The Role of Aberrant Neural Oscillations in the Hippocampal-Medial Prefrontal Cortex Circuit in Neurodevelopmental and Neurological Disorders

Nathanael Shing[1,2], Matthew C. Walker[1], Pishan Chang[3]*

1 Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London, WC1N 3BG, UK

2 Department of Medicine, University of Central Lancashire, Preston, PR17BH, UK

3 Department of Neuroscience, Physiology & Pharmacology, University College London, London, WC1E 6BT

* Correspondence: pi-shan.chang@ucl.ac.uk

Abstract

The hippocampus (HPC) and medial prefrontal cortex (mPFC) have well-established roles in cognition, emotion, and sensory processing. In recent years, interests have shifted towards developing a deeper understanding of the mechanisms underlying interactions between the HPC and mPFC in achieving these functions. Considerable research supports the idea that synchronized activity between the HPC and the mPFC is a general mechanism by which brain functions are regulated. In this review, we summarize current knowledge on the hippocampal-medial prefrontal cortex (HPC-mPFC) circuit in normal brain function with a focus on oscillations and highlight several neurodevelopmental and neurological disorders associated with aberrant HPC-mPFC circuitry. We further discuss oscillatory dynamics across the HPC-mPFC circuit as potentially useful biomarkers to assess interventions for neurodevelopmental and neurological disorders. Finally, advancements in brain stimulation, gene therapy and pharmacotherapy are explored as promising therapies for disorders with aberrant HPC-mPFC circuit dynamics.

Keywords: hippocampus; medial prefrontal cortex; neural oscillations; neurological disorders; neurodevelopmental disorders; therapy

Introduction

It is well established that the HPC and mPFC are important regions that facilitate cognition, emotion, and sensory processes (Jin and Maren et al., 2015; Ruggiero et al., 2021). A growing body of evidence suggests that information sharing between the HPC and mPFC is required for cognitive processes and successful execution of behaviours (Harris and Gordon, 2015; Negrón-Oyarzo et al., 2018; Preston and Eichenbaum, 2013; Salimi et al., 2021; Tang et al., 2021; Wirt and Hyman, 2017). Recent evidence further highlights the importance of communication between the HPC and mPFC during learning and memory processes (Dickson et al., 2022; Morici et al., 2022). Efforts to understand the pathophysiology of various disorders have focused on identifying abnormalities in regions of the HPC and mPFC underlying symptoms of these disorders. It is becoming increasingly clear that neurodevelopmental and neurological disorders are not only due to a circumscribed deficit in the HPC and/or mPFC, but also represent a distributed impairment involving HPC-mPFC connectivity (Bast et al., 2017; Calabro et al., 2020; Colgin, 2011; Godsil et al., 2013; Jones and Wilson, 2005; Li et al., 2015; Sigurdsson and Duvarci, 2016).

Neural oscillations are the fundamental mechanism to enable coordinated activity during normal brain functioning (Buzsáki and Draguhn, 2004; Singer, 1999). There is abundant evidence for a close relationship between the occurrence of oscillations and cognitive and behavioural responses (Fries et al., 2001; Uhlhaas and Singer, 2010). Neural oscillations and synchronization reflect regional and interregional communication between cortical areas. In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronized oscillations. Short-distance synchronization tends to occur at higher frequencies (>30 Hz), and long-distance synchronization often manifests in the low-frequency range (<20 Hz) (von Stein and Sarnthein, 2000). Recent studies further suggest that cross-frequency modulation across brain areas may serve a functional role in neuronal computation and communication (Womelsdorf et al., 2010). While high-frequency brain activity reflects local domains of cortical processing, low-frequency brain rhythms are dynamically entrained across distributed brain regions by both external sensory input and internal cognitive events. Therefore, cross-frequency modulation may serve as a mechanism to transfer information from large-scale brain networks operating at behavioural timescales to fast, local cortical processing required for effective computation and synaptic modification, thus integrating functional systems across multiple spatiotemporal scales (Canolty and Knight, 2010).

In this review, we present recent evidence that shows both anatomical and synchronous activity between the HPC and mPFC. We detail work revealing that the HPC-mPFC circuitry is essential for cognitive, emotional, and sensory processes. Based on anatomical and electrophysiological evidence, we further examine the possible neurobiological causes of impaired HPC-mPFC oscillations and the involvement of aberrant HPC-mPFC oscillatory activity underlying neurodevelopmental and neurological disorders. Finally, advancements in deep brain stimulation, gene therapy, and pharmacotherapy are explored as useful interventions for various disorders associated with aberrant HPC-mPFC circuitry.

Animal Models in Neuroscience Research

Animal research has formed vital contributions to understanding neural mechanisms and disorders. Non-human primates have been at the forefront of research efforts, and rodents have been the most widely used models in neuroscience research. Despite major differences in anatomical organization of brains and a 17,000-fold variability in brain volume across mammalian species, the temporal dynamics within and across brain networks remain remarkably preserved (Buzsáki et al., 2013; van Heukelum et al., 2020; Laubach et al., 2018). Furthermore, despite a small variability of individual oscillations across species, frequency ranges within species and their cross-frequency interactions are supported by the same fundamental mechanisms and can be adequately characterized across species (Buzsáki et al., 2013). Therefore, valuable insight from studies involving non-human primates and rodents help with incorporating findings across species into an integrated field of HPC-mPFC research.

Anatomical Organization of the HPC and mPFC

The HPC, located deep in the medial temporal lobe, can be classified by several subregions (subiculum, dentate gyrus, cornu ammonis regions CA1-CA3) (Fogwe et al., 2022; Nuñez and Buño, 2021) and compartments in rodents (ventral/dorsal) and primates (anterior/posterior) (Fanselow and Dong, 2010). Broadly, the mPFC refers to the cortical region anterior to the premotor cortex (Xu et al., 2019a). The precise homologies of prefrontal areas between rodents and primates remain elusive, but considerable evidence demonstrates similar patterns of interactions between hippocampal and prefrontal areas (Euston et al., 2012; Seamans et al., 2008). Anatomically, the HPC and medial PFC (mPFC) are linked by several direct (monosynaptic) and indirect (polysynaptic) pathways. Here, we provide a brief overview of the anatomy of HPC-mPFC connections, summarized in Fig. 1.

The mPFC receives monosynaptic projections from the ventral CA1 HPC (vHPC) and subiculum (Phillips et al., 2019; Sigurdsson and Duvarci, 2016). Ventral hippocampal neurons directly innervate three major GABAergic neurons in the mPFC (parvalbumin-expressing, somatostatin-expressing, and vasoactive intestinal peptide-expressing interneurons) to support contextual and spatial information (Jin and Maren, 2015). The dorsal CA3/CA1 HPC also receives a monosynaptic projection from the mPFC (predominantly anterior cingulate) (Rajasethupathy et al., 2015).

Several indirect pathways involving the thalamus, lateral entorhinal cortex (LEC) and amygdala further connect the HPC and mPFC. The thalamic nucleus reuniens (NR) is bidirectionally connected to both the mPFC and HPC, and this pathway is associated with global synchronization and associative learning (Griffin, 2015; Roy et al., 2017). Regarding cortical pathways, the LEC is bidirectionally connected to both the mPFC and HPC (Agster and Burwell, 2009; Eichenbaum, 2017; Isomura et al., 2006; Salimi et al., 2021), and this pathway involving the LEC is implicated in memory encoding and retrieval (Eichenbaum, 2017; Takehara-Nishiuchi, 2020). There are also bidirectional projections between the amygdala and the vHPC and the mPFC (Guirado et al., 2016; Hübner et al., 2014; Khastkhodaei et al., 2021), and some studies suggest that interactions between the HPC-mPFC regulate emotion and social behaviours through the basolateral amygdala (BLA)(Felix-Ortiz and Tye, 2014; Felix-Ortiz et al., 2013; Qi et al., 2018). Recent evidence further suggests that the mPFC supports the HPC in reconsolidating inhibitory avoidance memory through the amygdala (Fukushima et al., 2021).

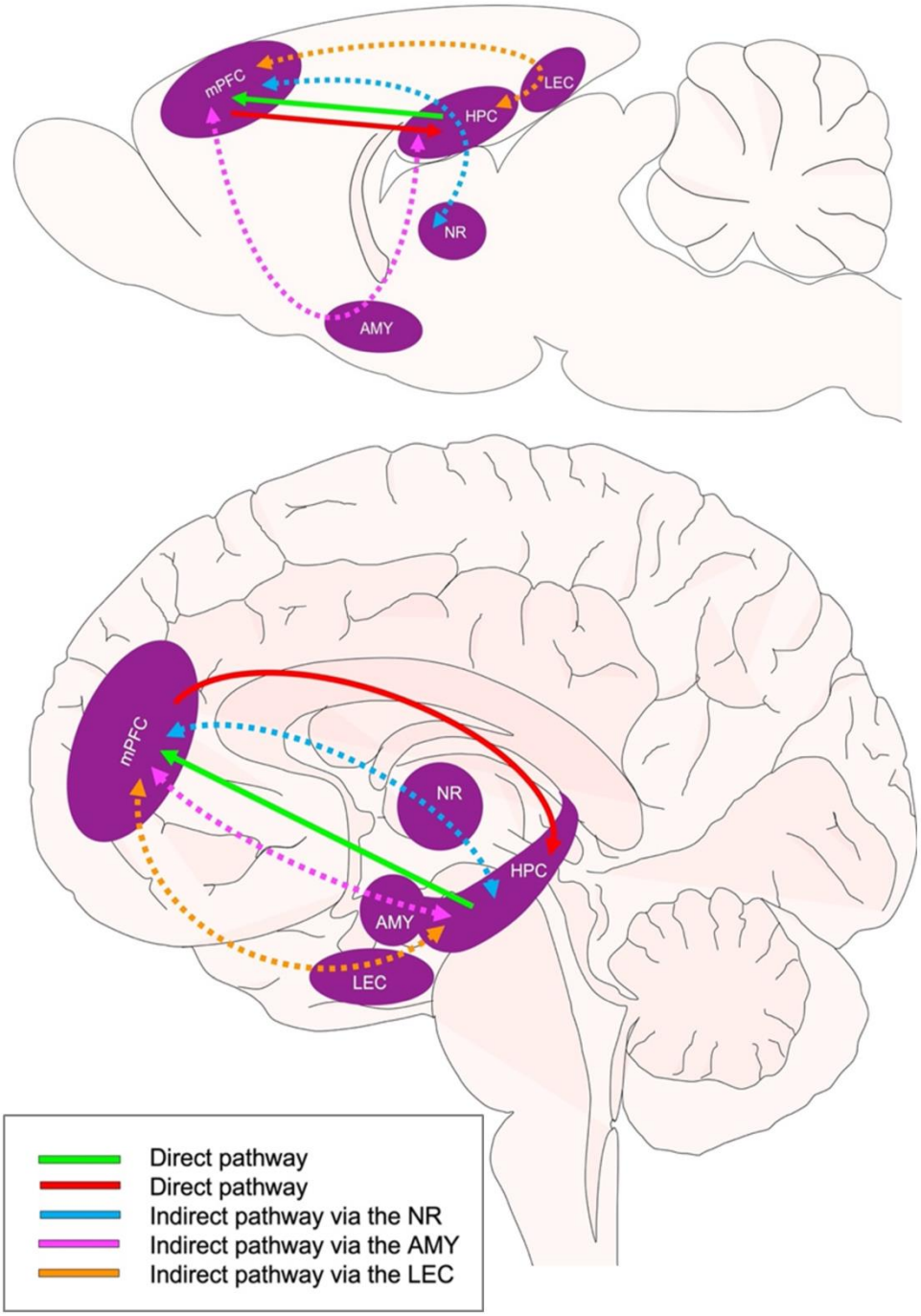

Figure 1 General schematic of direct and indirect pathways between the hippocampus (HPC) and medial prefrontal cortex (mPFC). Insight from rodent models (top) and primates (bottom) demonstrate that the HPC and mPFC are anatomically connected via direct and indirect (bidirectional) pathways. Arrows indicate direction of projections. Direct pathways involve monosynaptic projections from the CA1 ventral HPC (anterior HPC in primates) to the mPFC, and monosynaptic projections from the mPFC (predominantly anterior cingulate) to the dorsal CA3/CA1 HPC (posterior HPC in primates). Indirect HPC-mPFC pathways involve bidirectional projections between the HPC and mPFC through intermediary regions: the thalamic nucleus reuniens (NR), lateral entorhinal cortex (LEC) and amygdala (AMY). For details and supporting references, see main text.

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Oscillatory Synchrony in the HPC and mPFC

Oscillations are one of the prominent features of brain activity and play a crucial role in regional neural integration and inter-regional interactions in the brain. Oscillatory activity in groups of neurons generally arises from feedback connections between the neurons that result in the synchronization of their firing patterns. The interaction between neurons can give rise to oscillations at a different frequency than the firing frequency of individual neurons. These oscillations typically include Delta (δ, 2-4 Hz), Theta (θ, 5-7 Hz), Alpha (α, 8-12 Hz), Beta (β, 15-29 Hz) and Gamma (γ, low: 30-60 Hz and high: 60-100 Hz) (Cole and Voytek, 2017; Thut et al., 2012). Oscillations have been observed in brain regions including the HPC (Goyal et al., 2020), visual cortical areas (Galuske et al., 2019), and olfactory cortex (Salimi et al., 2021). Inter-regional oscillation coupling could modulate effective connectivity in a given behavioural period, such as while undertaking cognitive tasks, attentional selection and decision making (Berger et al., 2019; Doesburg et al., 2012; Gordon, 2011; Guise and Shapiro, 2017). Considerable evidence (Buzsáki and Draguhn, 2004; Goodman et al., 2018; Wirt et al., 2021) shows that indirect connectivity through HPC-mPFC oscillatory coupling plays a significant role across different cognitive domains, such as goal-directed behaviour (Womelsdorf et al., 2010), emotion (Jin and Maren, 2015), context-guided memory (Place et al., 2016), decision-making (Tamura et al., 2017) and spatial/episodic memory (Brincat and Miller, 2015; Igarashi, 2015; Spellman et al., 2015). Synchrony in different frequency bands may play functionally different roles in neural communication (Fries, 2005; Buzsáki and Draguhn, 2004). See **Table 1.**

(1) HPC-mPFC δ oscillation: δ-frequency network activity is commonly associated with sleep, but data from awake-behaving animals show δ-dominated network modes (HPC-mPFC coupling). Significantly elevated δ power can be observed in stationary animals during brief pauses between running bouts, whereas synchronization in the delta frequency band was minimal during locomotion. These findings suggest that HPC-mPFC δ oscillation represents functionally distinct circuit dynamics that are temporally and behaviourally alternated among θ-dominated oscillations during navigation. This oscillation is vital to coordinating encoding and retrieval mechanisms or decision-making processes at a timescale that segments event sequences within behavioural episodes (Schultheiss et al., 2020).

(2) HPC-mPFC θ oscillation: Modulation of mPFC and HPC oscillatory θ coupling by mnemonic demands of a working memory task correlated with behavioural performance both in animals (Brincat and Miller, 2015; Siapas et al., 2005) and in humans (Anderson et al., 2010; Kaplan et al., 2014; Backus et al., 2016), and θ-modulated rhythmic excitability is essential for long-term synaptic potentiation (Capocchi et al., 1992) and important for gating information flow and guiding plastic changes (Siapas et al., 2005). In addition, considerable evidence demonstrates HPC-mPFC θ coupling during spatial navigation when novel information was encoded and stored information was retrieved (Kaplan et al., 2014). An increase in HPC-mPFC θ coupling also occurs during active choice decision making (Guitart-Masip et al., 2013) and other memory tasks (Simons and Spiers, 2003).

(3) HPC-mPFC α/β oscillation: A study from macaques demonstrated that α/β-band synchrony driven by the HPC increased with learning, leading to the hypothesis that rapid object associative learning occurs in the PFC, whereas the HPC guides neocortical plasticity via oscillatory synchrony in α/β (success) or θ (failure) bands (Brincat and Miller, 2015).

(4) HPC-mPFC γ oscillation: γ rhythms have received a great deal of attention due to their relationship to higher brain functions (Buzsáki and Wang, 2012; Csicsvari et al., 2003). However, the role of HP-mPFC in synchronous γ activity is less explored. γ coupling between the HPC and mPFC was reported in relation to working memory (Sigurdsson et al., 2010) and

exploratory behaviour during anxiety (Adhikari et al., 2010). As mPFC fast γ oscillations may be coherent with fast γ in both the HPC and the entorhinal cortex (Colgin et al., 2009), the entorhinal–hippocampal–mPFC network could therefore coordinate information flow across these three regions during processing of information related to the external environment (Colgin, 2011).

(5) HPC-mPFC ripples: Ripples, discrete bouts of fast oscillations that are strongly associated with underlying bursts of spiking activity (Buzsáki, 2015), have been implicated in memory formation, consolidation, and retrieval (Buzsáki, 2015; Joo and Frank, 2018). The identification of HPC-mPFC ripples coupling with extensive cortico-cortical connections (Khodagholy et al., 2017)**,** reflected either a direct hippocampal–entorhinal cortex–neocortex excitation (Logothetis et al., 2012; Peyrache et al., 2011) and/or an indirect common drive by cortical slow oscillations (Isomura et al., 2006; Sirota et al., 2008). HPC-mPFC ripple association areas support roles in memory consolidation and links to navigational planning (Khodagholy et al., 2017).

(6) HPC-mPFC cross frequency: The cross-frequency coupling of distinct neural oscillations act as a mechanism for the dynamic co-ordination of brain activity over multiple spatial scales, with high-frequency activity within local ensembles coupled to large-scale patterns of low-frequency phase synchrony (Bonnefond et al., 2017).

Cross-frequency coupling is present during a range of cognitive functions and likely affects the organization of brain rhythms. Current data demonstrate its crucial role in long-range cross-frequency coupling in HPC–prefrontal circuit function. Hippocampal θ oscillations modulate mPFC assembly patterns by rhythmically biasing synchrony of local γ oscillations in behaving rats and mice (Sirota et al., 2008; Tamura et al., 2017), suggesting that oscillations mediate information flow from the HPC to the PFC. In addition, θ-δ coupling mediates information transfer from the PFC to the HPC via a relay mechanism through the thalamic NR (Roy et al., 2017). However, this result has been challenged in light of the possibility that δ oscillations has been attributed to respiratory-entrained oscillations in both structures (Lockmann and Tort, 2018).

Table 1 The physiological roles of oscillatory synchrony between the hippocampus (HPC) and medial prefrontal cortex (mPFC). Relevant studies with recordings from generalized regions of the prefrontal cortex and medial temporal lobe are also included in this table. (LFP=local field potentials; iEEG= intracranial EEG; MEG=Magnetoencephalography)

Oscillation	Region	Methods Used	Species	Frequency Range	Function	Reference
Delta (δ)	HPC-mPFC	LFPs	Rat	1-4 Hz	Decision-making	Schultheiss et al., 2020
Theta (θ)	vHPC-mPFC	LFPs	Mice	4-12 Hz	Anxiety	Adhikari, 2011
	dHPC-mPFC	LFPs	Mice	6-12 Hz	Decision-making	Chang, 2020
	vHPC-mPFC-dHPC	LFPs	Mice	4-2 Hz	Spatial working memory	O'Neill, 2013
	dHPC-mPFC	LFPs	Rat	4-12 Hz	Decision-making	Jones, 2005
	dHPC-mPFC	LFPs	Rat	4-10 Hz	Storage of information	Siapas et al., 2005
	HPC-PFC	LFPs	Rhesus macaques	~2-6 Hz	Working memory	Brincat & Miller, 2015
	MTL-PFC	iEEG	Human	4-8 Hz	Memory	K. L. Anderson et al., 2010
	HPC-mPFC	MEG	Human	3-7 Hz	Integrated memory	Backus et al., 2016
	mPFC-MTL	MEG	Human	4-8 Hz	Spatial memory retrieval	Kaplan et al., 2014
	mPFC-MTL	MEG	Human	4-7 Hz	Dynamic spatial imagery	Kaplan et al., 2017
	PFC-MTL	MEG	Human	4-8 Hz	Decision-making	Guitart-Masip et al., 2013
Alpha/Beta (α/β)	PFC-HPC	LFPs	Rhesus macaques	9-16 Hz	Learning	Brincat & Miller, 2015
Gamma (γ)	vHPC-mPFC	LFPs	Mice	30-100 Hz	Anxiety	Adhikari, 2011
	dHPC-mPFC	LFPs	Mice	30-80 Hz	Spatial memory	Sigurdsson et al., 2010
Ripples	HPC-mPFC	LFPs	Rat	100-150 Hz	Navigation planning	Khodagholy et al., 2017
Cross-frequency	θ (dHPC) - γ (mPFC)	LFPs	Rats and Mice	θ (3-5 Hz); γ (30-150 Hz)	Information flow	Sirota et al., 2008
	θ (vHPC) - γ (mPFC)	LFPs	Mice	θ (4-12 Hz); γ (30-120 Hz)	Working memory	Tamura et al., 2017
	δ (mPFC) - θ (dHPC and vHPC)	LFPs	Rat	δ (2-5 Hz); θ (4-8 Hz)	Unknown	Roy, 2017

The HPC-mPFC Circuit in Cognition, Emotion and Sensory Processing

Cognition: Memory and Learning

Important interactions between the HPC and mPFC support the encoding and retrieval of episodic memories (Eichenbaum, 2017; Jin and Maren, 2015; Kennedy and Shapiro, 2004; Weilbächer and Gluth, 2017). Considerable evidence demonstrates that in these interactions, the HPC organizes contextual memory and the mPFC facilitates retrieval of contextual memories through suppressing inappropriate memories from differing contexts (Eichenbaum, 2017; Preston and Eichenbaum, 2013). Recent functional MRI (fMRI) studies also demonstrate that persistent HPC-mPFC interactions promote long-term memory through context-based differentiation (Dugré et al., 2021; Ezzyat et al., 2018). Evidence from rodents involving paradigms such as the water maze (Vorhees and Williams, 2006), the T-maze (Deacon and Rawlins, 2006) and spatial win-shift on the radial arm maze (Taylor et al., 2003) further support the critical role of HPC-mPFC interactions in facilitating the successful execution of working memory (Liu et al., 2018; Salimi et al., 2022; Sigurdsson and Duvarci, 2016; Wirt et al., 2021). This is further observed in human studies. Increased HPC-mPFC θ coherence was predictive of successful memory integration in participants performing an inference task (Backus et al., 2016), and higher HPC-mPFC θ phase synchronization during encoding of contextually unexpected information was predictive of later memory performance in epileptic patients (Gruber et al., 2018).

Evidence from rodents demonstrate that the HPC-mPFC circuit is crucial for learning. Bilateral or crossed inactivation of the HPC (dorsal or ventral) or mPFC impaired flexible spatial learning (Avigan et al., 2020), and increased θ-band synchrony between HPC and mPFC pathways were observed during the transition from retrospective to prospective encoding (Myroshnychenko et al., 2017). It has also been shown that novel experiences alter vHPC θ oscillations and vHPC–mPFC connectivity, subsequently contributing to the modulation of learning-associated plasticity (Park et al., 2021). This implicates the crucial role of the HPC-mPFC circuitry in learning-associated circuit plasticity, where it can be primed for subsequent learning through novelty-induced changes to its circuit connectivity. It has also been shown in rhesus monkeys that frequency-specific interactions and oscillatory synchrony underlie relevant points during associative learning, suggesting that oscillatory signals from the HPC guides neocortical plasticity in the PFC during associative learning (Brincat and Miller, 2015). Studies in human further suggest that the HPC-mPFC circuit is not only activated and engaged in interactions with various brain regions to integrate information during new learning, but also play an important role in higher-level cognition, such as the acquisition of hierarchical concepts in category learning (Schlichting and Preston, 2016; Theves et al., 2021). Therefore, the HPC-mPFC circuit plays a crucial role in supporting cognitive processes involving memory and learning.

Emotion

The HPC and mPFC are critically implicated in the neurocircuitry of emotion involving the contextual modulation of fear (Hartley and Phelps, 2010; Ji and Maren, 2007; Kjelstrup et al., 2002), emotional judgment (Perry et al., 2011) and emotional memory (Engen and Anderson, 2018; Holland and Kensinger, 2010; Lovett-Barron et al., 2014; Richter-Levin and Akirav, 2000). The mPFC is implicated in the appraisal and expression of negative emotion (dorsal-caudal mPFC), and regulates limbic regions that facilitate emotional responses (ventral-rostral mPFC) (Etkin et al., 2011). Increasing evidence suggests that hippocampal-cortical pathways facilitate the emotional regulation of fear and emotional processing through oscillations (Jin

and Maren, 2015; Vertes, 2006). Enhanced ripple-δ-spindle coupling across the HPC-mPFC circuit is observed in mice exposed to exogenous acute stress, providing evidence that emotional encoding is supported by oscillations across this circuit (Lv et al., 2022). These findings support evidence from human studies that demonstrate the association between HPC-mPFC θ synchronization and anxiety-like behaviour (Khemka et al., 2017; Korn et al., 2017).

There is evidence to suggest that indirect HPC-mPFC pathways modulate emotional processes such as fear extinction and emotion regulation through circuits involving the amygdala (Hartley and Phelps, 2010; Jin and Maren, 2015; Ramanathan et al., 2018). The amygdala is a key structure in fear-conditioning and eliciting emotional states, assigning emotional dimensions to sensory stimuli through constant evaluation and integration of arousal states (Kim and Cho, 2020; Ressler and Maren, 2019; Šimić et al., 2021). Insight from studies using projection tracers and optogenetics in rodents have demonstrated that the amygdala is anatomically connected to the HPC and mPFC (Hintiryan et al., 2021; Orsini et al., 2011; Yang and Wang, 2017) and oscillatory synchrony between these regions are implicated in supporting emotional arousal and consolidation of emotional memories (Hermans et al., 2014; Paré et al., 2002). Further studies have found increased θ synchronization across the vHPC-BLA-mPFC circuit during heightened anxiety and learned fear expression, suggesting that oscillatory rhythms across this circuit are engaged during emotional states (Adhikari et al., 2010; Çalışkan and Stork, 2019). These findings are supported by studies in humans, providing evidence for unidirectional θ and α oscillations in the amygdala that modulate hippocampal γ activity during fear processing (Zheng et al., 2017), and synchronization of θ oscillations in the amygdala and mPFC to facilitate fear learning (Chen et al., 2021). Altogether, considerable evidence suggests a neurocircuitry of emotion regulation that involves the HPC-mPFC circuit via the amygdala (Hartley and Phelps, 2010; Jin and Maren, 2015; Richter-Levin and Akirav, 2000; Yang and Wang, 2017).

Sensory Processing

Sensory processing (SP) plays an important role in daily life as it synthesizes information from multiple sensory channels in response to the external environment into coherent behavioural and emotional patterns. Sensory processing involves a large network of brain areas that include the sensory cortices, motor cortices and associative areas (Le Merre et al., 2018; Martin-Cortecero and Nuñez, 2016; Zucchella et al., 2018). With extended studies, it is well documented that both the HPC and mPFC are involved in multisensory integration and sensory discrimination (Engel et al., 2012; Grion et al., 2016; Martin-Cortecero and Nuñez, 2016; Pereira Antonio et al., 2007). Moreover, synchronous linkage between these two areas have been shown to be sensitive to sensory, behavioural, and environmental changes (Hyman et al., 2005).

The influence of HPC-mPFC pathways on SP is further highlighted in studies where sensory signals are evaluated for learned motor output. In a study, mice were trained for a whisker-dependent detection task, and correct “licks” following whisker stimulation correlated with increased sensory-evoked signals in the dorsal CA1 HPC and mPFC (Le Merre et al., 2018). Inactivation of neural activity in the HPC and mPFC further impaired behavioural performance, corroborating studies in contextual learning that demonstrate the crucial role of HPC-mPFC interactions in translating sensory signals to relevant motor behaviour (Martin-Cortecero and Nuñez, 2016; Ong et al., 2019), and that HPC-mPFC oscillatory synchrony underlie sensory gating deficits (Dickerson et al., 2010). In addition, studies have shown that HPC-mPFC oscillatory synchrony at various frequencies including increased θ coherence support auditory

predictive processing and multisensory attention in humans (Friese et al., 2016; Grunwald et al., 2003; Recasens et al., 2018). HPC-mPFC interactions are further crucial for supporting SP during postnatal development, as the HPC provides excitatory signals to drive functional mPFC maturation during the sensitive period of tactile development (Xu et al., 2020). These include HPC θ oscillations that boost prefrontal oscillations in the neonatal mouse, and the emergence of θ-γ oscillations during maturation across the hippocampal-prefrontal network (Ahlbeck et al., 2018; Bitzenhofer et al., 2017; Brockmann et al., 2011; Xu et al., 2020). Thus, oscillations across the HPC-mPFC circuitry are not only important for cognition and emotional processes, but also facilitates normal SP.

The Impact of Abnormal HPC-mPFC Circuit Dynamics in Neurodevelopmental and Neurological Disorders

The HPC-mPFC circuit supports cognition, emotion, and sensory processing. These regions are anatomically and functionally intertwined, and oscillations regulate communication and information flow to support cognitive and behavioural processes. In this section, we discuss relevant disorders involving dysfunctional neural dynamics with a focus on the HPC-mPFC circuit. **See Table 2**.

Abnormal HPC-mPFC Circuit Dynamics in Neurodevelopmental Disorders

Abnormal brain development affects the structural and functional connectivity across the HPC-mPFC circuit, resulting in alteration at different spatial scales from cellular levels to network level. Neurodevelopmental disorders have been associated with maladaptive formation of cortical networks and faulty programming of synaptic connections, as neural oscillations and synchrony may have crucial roles in synaptic modifications (Galuske et al., 2019; Zarnadze et al., 2016). In this section, we highlight aberrant oscillations within and across the HPC-mPFC network associated with a variety of cognitive and behavioural deficits in several neurodevelopmental disorders.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in memory, executive function, and social skills (Hodges et al., 2020). Disruptions in oscillatory synchronization are core deficits in ASD, occurring at frequencies involving long range (δ, θ, α, β) and short range (β, γ) connectivity (Simon and Wallace, 2016). Altered neural circuitries in numerous brain regions including the orbitofrontal and sensory-motor networks are observed in ASD individuals, suggesting that cortical asynchronization during sensory and perceptual processing is a pathological hallmark of ASD (Hull et al., 2017; Oldehinkel et al., 2019; Xu et al., 2019b).

To date, only a few studies have focused on HPC-mPFC pathways in ASD. Cytoskeleton anomalies including fewer dendrites, smaller dendritic processes, and shorter dendritic processes in pyramidal neurons of the HPC and mPFC are associated with ASD (Barón-Mendoza et al., 2018). These morphological changes implicate altered synaptic connections, aberrant HPC-mPFC connectivity and contribute to autistic-like behaviours including impaired social behaviour (Barón-Mendoza et al., 2019). In addition, they affect pyramidal-mediated excitatory transmission and disturb the balance of excitation/inhibition (E/I) signals that support social behaviour. A study found reduced θ synchronization between the vHPC-mPFC

and loss of excitatory signalling from the vHPC to prefrontal GABAergic interneurons in mice heterozygous for *Pogz* (high confidence autism gene) with anxiety-related avoidance behaviour (Cunniff et al., 2020). This corroborates evidence for the crucial role of vHPC-mPFC in aberrant social behaviour (Sun et al., 2020), where dysfunctional interactions across this circuit may alter GABAergic circuits and impair long-range communication between the HPC and mPFC in the pathophysiology of ASD (Nelson and Valakh, 2015; Sohal and Rubenstein, 2019; Zhao et al., 2022).

In addition, social deficits associated with hyperactivity of the vHPC-mPFC signalling were observed and long-term inhibition of mPFC pyramidal neurons rescued social memory deficits in a mouse model of Rett syndrome (classified as an ASD disorder) (Phillips et al., 2019). Another study found that there were monosynaptic connections from HPC pyramidal neurons to mPFC GABAergic neurons, and inhibition of this pathway negatively impacted social behaviour in mice (Sun et al., 2020). Importantly, activation of mPFC parvalbumin-positive (PV+) neurons rescued social memory impairments caused by inhibition of vHPC (Sun et al., 2020). Deficits in hippocampal PV+ interneurons, circuit changes (altered γ oscillations, sharp wave-ripples, and θ-γ coupling), and impaired spatial discrimination were further found in a mouse model of ASD, *Cntnap2* mice (Paterno et al., 2021). Altered oscillatory θ and α activity associated with increased memory load have also been demonstrated in individuals with ASD (Larrain-Valenzuela et al., 2017). In addition, studies have shown substantially reduced hippocampal functional connectivity with frontal regions during episodic memory retrieval (Cooper et al., 2017), as well as rest-associated functional abnormalities in the mPFC correlating with social impairment in individuals with ASD (Kennedy et al., 2006).

These findings from animal models and ASD individuals suggest that ASD phenotypes may result from HPC cellular and circuit changes that disrupt proper HPC-mPFC communication during cognitive and behavioural processes (Schmidt and Redish, 2021). Future research investigating HPC-mPFC interactions will provide insight into the mechanistic links between aberrant oscillations across the HPC-mPFC network and ASD-associated behaviours.

Fragile X Syndrome

Aberrant HPC-mPFC connectivity is characteristic of Fragile X Syndrome (FXS), the most common form of inherited disability and leading cause of ASD. FXS develops from a mutation to the Fragile X mental retardation-1 gene (*FMR1*) located on the X chromosome, resulting in loss or heavy reduction in the Fragile X Mental Retardation Protein (FMRP). The absence of FMRP is concurrent with characteristic social impairments, learning disabilities and cognitive dysfunction including memory dysfunction and abnormal sensory processing (Berzhanskaya et al., 2016; Ciaccio et al., 2017; Huddleston et al., 2014; Razak et al., 2020). These impairments have been linked to changes in synaptic plasticity and circuitry involving excitatory and inhibitory activity in *Fmr1-KO* mice (Gibson et al., 2008; Morin-Parent et al., 2019; Sidorov et al., 2013; Contractor et al., 2015). Evidence from rodents and humans suggest that abnormal HPC-mPFC oscillatory dynamics are associated with FXS. Major electrophysiological observations from recordings in the HPC CA1 pyramidal cell layer included abnormally greater power of θ oscillations associated with increased slow γ, and decreased spike-count correlations of interneurons hyper-synchronized with θ and slow γ oscillations in the FXS mouse model (Fmr1-KO) during free exploration (Arbab et al., 2018). In FXS patients, abnormal oscillatory dynamics including enhanced global θ connectivity and reduced α and β connectivity between wider network have been characterized (Molen et al., 2014). Deficits in social and sensory processing in FXS patients were further correlated with abnormal oscillatory activity, including increased γ power and θ-γ coupling (Wang et al., 2017).

This suggests that altered oscillations such as changes to γ, are putative substrates for global and HPC-mPFC circuit hyper-excitability underlying social deficits in FXS (Arbab et al., 2018; Goswami et al., 2019; Kozono et al., 2020; Liu et al., 2022; Wang et al., 2017).

In *Fmr*1-KO mice, changes in mPFC GABAergic signalling were further observed during crucial time points of postnatal development (Kramvis et al., 2020). At prepubescence, there was increased inhibition of the mPFC with decreased inhibitory synaptic depression. This contrasted prolonged synaptic kinetics with reduced inhibition of the mPFC at adolescence, and dynamic changes to mPFC pathways in Fmr1-KO during development is functionally relevant for downstream impairments (Kramvis et al., 2020). Since the regulation of social behaviour relies on long-range GABAergic projections from regions such as the vHPC and basolateral amygdala (BLA) to the mPFC (Yang et al., 2021), these abnormalities reflect an imbalance in GABAergic signalling persisting throughout development with consequential phenotypes in FSX (Van der Aa and Kooy, 2020). D'Hulst et al. (D'Hulst et al., 2015) demonstrated an average of 10% reduction in $GABA_A$ receptor availability and binding potential throughout the brain in FXS patients. Using FXS human pluripotent stem cells (hPSCs), Zhang et al., (Zhang et al., 2022) further found delayed maturation of human GABAergic neurogenesis in hPSCs, and at later stages of GABAergic neurogenesis, including (1) increased neuronal networks activity, (2) increased proliferation of neuroblast progenitors and (3) a downregulation of gene expression associated with neuronal GABAergic maturation. Thus, a delay in GABAergic neuron differentiation may contribute to recognized deficits in the GABAergic system in FXS patients (Van der Aa and Kooy, 2020), resulting in altered inhibitory signals and abnormal homeostatic development of excitatory/inhibitory circuits (Paluszkiewicz et al., 2011). Consequently, altered local and long-range GABA-dependent HPC-mPFC interactions expressed in the θ and γ ranges (Molen et al., 2014; Wulff et al., 2009; Contractor et al., 2015) may further lead to impairments in learning (Gao et al., 2018), social behavior (Black et al., 2021), fear expression (Yang et al., 2021) and working memory (Lanfranchi et al., 2009). Future work exploring how GABAergic circuit impairments influence oscillations at various frequency bands across the HPC-mPFC network will provide insight into mechanisms linking circuit level to behavioural changes in FSX.

Down Syndrome

Down syndrome (DS) is a complex genetic disorder characterized by altered HPC and mPFC neural dynamics associated with cognitive deficits in rodent models (Cramer and Galdzicki, 2012; Witton et al., 2015; Zorrilla de San Martin et al., 2020). We have previously demonstrated in DS mouse models atypical neural circuitry involving altered θ frequency, altered hippocampal phase-amplitude coupling, modulation of hippocampal high γ, and altered HPC-mPFC θ coherence (Chang et al., 2020). These abnormalities were segregated with behavioural changes associated with impaired spatial working memory and prolonged decision-making (Chang et al., 2020). Recent evidence further demonstrates increased hypersynchrony, altered θ oscillations, altered cross-frequency coupling, and reduced HPC SPW-Rs in the Ts65Dn mouse model of DS (Alemany-González et al., 2020). As HPC SPW-Rs are coupled to cortical networks including the mPFC to facilitate cognitive processes (Buzsáki, 2015; Schmidt and Redish, 2021), a reduction in HPC SPW-Rs potentially disrupts proper communication between the HPC and mPFC to mediate memory impairments and intellectual disabilities (Martin-Cortecero and Nuñez, 2016). These findings suggest that atypical neural circuitries associated with aberrant HPC-mPFC pathways are important mechanisms in the pathophysiology of DS (Chang et al., 2020).

Abnormal brain synchrony is well established in people with DS. Notably, enhanced synchronization between adjacent brain regions and widespread alterations in default mode network (DMN) connectivity including weakened long range connections are largely characterized (Anderson et al., 2013; Rosas et al., 2021; Wilson et al., 2019). Recently, reduced long-range DMN connectivity associated with cognitive decline were found in DS individuals, providing evidence that altered connectivity between the HPC and prefrontal cortices underlie cognitive impairments in DS (DiProspero et al., 2022). In addition, the attenuation of early exploratory behaviour associated with developmental delays in DS (Fidler et al., 2019) may be the consequence of abnormal HPC-mPFC interactions. A recent study demonstrated that direct long-range GABAergic projections from the PFC regulate disinhibitory HPC microcircuits to facilitate object-related spatial encoding and exploratory behaviours (Malik et al., 2022). Long-range GABAergic projections promoted network oscillations that facilitate object exploration such as increased PFC-HPC low-γ synchrony and greater high-γ and θ power (Malik et al., 2022). These findings implicate that dysfunctional GABAergic innervation may alter HPC-mPFC oscillatory synchrony and mediate cognitive and behavioural deficits in DS (Alemany-González et al., 2020; Chang et al., 2020). Therefore, aberrant HPC-mPFC connectivity may be a potential biomarker predicting clinical conversion to Alzheimer's Disease (AD) in people with DS (DiProspero et al., 2022; Koenig et al., 2021; Liang et al., 2020).

Abnormal HPC-mPFC Circuit Dynamics in Neurological Disorders

Aging is associated with alterations in cognitive processing and brain neurophysiology. Studies demonstrate that physiological aging represent a global alteration in oscillation and disruption of brain functional connectivity (Murty et al., 2020; Rondina et al., 2016). Pathological changes of synaptic integrity and coordinated network activity has been associated with neurodegenerative and age-related neural disorders. Recent research further suggests that altered oscillatory activity in the brain may be an early warning sign of age-related neurological diseases (Murty et al., 2021). As the HPC and mPFC have well-established roles in cognitive and memory functions, we discuss relevant age-related neurological disorders that have aberrant HPC-mPFC circuitry.

Alzheimer's Disease

Alzheimer's Disease is a progressive neurodegenerative disorder with widely characterized abnormalities in neural oscillations and cognitive deficits (Byron et al., 2021; Hamm et al., 2015; Isla et al., 2021; Kitchigina, 2018). It has been shown that prominent neural HPC-mPFC oscillations, particularly slow-frequency θ and fast-frequency γ, are significantly altered in mouse models of AD (Kitchigina, 2018; Mehak et al., 2022) and in patients with early and late stage AD (Başar et al., 2017; Goodman et al., 2018; McDermott et al., 2018). Additionally, abnormal oscillations across the HPC-mPFC circuit are associated with AD pathology such as extracellular insoluble β-amyloid (Aβ) plaques, intracellular neurofibrillary tangles (NFTs), and tau aggregation (Ahnaou et al., 2017). A study found that Aβ significantly reduces synaptic inputs of hippocampal fibres to the PFC at different frequencies (5–50 Hz) measured by mean amplitudes of field excitatory postsynaptic potentials (fEPSPs) in vitro (Flores-Martínez and Peña-Ortega, 2017). Intracranial recordings from the HPC and mPFC of TgF344-AD rats reveal impaired HPC-mPFC θ-γ coherence and attenuated phase-amplitude coupling concomitant to Aβ deposition and NFTs (Bazzigaluppi et al., 2018). In tau-expressing rats, Tanninen and colleagues revealed a significant attenuation of inter-region θ and γ phase-

phase and amplitude-amplitude oscillatory coupling between the HPC and prelimbic mPFC during associative learning (Tanninen et al., 2017). Notably, these changes in neural oscillations were observed prior to cognitive deficits, implicating oscillatory changes detectable in preclinical AD. Further evidence from rodents reveal the crucial role of mPFC spindle-band coupling with hippocampal ripples (Maingret et al., 2016; Zhurakovskaya et al., 2019).

The significance of HPC-mPFC in AD is further understood through studies of memory. Episodic memory is one of the first systems to decline in AD, and affected individuals show deficits in object and spatial recognition memory consolidation (Tromp et al., 2015). These processes rely on concurrent activity in the dHPC and mPFC, and chemogenetic inactivation of these regions impairs memory consolidation in mice (Tuscher et al., 2018). Recent work demonstrates that CA1 and mPFC θ sequences are temporally coordinated to support memory-guided decision-making processes in rats (Tang et al., 2021), and synchronization of θ and γ oscillations regulate HPC-mPFC communication during cognitive processes particularly learning and memory (Colgin, 2011; Hyman et al., 2005; Wirt et al., 2021; Buzsáki and Draguhn, 2004). Low levels of θ-γ coupling associated with working memory deficits are further reported in patients with mild cognitive impairment (MCI) and AD (Abubaker et al., 2021; Goodman et al., 2018; Kitchigina, 2018). Although it is well established that aberrant HPC-mPFC circuit dynamics are found in AD, it remains unclear whether oscillatory abnormalities cause cognitive deficits or are a by-product of cellular changes. Nevertheless, pathological circuits in AD include abnormal θ and γ oscillatory activity across the HPC-mPFC circuit that leads to impairments in cognition and memory (Mably and Colgin, 2018).

Epilepsy

Epilepsy is a common neurological disorder that is characterized by frequent seizures. It affects nearly 1% of the population with substantial morbidity and mortality (Fiest et al., 2017) There is increasing interest to study the pathophysiological mechanisms underpinning seizure generation in epilepsy, particularly abnormal connectivity in certain brain regions (Engel et al., 2013; Englot et al., 2016; Jiruska et al., 2013). Studies in patients with focal epilepsy showed widespread network alterations that extend beyond the epileptogenic zone (Braakman et al., 2013; Luo et al., 2012; Widjaja et al., 2015). In rodent and human studies, altered connectivity between the HPC and mPFC has been correlated with epilepsy conditions (Englot et al., 2015; Jin and Maren, 2015). Individuals with temporal lobe epilepsy (TLE) show HPC-mPFC hypersynchrony and abnormally greater coherence in θ bands (Holmes, 2015), suggesting that epileptiform events are facilitated by the slow oscillation state biasing hippocampal pathways towards hyperexcitability and enhancing hypersynchrony across HPC and cortical networks (Nazer and Dickson, 2009). In a rat model of TLE, coherence in θ band synchrony between the dHPC and mPFC was further found to be increased in the pre-ictal period preceding seizures, suggesting that altered HPC-mPFC connectivity may promote seizure generation (Broggini et al., 2016).

Further evidence revealed that prolonged or recurrent seizures can cause or exacerbate cognitive impairments (Blake et al., 2000; Butler and Zeman, 2008; Butler et al., 2009). Numerous studies suggest that altered HPC-mPFC connectivity may be related to neurocognitive deficits in patients with epilepsy (Doucet et al., 2013; Voets et al., 2014). One study found fewer physiological hippocampal ripples, greater spontaneous HPC interictal epileptiform discharges (IEDs), and impaired spatial memory consolidation associated with strongly coupled HPC IEDs-mPFC spindles during sleep and awake states in a rat model of TLE (Gelinas et al., 2016). In patients with focal epilepsy, the coupling of IEDs with spindles in regions distinct from the epileptic network were further shown to alter spatiotemporal

oscillatory properties and mediate abnormal patterns of brain connectivity (Dahal et al., 2019). It is becoming increasingly clear that precisely coordinated HPC IEDs-prefrontal cortex spindles exacerbate aberrant HPC θ-γ coupling during rapid eye movement (REM) in the epileptic brain (Jansen et al., 2021; Mendes et al., 2021). Consequently, the generation of pathological HPC oscillations and IED-mediated abnormal coupling of oscillations may alter HPC-mPFC network activity and disrupt normal HPC ripples-mPFC spindles coupling crucial for supporting memory processes in the epileptic brain (Azimi et al., 2021; Mendes et al., 2021; Siapas and Wilson, 1998; Xia et al., 2017). Overall, connectivity studies in epilepsy are critical endeavours that may lead to improved strategies for localization epileptogenic area, aid surgical intervention and outcome prediction in epilepsy.

Therapeutic Strategies for Targeting HPC-mPFC Circuit Dynamics

Medical treatments and neural substrates for therapeutic approaches can be guided by the study of brain oscillations. Oscillotherapeutics is an exciting area of therapy that uses oscillations as biomarkers or therapeutic targets to treat disorders with brain network dysfunction (Takeuchi and Berényi, 2020). Here, we discuss advancements in brain stimulation, gene therapy, and pharmacotherapy, highlighting evidence for the use of oscillotherapeutics to treat disorders with aberrant HPC-mPFC circuit dynamics.

Brain Stimulation

An emerging application in brain stimulation therapy is the use of neuromodulation to restore network abnormalities in cognitive disorders such as AD (Chan et al., 2021a). Methods include non-invasive and invasive approaches that stimulate the brain at targeted sites to restore balance of neural circuits via manipulation of oscillatory activity in local and network-wide activity. In this section, we highlight Non-invasive Gamma Entrainment Using Sensory Stimulation (GENUS) and deep brain stimulation (DBS) as promising approaches in disorders with aberrant neural oscillations.

Since γ brain activity has well-established roles in cognition, γ entrainment therapy has been explored for neurological disorders such as AD (Adaikkan and Tsai, 2020; Traikapi and Konstantinou, 2021). Visual GENUS at 40 Hz entrained γ oscillatory activity in the HPC and prefrontal cortices and enhanced inter-regional γ oscillatory activity in mouse models of neurodegeneration (Adaikkan and Tsai, 2020; Adaikkan et al., 2019). Auditory and audiovisual GENUS at 40 Hz further reduced amyloid load in the HPC and mPFC respectively, and hippocampal-dependent recognition and spatial memory tasks were also improved by auditory GENUS at 40 Hz in the neurodegeneration mouse model, 5XFAD mice (Martorell et al., 2019). These findings demonstrate the potential for GENUS to ameliorate AD pathology and improve cognitive function (Iaccarino et al., 2016).

Preliminary data from human studies highlights its potential application in treatment for AD. Chan et al. (Chan et al., 2021b) conducted a randomized, placebo-controlled trial in participants with mild AD dementia and found that one-hour daily treatment of audio-visual GENUS at 40 Hz delivered over 3 months improved memory performance and reduced brain atrophy in the active group. Fatemi et al. (2022) employed simultaneous auditory and visual stimulation in cognitive healthy participants and found significantly enhanced θ-γ phase-amplitude coupling (PAC). This corroborates evidence for GENUS as a potential treatment for AD, as it may be able to correct abnormal oscillations across the HPC-mPFC circuitry and

restore cognitive functions (Belluscio et al., 2012; Chan et al., 2021b; Fatemi et al., 2021; Lisman & Jensen, 2013; Tort et al., 2009).

The application of DBS to target HPC-mPFC circuit dynamics is hypothesized in its ability to modulate oscillations in these regions (Cervera-Ferri et al., 2016; Muthuraman et al., 2020; Zhu et al., 2019). DBS therapy is a neurosurgical intervention where electrical activity is constantly or intermittently delivered to the brain through electrodes. The ability for DBS to modulate oscillatory rhythms is actively explored in diseases with pathological brain circuitries (Herrington et al., 2016; Lozano et al., 2019). DBS of the subthalamic nucleus (STN) and globus pallidus interna (GPi) was shown to effectively reduce pathological β band activity (13-30 Hz) in the corticothalamic-basal ganglia network responsible for hallmark Parkinsonian rhythms (Müller and Robinson, 2018). Central thalamus-DBS (CT-DBS) increased hippocampal θ oscillations and improved SWM in SD rats (Chang et al., 2019), and ventral internal capsule/ventral striatum DBS therapy increased mPFC θ oscillations and improved cognitive control in human subjects with MDD Obsessive Compulsory Disorder (Widge et al., 2019). Recent work further demonstrated that acute DBS in the mPFC with 130 Hz improved mPFC-vHPC θ and γ coupling in a rat model of developmental schizophrenia (Lippmann et al., 2021).

Insight from DBS for epilepsy further implicates its beneficial impact in treating disorders with pathological neural circuitries (Laxpati et al., 2014; Wu et al., 2021). Recent evidence found that DBS in the medial septum entrained the hippocampal θ rhythm to facilitate anti-seizure effects in patients with temporal lobe epilepsy (TLE), (Wang et al., 2021). In another large, prospective double-blind study, HPC-DBS significantly reduced seizures in patients with refractory TLE, and 50% of these patients became seizure-free 8 months post-surgery (Cukiert et al., 2017). Given that prominent oscillations regulate communication between the HPC and mPFC, the ability for DBS to entrain oscillations in the HPC may restore normal HPC-mPFC oscillatory coupling disturbed in neurological disorders with global network dysfunction such as epilepsy. With increasing evidence that IED-spindle coupling is associated with aberrant hippocampal-cortical connectivity in epilepsy, future work using DBS to restore physiological HPC ripple-mPFC spindles may improve cognitive deficits found in patients with epilepsy. Further studies examining the ability for DBS to alter HPC-mPFC oscillations at different frequencies will significantly contribute to advancing progress in using DBS to treat neurological disorders with aberrant HPC-mPFC circuitry.

Gene Therapy

The use of gene therapy to modulate HPC-mPFC circuit dynamic is a relatively new area of research. However, preliminary findings from clinical trials suggest that gene therapy can target diseases like AD that have aberrant neural circuitries. There are over 40 ongoing clinical trials in treatment for neurodegenerative diseases (Sun and Roy, 2021) and for example, currently, much optimism surrounds the Phase 1 clinical trial of the AAV2-Brain Derived Nerve Growth Factor (BDNF) gene therapy to treat AD or MCI (National Institute of Health (NIH), NCT05040217). Since BDNF regulates key memory circuits involving the HPC and mPFC (Rosas-Vidal et al., 2014), AAV2-BDNF gene therapy represents a promising therapeutic approach to treating neurodegenerative diseases like AD by targeting the modulation of synaptic signalling (Gao et al., 2022); National Institute of Health (NIH), NCT05040217). A recent study further demonstrated that SynCav1 gene therapy may also be a promising therapy for AD. First, the authors demonstrated that PSAPP AD model mice at 9 and 11 months of age exhibited deficits in caveolin-1 (Cav-1), a protein essential for synaptic and neuroplasticity and associated learning and memory impairments (Wang et al., 2021). Then,

they found that delivery of SynCav1 to the HPC at 3 months using adeno-associated virus serotype 9 (AAV9) improved memory and improved morphological changes including a greater number of CA1 dendritic spines and dendritic arborization which support important rhythms like θ in the HPC-mPFC circuit (Nuñez and Buño, 2021; Wang et al., 2021). Interestingly, these effects were seen without the reduction of amyloid deposits and implicates the role of this novel gene therapy for later stages of neurodegeneration where there may be high levels of amyloid deposition (Wang et al., 2021).

The application of gene therapy for neural circuit disorders is further highlighted in its potential to treat developmental disorders with heritable components (Mirzayi et al., 2022; Sahin and Sur, 2015; Sternson and Bleakman, 2020). There is increasing evidence that gene therapy technologies including chemogenetics (Sternson and Bleakman, 2020), optogenetics (Mirzayi et al., 2022) and CRISPR-based gene editing (Heidenreich and Zhang, 2016) are viable tools for dissecting and restoring neuronal circuits fundamental to developmental and neurological diseases. In a recent study, adeno-associated viruses (AAV)-mediated expression of human FMRP isoform 17 orthologs corrected abnormal γ activity and autism-related behaviours in *Fmr1* KO rodents (Hooper et al., 2021), and AAV-FMRP-injected mice demonstrated the ability to restore cellular expression in hippocampal and cortical neurons to 50% WT levels 56 days after injection (Gholizadeh et al., 2014). These findings implicate the potential for gene therapy to restore cellular changes (e.g. GABAergic deficits) and correct circuit imbalances (neuronal hyperexcitability) associated with learning disabilities, sensory hypersensitivities, and social deficits in FXS and other neurodevelopmental disorders (Bülow et al., 2022; Contractor et al., 2015). As of now, the efficacy of gene therapy in restoring abnormal HPC-mPFC circuitry remains unclear and clinical trials are warranted. Future work to improve gene delivery and increase understanding of post-transcriptional regulation systems will further optimize gene therapy to correct aberrant HPC-mPFC circuitry associated with developmental and neurological disorders (Ingusci et al., 2019).

Pharmacotherapy

In pharmacotherapy for AD, there is an emerging paradigm shift from solely targeting pathological hallmarks like amyloid plaques to modulating neural circuitries. Considerable evidence demonstrates that critical oscillatory rhythms (θ and γ) supporting memory processes are altered from early stages of AD (Başar et al., 2016; Grunwald et al., 2001; Traikapi and Konstantinou, 2021). Several AD drugs have been shown to modulate these rhythms (Isla et al., 2021). Notably, the AChE inhibitor donepezil was found to increase stimulation-induced hippocampal θ oscillation power, enhance θ phase to γ amplitude coupling, reduce cortical hyperexcitability and reduce occurrences of high-voltage spindle activity in a transgenic AD mouse model (Stoiljkovic et al., 2018). In addition, current drugs approved for the symptomatic treatment of dementia (rivastigmine, tacrine, galantamine and memantine) have been shown to enhance cortical slow θ (4.5-6 Hz) and γ (30.5-50 Hz) oscillations (Ahnaou et al., 2014; Drinkenburg et al., 2015). Recently, the histone deacetylase inhibitor (HDAC) suberoylanilide hydroxamic acid (SAHA), was found to rescue impairment of hippocampal γ (20-40 Hz) oscillations and restore activity of fast spiking interneurons in basal and active states in a model of AD (PSAPP transgenic mice) (Takasu et al., 2021). These findings implicate the ability for SAHA to modulate hippocampal γ oscillations through its effect on fast-spiking PV+ GABA-containing interneurons (Bartos et al., 2007). Since PV+ interneurons mediate crucial HPC-mPFC interactions underlying memory consolidation (ripple-spindle oscillatory coupling) (Xia et al., 2017), SAHA represents the crucial role of

pharmacotherapies in targeting HPC-mPFC circuit dynamics for treating cognitive impairments in AD.

The potential for pharmacotherapies to modulate aberrant HPC-mPFC circuit dynamics is further implicated in treatment for schizophrenia, a complex disorder associated with significant abnormal neuronal synchrony and impairments in spatial and temporal integration of brain network activity (Başar et al., 2016; Orellana and Slachevsky, 2013; Rame et al., 2017; Uhlhaas and Singer, 2010). The “pharmaco-EEG” approach has been used in schizophrenia therapy to study and predict clinical efficacy of drugs through EEG parameters (Drinkenburg et al., 2015; Galderisi, 2002). Recently, Cariprazine (United States: Vraylar; Europe: Reagila), a third-generation antipsychotic approved for the treatment of schizophrenia (Stępnicki et al., 2018), demonstrated evidence for stabilizing the aberrant increase and accelerating the resynchronization of hippocampal γ oscillations in a rat model of acute first-episode schizophrenia (MK-801) (Meier et al., 2020). Clozapine have also shown efficacy in restoring hippocampal-prefrontal cortical synaptic plasticity and augmenting long-term potentiation in the HPC-mPFC pathway via dopaminergic modulation in animal models of schizophrenia (Matsumoto et al., 2008; Rame et al., 2017; Ruggiero et al., 2021). The development of effective pharmacotherapies that restore aberrant neural dynamics is a growing and important area of research. Abnormal neural synchrony significantly contributes to various pathologies, and further advancements in pharmacotherapies should consider targeting neural circuitries in treatment, particularly in diseases with prominent aberrant HPC-mPFC circuit dynamics like AD and schizophrenia to restore normal function (Canter et al., 2016).

734 **Table 2** Overview of neurodevelopmental and neurological disorders associated with
735 abnormal hippocampus-medial prefrontal cortex circuit dynamics. For a more thorough
736 discussion, refer to text. (AD=Alzheimer's Disease; dHPC=dorsal hippocampus;
737 DMN=default mode network; HPC=hippocampus; HPC-mPFC=hippocampal-medial
738 prefrontal cortex; human pluripotent stem cells=hPSCs; interictal epileptiform
739 discharges=IEDs; MCI=mild cognitive impairment; mPFC=medial prefrontal cortex;
740 PV+=parvalbumin-positive; SPW-Rs=sharp wave-ripples; vHPC=ventral hippocampus)
741

Category	Disorder	Species	Relevant Findings	Reference
Neurodevelopmental Disorders	Autism Spectrum Disorder	Rodents	Dendritic changes in the HPC and mPFC pyramidal neurons.	(Barón-Mendoza et al., 2018, 2019)
		Rodents	(1) Reduced θ synchronization between the vHPC and mPFC. (2) Loss of excitatory signalling from the vHPC to prefrontal GABAergic interneurons.	(Cunniff et al., 2020)
		Rodents	Hyperactivity of vHPC to mPFC projections impaired social memory.	(Phillips et al., 2019)
		Rodents	Altered mPFC GABAergic innervation from vHPC negatively impacted social behaviour.	(Sun et al., 2020)
		Rodents and Humans	Dysfunctional sensory oscillations at frequency ranges associated with long range (δ, θ, α, β) and short range (β, γ) connectivity.	(Simon and Wallace, 2016)
		Rodents and Humans	Impaired θ and α oscillatory activity associated with working memory deficits.	(Larrain-Valenzuela et al., 2017)
		Humans	Altered short- and long-range (hippocampal-frontal cortices) connectivity.	(Hull et al., 2017; Oldehinkel et al., 2019)

	Fragile X Syndrome	Rodents and Humans	Altered GABAergic signalling due to dysfunctional vHPC-mPFC long-range GABAergic projections crucial for regulating social behaviour.	(Kramvis et al., 2020; Van der Aa and Kooy, 2020; Yang et al., 2021)
		Rodents	Oscillatory changes in the HPC that potentially disrupts HPC-mPFC circuitry: (1) Abnormally greater power of θ associated with increased slow γ. (2) Decreased spike-count correlations of interneurons hyper-synchronized with θ and slow γ.	(Arbab et al., 2018)
		Humans	Evidence suggesting impaired GABAergic HPC-mPFC signalling in FXS patients: (1) A 10% reduction in $GABA_A$ receptor availability. (2) Reduced GABA binding potential throughout the brain.	(D'Hulst et al., 2015)
		Humans	Evidence suggesting impaired HPC-mPFC local and long-range GABA-dependent interactions: (1) Delayed maturation of GABAergic neurogenesis in hPSCs (2) Increased neuronal networks activity. (3) Increased proliferation of	(Zhang et al., 2022)

			neuroblast progenitors. (4) Downregulation of proteins associated with GABAergic neuronal maturation.	
	Down Syndrome	Rodents	Altered HPC-mPFC neural dynamics: (1) θ frequency (2) HPC phase-amplitude coupling (3) modulation of HPC high γ (4) θ coherence	(Chang et al., 2020)
		Rodents	Reduced HPC SPW-Rs coupling with cortical networks and impaired working memory.	(Alemany-González et al., 2020)
		Rodents	Altered GABAergic signalling; loss of fast-spiking phenotypic PV+ cells and increased excitability.	(Zorrilla de San Martin et al., 2020)
		Rodents and Humans	Abnormal coordination of θ oscillatory activity across the HPC and mPFC.	(Goodman et al., 2018; Wirt et al., 2021)
		Humans	Widespread alterations in DMN connectivity and weakened DMN-frontal cortices connectivity	(Anderson et al., 2013; Wilson et al., 2019)
		Humans	Reduced long-range hippocampal-prefrontal connectivity associated with cognitive decline in people with DS converting to AD.	(DiProspero et al., 2022)

Neurological Disorders	Alzheimer's Disease	Rodents and Humans	Abnormal mPFC spindle-band coupling with HPC ripples.	(Maingret et al., 2016; Zhurakovskaya et al., 2019)
		Rodents	Inactivation of the dHPC and mPFC impaired object and spatial recognition memory consolidation.	(Tuscher et al., 2018)
		Rodents	Altered CA1 HPC-mPFC θ temporal synchronization.	(Tang et al., 2021)
		Rodents	HPC-mPFC hypersynchrony associated with cognitive impairments.	(Holmes, 2015)
		Humans	Reduced θ-γ coupling associated with working memory deficits in patients with MCI and AD.	(Abubaker et al., 2021; Goodman et al., 2018; Kitchigina, 2018)
	Epilepsy	Rodents	Increased coherence at θ band synchrony between the dHPC and mPFC in pre-ictal seizure periods.	(Broggini et al., 2016)
		Rodents and Humans	Altered hippocampal-cortical coupling: (1) Aberrant HPC IEDs induce mPFC spindles. (2) Degree of HPC IEDs-mPFC spindles coupling correlated with memory impairments.	(Gelinas et al., 2016; Mendes et al., 2021)
		Rodents and Humans	Increased HPC-mPFC θ asynchrony and atypical γ oscillations associated with cognitive impairments.	(Bowie and Harvey, 2006; Chang et al., 2019; Choi et al., 2016; Skirzewski et al., 2018)

742

Conclusion

Considerable evidence from neuroanatomical and physiological studies demonstrates that the HPC and mPFC are anatomically and functionally intertwined. The HPC-mPFC circuit includes direct and indirect pathways that have well-established roles in supporting cognitive, emotional and sensory processes. For example, critical HPC-mPFC oscillatory rhythms facilitate episodic memory and spatial memory, persistent HPC-mPFC interactions promote long-term memory through context-based differentiation, and emotional processes are closely associated with oscillatory coupling of the HPC and BLA receiving direct projections from the mPFC. In this review, we have highlighted several neurodevelopmental (ASD, DS, FXS) and neurological disorders (AD, epilepsy) with altered HPC-mPFC circuit dynamics. Since oscillations across the HPC-mPFC circuit are crucial for supporting cognitive and behavioural functions, oscillotherapeutics that modulate pathological brain rhythms in neurodevelopmental and neurological disorders should be thoroughly explored (Földi et al., 2021; Widge et al., 2019; Traikapi and Konstantinou, 2021; Takeuchi and Berényi, 2020). However, the current body of research on oscilliotherapeutics for abnormal HPC-mPFC circuitry is limited by the use of singular modalities (Liang and Mody, 2022). Since EEG and MEG presents with spatial resolution limitations, it makes it difficult to pinpoint sources of abnormal neural circuitry. Future research should employ multimodal imaging, combining EEG, MEG, and fMRI to better integrate spatial and temporal information of aberrant circuitries underlying disorders such as AD with cognitive and behavioural deficits. Furthermore, disorders such as ASD with heterogeneous pathophysiology makes it difficult to assess the extent by which aberrant oscillations contribute to cognitive/behavioural deficits. This can be improved by disease stratification (genetics and behavioural) and breaking down heterogenous disorders into smaller parts, making it easier to investigate oscillatory dynamics associated with specific phenotypes. In conclusion, oscillatory dynamics across the HPC-mPFC circuit could be useful biomarkers for assessing interventions in neurodevelopmental and neurological disorders, and advancements in brain stimulation, gene therapy and pharmacotherapy will accelerate effective treatments for various disorders with aberrant HPC-mPFC circuitry. For a graphical summary, see **Figure 2.**

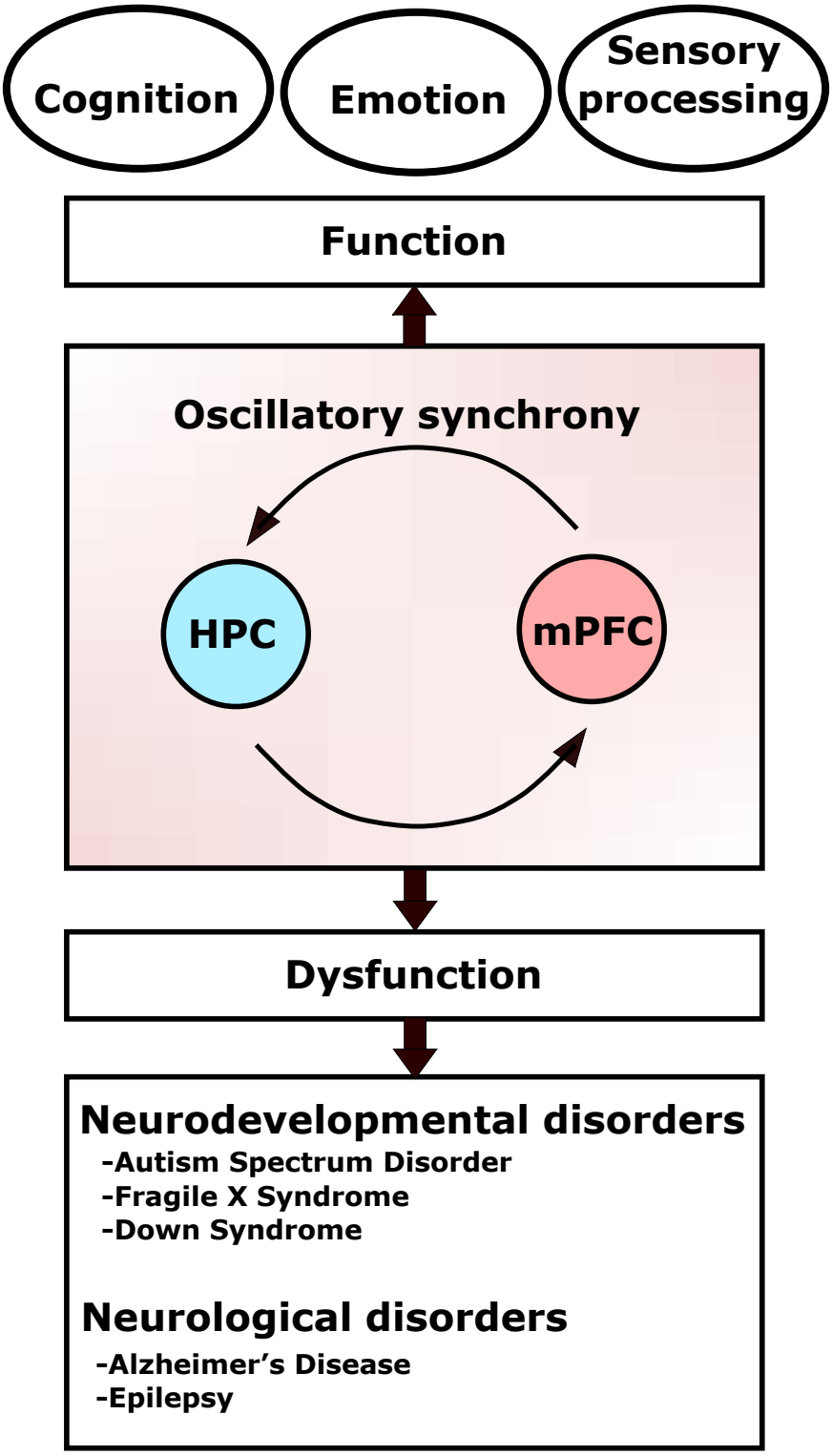

Figure 2 Graphical Summary. Oscillatory synchrony across the hippocampal-medial prefrontal cortex (HPC-mPFC) network facilitates normal brain function including cognition, emotion, and sensory processing. Aberrant oscillatory synchrony across the HPC-mPFC network contributes to brain dysfunction and facilitates a variety of neurodevelopmental and neurological disorders.

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