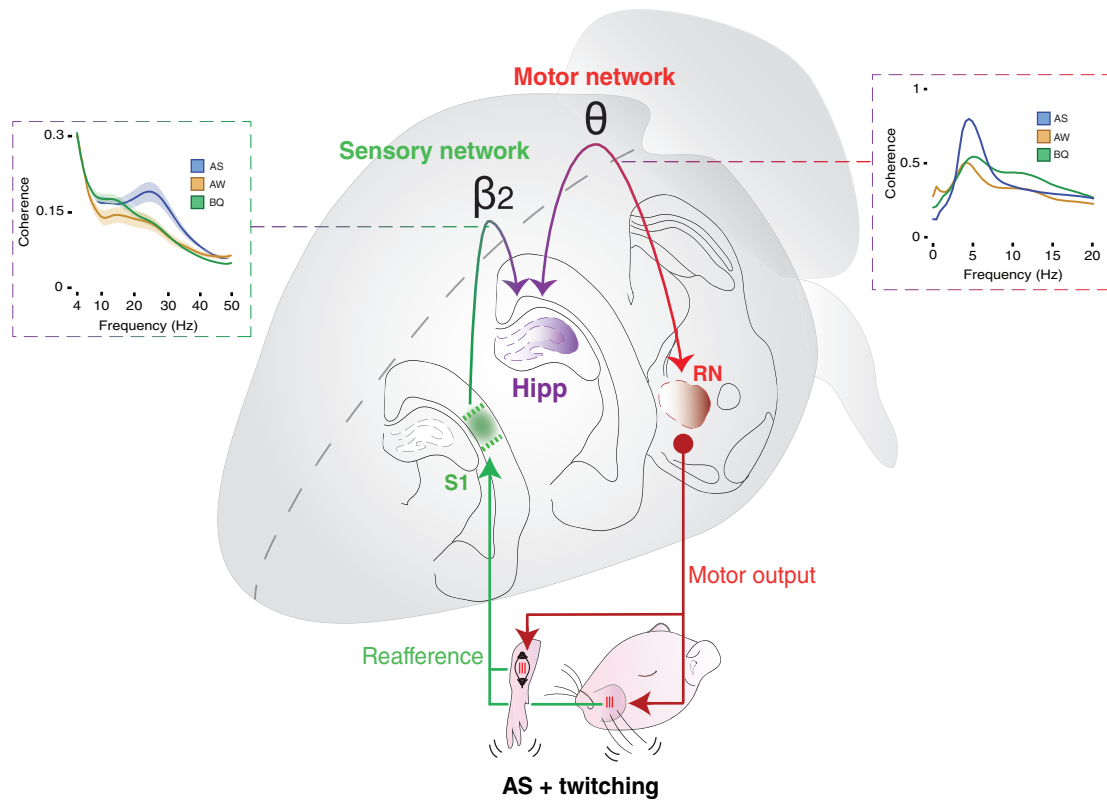


FIGURE 1 Active sleep and twitching promote oscillatory coherence across hippocampal-related sensorimotor networks in early development. The hippocampus (Hipp) of infant rats exhibits sleep-dependent oscillations that are temporally coupled with the red nucleus (RN, red) and primary somatosensory cortex (S1, green). As shown in the insets, AS promotes coherent theta oscillations between the hippocampus and RN (Del Rio-Bermudez et al., 2017) and coherent beta2 oscillations between the hippocampus and S1 (Del Rio-Bermudez et al., 2020). In addition, reafference from myoclonic twitches during AS enhances coherent oscillatory activity between the hippocampus and these two areas. AS, active sleep; AW, active wake; BQ, behavioral quiescence

the RN for four reasons, namely (a) the infant RN is involved in the generation of movements during sleep and wake (Del Rio-Bermudez, Sokoloff, & Blumberg, 2015), (b) the RN processes exafferent and refferent sensory information in a somatotopic manner, thereby implicating it in sensorimotor integration at early ages (Del Rio-Bermudez et al., 2015; Del Rio-Bermudez, Plumeau, Sattler, Sokoloff, & Blumberg, 2016), (c) the adult RN is functionally connected with the hippocampus (Dyppvik & Bland, 2004; Nioche, Cabanis, & Habas, 2009; Ryou, Cho, & Kim, 1998) and other sensorimotor structures, including spinal cord (Kuypers, 1982), cerebellum (Flumerfelt, 1980; Giuffrida, Volsi, & Perciavalle, 1988), and sensorimotor cortex (Giuffrida et al., 1988), and (d) in adult rats, RN activity modulates theta activity in the hippocampal formation (Dyppvik & Bland, 2004).

Recording from the RN of P8 rats, we were surprised to find brief theta bursts during active sleep, particularly following twitches. By P12, these fragmented oscillations were replaced by continuous theta that, again, was restricted to periods of activity sleep and whose amplitude was enhanced following twitches (Del Rio-Bermudez et al., 2017). Next, to determine whether the newly identified theta in the RN was temporally coupled with hippocampal theta (i.e., whether the two structures were functional connected), we recorded neural activity simultaneously in the RN and dorsal CA1 at P12 (see

Figure 1). Unlike periods of wakefulness and quiescence, theta oscillations in the two structures during active sleep were coherent and comodulated (i.e., theta amplitude in the RN and hippocampus increased and decreased in unison). Finally, pharmacological inactivation of the medial septum yielded a near-total suppression of sleep-related theta—though not twitch-related theta—in both RN and hippocampus. This last finding suggests distinct anatomical pathways for the generation of state- and sensory-dependent theta in the rubro-hippocampal system. Further, our finding that the RN exhibits theta oscillations and that this is tightly coupled with hippocampal theta raises the possibility of a broad motor network that uses the theta band to establish functional connectivity with the adult hippocampus. In fact, it was recently demonstrated in adult rats that the mesencephalic locomotor region exhibits increased theta activity during locomotion in a speed-dependent fashion (Noga et al., 2017), similar to what is observed in the hippocampus itself (Bender et al., 2015; Kramis, Vanderwolf, & Bland, 1975).

In summary, the earliest manifestation of functional connectivity between the hippocampus and related cortical and subcortical sensorimotor networks is closely tied to the state of active sleep and the twitches that characterize that state (Del Rio-Bermudez et al., 2017, 2020; Mohs & Blumberg, 2008, 2010).

6 | IMPLICATIONS FOR FUTURE RESEARCH

6.1 | Bridging the gap between sensorimotor and cognitive networks

Beyond S1 and RN, the developing hippocampus is also functionally connected with prefrontal cortex (PFC), a structure that supports executive and mnemonic functions in adults. In the early postnatal period, discontinuous theta bursts in the ventral CA1 drive theta-gamma oscillations in the PFC (Bitzenhofer et al., 2015; Brockmann et al., 2011; Hartung, Brockmann, Pöschel, de Feo, & Hanganu-Opatz, 2016); consequently, functional impairment of the hippocampus leads to decreased PFC activity in neonatal rats (Brockmann et al., 2011). Thus, the emergence of hippocampal activity is tied to the development of prefrontal networks.

As discussed above, tactile and proprioceptive stimulation in early development promote the sequential activation of neural networks along sensorimotor pathways, ultimately driving hippocampal activity (Del Rio-Bermudez et al., 2020; Valeeva et al., 2019). This finding opens the intriguing possibility of a sensory cascade that further propagates to the PFC, thereby contributing to the development of hippocampus-PFC connectivity. Future investigations involving simultaneous multisite recordings and targeted lesions along the entorhinal-S1-hippocampus-PFC pathway in behaving pups are necessary to determine the specific contributions of early sensory experience and sleep to this process. Elucidating the mechanisms that bridge the gap between sensorimotor and cognitive networks in infancy is important given that both disrupted hippocampal sensory processing and aberrant connectivity among sensorimotor and social-cognitive brain regions are thought to underlie later-emerging disorders such as schizophrenia (Berman et al., 2016; Freedman et al., 1996). In addition, if sleep is as critical for the activity-dependent development of both sensory and cognitive networks as we suggest, sleep disruption or restriction during sensitive developmental periods may result in the atypical wiring of critical networks and the emergence of such neurodevelopmental disorders as autism (Kamara & Beauchaine, 2020; Limoges, Mottron, Bolduc, Berthiaume, & Godbout, 2005; MacDuffie et al., 2020; Wang, Kloth, & Badura, 2014).

6.2 | The construction of embodiment

Embodied cognition is the notion that cognitive processing is highly dependent upon the physical properties of the body and the sensorimotor experiences arising from body-environment interactions (Blumberg & Dooley, 2017; Borghi & Cimatti, 2010; Munari, 2009). In this context, the *egocentric* representation and experience of one's own body (i.e., the body schema) precedes the development of *allocentric* knowledge (i.e., the body image). In the perinatal period, this process commences with the integration of interoceptive signals with proprioceptive and vestibular information. The subsequent

integration of sensory information from different modalities (e.g., visual, vestibular, and auditory) in the egocentric frame gives rise to the emergence of awareness of the body and its spatial location within the environment (Riva, 2018).

An organism's perception of its location in space largely depends on hippocampal place cells and other functionally related cells within and outside the hippocampus (Danjo, Toyozumi, & Fujisawa, 2018; Deshmukh & Knierim, 2013; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Moser et al., 2017). As argued above, these cells must in turn process sensory information to build spatial maps of the surrounding environments. Place cells, for instance, are thought to integrate information from distinct cortical inputs, regarding both specific metric information regarding distance and orientation (in coordination with grid and head direction cells) and heterogeneous contextual information informing the animal's position in space (Jeffery, 2007). If the hippocampus is indeed an integrator of sensory, motor, and contextual signals, cues associated with an animal's movements must also be processed to successfully navigate the environment. This idea was recently tested in a robot model of place-cell-based navigation (Cazin, Sclaidorovich, Weitzenfeld, & Dominey, 2020) in which the coding of self-motion cues optimized navigation to a target location. The authors concluded that physical embodiment significantly reduces the noise that can disrupt movement toward a goal.

It follows from the above that a developing organism must first gain awareness of the physical and kinematic properties of the body before learning its position in space, an ability that relies on sensorimotor integration in the hippocampus. Here, we have presented the view that active sleep and twitching is key to the development of later-emerging spatial navigation abilities by providing a context for self-generated motor experiences that promote the emergence of long-range connectivity between the hippocampus with other key structures, including sensorimotor cortex (Del Rio-Bermudez et al., 2020; Mohns & Blumberg, 2010). Our approach contrasts with others that rely on the archaic concept of innateness to explain the development of this system (see Blumberg, 2015b).

The specific role of the hippocampus in the development of an embodied mind has remained largely unexplored. The established relationship between body awareness and location in space opens the possibility that the hippocampus processes sensory feedback from self-generated movements in a somatotopic fashion. In the somatosensory cortex, for instance, somatotopic processing seems to play a key role in high-level embodied cognition (Galetzka, 2017). Although there is no evidence of somatotopic organization in the hippocampus, recordings in adult rats show that hippocampal neurons exhibit specific responses to tactile stimulation of various parts of the body (Bellistri et al., 2013). Moreover, tactile input from the whiskers modulates the firing rate of place cells and the size of place fields (Gener, Perez-Mendez, & Sanchez-Vives, 2013). The fact that the hippocampus tracks specific sensory input has important implications for our understanding not only of spatial navigation, but also of the broader relationship between the self and its surrounding environment.

6.3 | Slow-wave sleep

Here, we have focused on the putative contributions of AS in the development of hippocampal sensorimotor functions. In adults, slow-wave sleep (SWS) is known to play a key role in the consolidation of hippocampal-dependent memories (Ólafsdóttir, Bush, & Barry, 2018). Indeed, the reactivation of past place cell sequences and the synchronized activity of hippocampal ripples (~200 Hz), cortical delta waves (1–4 Hz), and spindle events (10–20 Hz) during SWS correlates with spatial learning and is thought to support memory consolidation in rodents (Girardeau, Benchenane, Wiener, Buzsáki, & Zugaro, 2009; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Ólafsdóttir, Carpenter, & Barry, 2016). From a developmental perspective, delta activity in cortical networks is not evident until P11, where it emerges in close association with periods of behavioral quiescence (Seelke and Blumberg, 2008). Similarly, hippocampal ripples activity in developing rats is not observed until the end of the second postnatal week and show a gradual increase through P18 (Buhl & Buzsáki, 2005).

Before the emergence of these key electrophysiological events, both hippocampal activity and coupled oscillatory activity between the hippocampus and related cortical and subcortical structures are more prominent during AS than other states (Del Rio-Bermudez et al., 2017, 2020). This observation suggests that AS-related activity is better situated to play a role in the development of hippocampal-dependent sensorimotor functions in the early perinatal period. The relative functional contributions and interplay between AS (including twitches) and SWS at later ages remains to be investigated.

6.4 | Implications for human development

Early oscillatory activity and temporal coupling in cortical networks is also thought to play a role in the emergence of functional connectivity and subsequent brain growth and cognitive development in human infants (Benders et al., 2015; Iyer et al., 2015; Uhlhaas et al., 2010). Although behavioral states also modulate the expression of functional connectivity in individuals with neurodevelopmental disorders such as autism (Daoust et al., 2004; Limoges et al., 2005), the specific contributions of AS and twitching to this process in early development have not been investigated.

Similar to developing rats, sleep-related twitching is a pervasive behavior in human infants (Sokoloff et al., 2020). In preterm infants, limb twitches trigger increased oscillatory activity (i.e., spindle bursts) in topographically associated regions of sensorimotor cortex (Milh et al., 2007). Although twitch-triggered spindle bursts during AS disappear within the first postnatal month (Whitehead, Meek, & Fabrizi, 2018), this should not be interpreted as evidence that twitches fail to trigger neural activity in cortical and subcortical structures at later ages. Moreover, beginning around 3 months of age, twitches begin to emerge during quiet sleep and, as they do so, they occur in synchrony with sleep spindles (Sokoloff et al., 2021). Importantly, in humans across the lifespan, sleep spindles have been implicated in a

variety of functions associated with learning and memory (Mason, Lokhandwala, Riggins, & Spencer, 2021; Rasch & Born, 2013).

Thus, we are just beginning to appreciate the significance of sleep-related twitching to human development. In the meantime, the findings summarized above lead us to propose that twitch-triggered cortical activity in human infants is conveyed to downstream and functionally related subcortical structures, including the hippocampus. If true, this would suggest that sleep, by enabling the expression of twitching, provides a critical context for the early expression of coordinated activity in cortico-hippocampal sensorimotor networks. It would follow from such a finding that sleep disruption or deprivation in early life could lead to aberrant connectivity in cortico-hippocampal networks, with potential implications for understanding the origins of the sensorimotor and cognitive impairments that characterize such neurodevelopmental disorders as autism and schizophrenia (Del Rio-Bermudez & Blumberg, 2018).

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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