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1 The Role of Aberrant Neural Oscillations in the Hippocampal-Medial Prefrontal Cortex 2 Circuit in Neurodevelopmental and Neurological Disorders

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12 Abstract

The hippocampus (HPC) and medial prefrontal cortex (mPFC) have well-established roles in 13 14 cognition, emotion, and sensory processing. In recent years, interests have shifted towards developing a deeper understanding of the mechanisms underlying interactions between the 15 HPC and mPFC in achieving these functions. Considerable research supports the idea that 16 synchronized activity between the HPC and the mPFC is a general mechanism by which 17 18 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 19 focus on oscillations and highlight several neurodevelopmental and neurological disorders 20 21 associated with aberrant HPC-mPFC circuitry. We further discuss oscillatory dynamics across the HPC-mPFC circuit as potentially useful biomarkers to assess interventions for 22 neurodevelopmental and neurological disorders. Finally, advancements in brain stimulation, 23 gene therapy and pharmacotherapy are explored as promising therapies for disorders with 24 aberrant HPC-mPFC circuit dynamics. 25

27	Keywords: hippocampus; medial prefrontal cortex; neural oscillations; neurological disorders;
28	neurodevelopmental disorders; oscillotherapeutics

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39 Introduction

It is well established that the HPC and mPFC are important regions that facilitate cognition, 40 41 emotion, and sensory processes (Jin and Maren, 2015; Ruggiero et al., 2021). A growing body 42 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; 43 Negrón-Oyarzo et al., 2018; Preston and Eichenbaum, 2013; Salimi et al., 2021; Tang et al., 44 45 2021; Wirt and Hyman, 2017). Recent evidence further highlights the importance of communication between the HPC and mPFC during learning and memory processes (Dickson 46 et al., 2022; Morici et al., 2022). Efforts to understand the pathophysiology of various disorders 47 have focused on identifying abnormalities in regions of the HPC and mPFC underlying 48 49 symptoms of these disorders. It is becoming increasingly clear that neurodevelopmental and 50 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., 51 2017; Calabro et al., 2020; Colgin, 2011; Godsil et al., 2013; Jones and Wilson, 2005; Li et al., 52 53 2015; Sigurdsson and Duvarci, 2016).

Neural oscillations are the fundamental mechanism to enable coordinated activity during 54 normal brain functioning (Buzsáki and Draguhn, 2004; Singer, 1999). There is abundant 55 evidence for a close relationship between the occurrence of oscillations and cognitive and 56 behavioural responses (Fries et al., 2001; Uhlhaas and Singer, 2010). Neural oscillations and 57 58 synchronization reflect regional and interregional communication between cortical areas. In 59 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 60 occur at higher frequencies (>30 Hz), and long-distance synchronization often manifests in 61 62 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 63 neuronal computation and communication (Womelsdorf et al., 2010). While high-frequency 64 65 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 66 internal cognitive events. Therefore, cross-frequency modulation may serve as a mechanism 67 to transfer information from large-scale brain networks operating at behavioural timescales to 68 fast, local cortical processing required for effective computation and synaptic modification, 69 thus integrating functional systems across multiple spatiotemporal scales (Canolty and Knight, 70 71 2010).

72 In this review, we present recent evidence for anatomical and synchronous activity between the HPC and mPFC. We detail work revealing that the HPC-mPFC circuitry is essential for 73 cognitive, emotional, and sensory processes. Based on anatomical and electrophysiological 74 evidence, we further examine the possible neurobiological causes of impaired HPC-mPFC 75 76 oscillations and the involvement of aberrant HPC-mPFC oscillatory activity underlying several neurodevelopmental and neurological disorders. Finally, advancements in deep brain 77 stimulation, gene therapy, and pharmacotherapy are explored as useful interventions for 78 79 various disorders associated with aberrant HPC-mPFC circuitry.

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85 Animal Models in Neuroscience Research

Animal research has formed vital contributions to understanding neural mechanisms and 86 87 disorders. Non-human primates have been at the forefront of research efforts, and rodents 88 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 89 mammalian species, the temporal dynamics within and across brain networks remain 90 91 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 92 ranges within species and their cross-frequency interactions are supported by the same 93 94 fundamental mechanisms and can be adequately characterized across species (Buzsáki et 95 al., 2013). Therefore, valuable insight from studies involving non-human primates and rodents 96 help with incorporating findings across species into an integrated field of HPC-mPFC research.

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98 Anatomical Organization of the HPC and mPFC

The HPC, located deep in the medial temporal lobe, is typically classified by several 99 subregions (subiculum, dentate gyrus, cornu ammonis regions CA1-CA3) (Fogwe et al., 2022; 100 Nuñez and Buño, 2021) and compartments (ventral-dorsal in rodents corresponding to 101 anterior-posterior in humans) (Fanselow and Dong, 2010). The mPFC broadly refers to the 102 103 cortical region anterior to the premotor cortex, and can be organized into dorsal and ventral 104 subdivisions in rodents (Heidbreder and Groenewegen, 2003; Jobson et al., 2021; Xu et al., 2019a) and humans (Bzdok et al., 2013; Xu et al., 2019a). Based on cytoarchitectural and 105 functional differences, the mPFC is also separated into dorsomedial and ventromedial 106 subregions in rodents, non-human primates and humans (Jobson et al., 2021; Sigurdsson and 107 Duvarci, 2016). Studies using tractography and neuroimaging techniques such as diffusion 108 109 weighted imaging further provide evidence that HPC-mPFC interactions in humans (Bzdok et 110 al., 2013; Croxson, 2005; Godsil et al., 2013; Jobson et al., 2021; Seamans et al., 2008) are similarly observed in rodents (Condé et al., 1995; Eichenbaum, 2017; Ghoshal and Conn, 111 2015; Hoover and Vertes, 2007; Jin and Maren, 2015). These interactions include prominent 112 direct (monosynaptic) and indirect (polysynaptic) HPC-mPFC pathways (Eichenbaum, 2017; 113 Godsil et al., 2013; Jin and Maren, 2015; Sigurdsson and Duvarci, 2016). Here, we provide a 114 brief anatomical overview of HPC-mPFC connections in Fig. 1. 115

Insight from rodents (Adhikari et al., 2011; Binder et al., 2019; Eichenbaum, 2017; Hoover and 116 Vertes, 2007), non-human primates (Barbas and Blatt, 1995; Shamy et al., 2010) and humans 117 (Croxson, 2005; Godsil et al., 2013; Li et al., 2015; Preston and Eichenbaum, 2013) reveal 118 monosynaptic projections from the ventral CA1 HPC and subiculum to the mPFC. Ventral 119 hippocampal neurons directly innervate three major GABAergic neurons in the mPFC 120 (parvalbumin-expressing, somatostatin-expressing, and vasoactive intestinal peptide-121 expressing interneurons) to support contextual and spatial information (Jin and Maren, 2015). 122 A monosynaptic projection from the mPFC (predominantly anterior cingulate) to the dorsal 123 CA3/CA1 HPC is also identified in mice, implicated in the regulation of contextual fear memory 124 generalization (Bian et al., 2019; Rajasethupathy et al., 2015). 125

Several indirect pathways involving the thalamus, lateral entorhinal cortex (LEC) and amygdala further connect the HPC and mPFC. Rodent studies reveal that 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). The lateral entorhinal cortex (LEC) is also bidirectionally connected to both the mPFC and HPC in rodents (Agster and Burwell, 2009; Eichenbaum, 2017; Isomura et al.,

132 2006; Salimi et al., 2021), and this pathway involving the LEC is implicated in memory encoding and retrieval (Eichenbaum, 2017; Takehara-Nishiuchi, 2020). In rodents, 133 bidirectional projections between the amygdala and both the vHPC and the mPFC are further 134 described (Fukushima et al., 2021; Guirado et al., 2016; Hübner et al., 2014; Khastkhodaei et 135 al., 2021; Kim and Kim, 2019). These findings implicate that emotion and social behaviours 136 may be regulated by HPC-mPFC pathways through the basolateral amygdala (BLA) (Felix-137 Ortiz and Tye, 2014; Felix-Ortiz et al., 2013; Qi et al., 2018), and suggests that the mPFC 138 139 supports the HPC in reconsolidating inhibitory avoidance memory through the amygdala (Fukushima et al., 2021). 140



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Figure 1 General schematic of direct and indirect pathways between the hippocampus (HPC) 142 and medial prefrontal cortex (mPFC). Insight from rodents (top) and humans (bottom) 143 demonstrate that the HPC and mPFC are anatomically connected via direct and indirect 144 (bidirectional) pathways. Arrows indicate direction of projections. Direct pathways involve 145 146 monosynaptic projections from the ventral CA1 HPC and subiculum (anterior HPC in humans) to the mPFC, and monosynaptic projections from the mPFC (predominantly anterior cingulate) 147 to the dorsal CA3/CA1 HPC are reported in rodents. Indirect HPC-mPFC pathways involve 148 bidirectional projections between the HPC and mPFC through intermediary regions: the 149 thalamic nucleus reuniens (NR), lateral entorhinal cortex (LEC) and amygdala (AMY). For 150 details and supporting references, see main text. 151

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154 Oscillatory Synchrony in the HPC and mPFC

Oscillations are one of the prominent features of brain activity and play a crucial role in regional 155 neural integration and inter-regional interactions in the brain. Oscillatory activity in groups of 156 157 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 158 oscillations at a different frequency than the firing frequency of individual neurons. These 159 160 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 (y, low: 30-60 Hz and high: 60-100 Hz) (Cole and Voytek, 2017; Thut 161 et al., 2012). Oscillations have been observed in brain regions including the HPC (Goyal et 162 al., 2020), visual cortical areas (Galuske et al., 2019), and olfactory cortex (Salimi et al., 2021). 163 164 Inter-regional oscillation coupling could modulate effective connectivity in a given behavioural period, such as while undertaking cognitive tasks, attentional selection and decision making 165 (Berger et al., 2019; Doesburg et al., 2012; Gordon, 2011; Guise and Shapiro, 2017). 166 Considerable evidence (Buzsáki and Draguhn, 2004; Goodman et al., 2018; Wirt et al., 2021) 167 168 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., 169 2010), emotion (Jin and Maren, 2015), context-guided memory (Place et al., 2016), decision-170 171 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 172 different roles in neural communication (Fries, 2005; Buzsáki and Draguhn, 2004). See Table 173 174 1.

(1) HPC-mPFC δ oscillation: δ -frequency network activity is commonly associated with 175 sleep, but data from awake-behaving animals show δ -dominated network modes (HPC-mPFC 176 177 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 178 minimal during locomotion. These findings suggest that HPC-mPFC δ oscillation represents 179 180 functionally distinct circuit dynamics that are temporally and behaviourally alternated among θ-dominated oscillations during navigation. This oscillation is vital to coordinating encoding 181 and retrieval mechanisms or decision-making processes at a timescale that segments event 182 183 sequences within behavioural episodes (Schultheiss et al., 2020).

(2) HPC-mPFC θ oscillation: Modulation of mPFC and HPC oscillatory θ coupling by 184 mnemonic demands of a working memory task correlated with behavioural performance both 185 186 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 187 essential for long-term synaptic potentiation (Capocchi et al., 1992) and important for gating 188 information flow and guiding plastic changes (Siapas et al., 2005). In addition, considerable 189 evidence demonstrates HPC-mPFC θ coupling during spatial navigation when novel 190 information was encoded and stored information was retrieved (Kaplan et al., 2014). An 191 increase in HPC-mPFC θ coupling also occurs during active choice decision making (Guitart-192 Masip et al., 2013) and other memory tasks (Simons and Spiers, 2003). 193

(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 207 208 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 209 of HPC-mPFC ripples coupling with extensive cortico-cortical connections (Khodagholy et al., 210 211 2017), reflected either a direct hippocampal-entorhinal cortex-neocortex excitation 212 (Logothetis et al., 2012; Peyrache et al., 2011) and/or an indirect common drive by cortical 213 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 214 215 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).

220 Cross-frequency coupling is present during a range of cognitive functions and likely affects the organization of brain rhythms. Current data demonstrates its crucial role in long-range 221 222 cross-frequency coupling in HPC-prefrontal circuit function. Hippocampal θ oscillations modulate mPFC assembly patterns by rhythmically biasing synchrony of local y oscillations in 223 behaving rats and mice (Sirota et al., 2008; Tamura et al., 2017), suggesting that oscillations 224 mediate information flow from the HPC to the PFC. In addition, θ - δ coupling mediates 225 information transfer from the PFC to the HPC via a relay mechanism through the thalamic NR 226 (Roy et al., 2017). However, this result has been challenged in light of the possibility that δ 227 228 oscillations has been attributed to respiratory-entrained oscillations in both structures 229 (Lockmann and Tort, 2018).

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242 **Table 1** The physiological roles of oscillatory synchrony between the hippocampus (HPC) and

243 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

245 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

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

248 Cognition: Memory and Learning

Important interactions between the HPC and mPFC support the encoding and retrieval of 249 episodic memories (Eichenbaum, 2017; Jin and Maren, 2015; Kennedy and Shapiro, 2004; 250 Weilbächer and Gluth, 2017). Considerable evidence demonstrates that in these interactions, 251 the HPC organizes contextual memory and the mPFC facilitates retrieval of contextual 252 memories through suppressing inappropriate memories from differing contexts (Eichenbaum, 253 2017; Preston and Eichenbaum, 2013). Recent functional MRI (fMRI) studies also 254 demonstrate that persistent HPC-mPFC interactions promote long-term memory through 255 256 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 257 258 (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 259 execution of working memory (Liu et al., 2018; Salimi et al., 2022; Sigurdsson and Duvarci, 260 2016; Wirt et al., 2021). This is further observed in human studies. Increased HPC-mPFC θ 261 262 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 263 encoding of contextually unexpected information was predictive of later memory performance 264 in epileptic patients (Gruber et al., 2018). 265

Evidence from rodents demonstrate that the HPC-mPFC circuit is crucial for learning. Bilateral 266 267 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 268 pathways were observed during the transition from retrospective to prospective encoding 269 (Myroshnychenko et al., 2017). It has also been shown that novel experiences alter vHPC θ 270 oscillations and vHPC-mPFC connectivity, subsequently contributing to the modulation of 271 learning-associated plasticity (Park et al., 2021). This implicates the crucial role of the HPC-272 273 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 274 rhesus monkeys that frequency-specific interactions and oscillatory synchrony underlie 275 relevant points during associative learning, suggesting that oscillatory signals from the HPC 276 guides neocortical plasticity in the PFC during associative learning (Brincat and Miller, 2015). 277 Studies in human further suggest that the HPC-mPFC circuit is not only activated and engaged 278 279 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 280 in category learning (Schlichting and Preston, 2016; Theves et al., 2021). Therefore, the HPC-281 mPFC circuit plays a crucial role in supporting cognitive processes involving memory and 282 283 learning.

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285 *Emotion*

286 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., 287 2002), emotional judgment (Perry et al., 2011) and emotional memory (Engen and Anderson, 288 2018; Holland and Kensinger, 2010; Lovett-Barron et al., 2014; Richter-Levin and Akirav, 289 2000). The mPFC is implicated in the appraisal and expression of negative emotion (dorsal-290 291 caudal mPFC), and regulates limbic regions that facilitate emotional responses (ventral-rostral mPFC) (Etkin et al., 2011). Increasing evidence suggests that hippocampal-cortical pathways 292 facilitate the emotional regulation of fear and emotional processing through oscillations (Jin 293

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).

300 There is evidence to suggest that indirect HPC-mPFC pathways modulate emotional processes such as fear extinction and emotion regulation through circuits involving the 301 amygdala (Hartley and Phelps, 2010; Jin and Maren, 2015; Ramanathan et al., 2018). The 302 amygdala is a key structure in fear-conditioning and eliciting emotional states, assigning 303 304 emotional dimensions to sensory stimuli through constant evaluation and integration of 305 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 306 amygdala is anatomically connected to the HPC and mPFC (Hintiryan et al., 2021; Orsini et 307 308 al., 2011; Yang and Wang, 2017) and oscillatory synchrony between these regions are implicated in supporting emotional arousal and consolidation of emotional memories 309 (Hermans et al., 2014; Paré et al., 2002). Further studies have found increased θ 310 synchronization across the vHPC-BLA-mPFC circuit during heightened anxiety and learned 311 312 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 313 314 supported by studies in humans, providing evidence for unidirectional θ and α oscillations in the amygdala that modulate hippocampal y activity during fear processing (Zheng et al., 2017), 315 and synchronization of θ oscillations in the amygdala and mPFC to facilitate fear learning 316 (Chen et al., 2021). Altogether, considerable evidence suggests a neurocircuitry of emotion 317 regulation that involves the HPC-mPFC circuit via the amygdala (Hartley and Phelps, 2010; 318 Jin and Maren, 2015; Richter-Levin and Akirav, 2000; Yang and Wang, 2017). 319

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321 Sensory Processing

Sensory processing (SP) plays an important role in daily life as it synthesizes information from 322 multiple sensory channels in response to the external environment into coherent behavioural 323 and emotional patterns. Studies in rodents (Le Merre et al., 2018; Martin-Cortecero and 324 Nuñez, 2016) and humans (Acevedo et al., 2014; Zucchella et al., 2018) demonstrate the 325 326 involvement of a large network of brain areas including the sensory cortices, motor cortices and associative areas in SP. Rodent studies further reveal that the HPC and mPFC are 327 involved in multisensory integration and sensory discrimination (Engel et al., 2012; Grion et 328 al., 2016; Martin-Cortecero and Nuñez, 2016; Pereira Antonio et al., 2007). Insight from rodent 329 models of classical eyeblink conditioning further demonstrates that HPC-mPFC pathways can 330 dynamically modulate SP of conditioned stimulus as part of a secondary modulatory system 331 (Zhang et al., 2019). 332

The influence of HPC-mPFC pathways on SP is further highlighted in studies where sensory 333 signals are evaluated for learned motor output. In a study, mice were trained for a whisker-334 dependent detection task, and correct "licks" following whisker stimulation correlated with 335 increased sensory-evoked signals in the dorsal CA1 HPC and mPFC (Le Merre et al., 2018). 336 Inactivation of neural activity in the HPC and mPFC further impaired behavioural performance. 337 corroborating studies in contextual learning that demonstrate the crucial role of HPC-mPFC 338 interactions in translating sensory signals to relevant motor behaviour (Martin-Cortecero and 339 Nuñez, 2016; Ong et al., 2019), and that HPC-mPFC oscillatory synchrony underlie sensory 340 gating deficits (Dickerson et al., 2010). In addition, studies in humans provide evidence that 341

342 HPC-mPFC oscillatory synchrony at various frequencies including increased θ coherence supports auditory predictive processing and multisensory attention (Friese et al., 2016; 343 Grunwald et al., 2003; Recasens et al., 2018). HPC-mPFC interactions are further 344 demonstrated to be crucial for supporting SP during postnatal development, as the HPC 345 provides excitatory signals to drive functional mPFC maturation during the sensitive period of 346 347 tactile development in rodents (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 348 maturation across the hippocampal-prefrontal network (Ahlbeck et al., 2018; Bitzenhofer et 349 al., 2017; Brockmann et al., 2011; Xu et al., 2020). Thus, oscillations across the HPC-mPFC 350 351 circuitry are not only important for cognition and emotional processes, but also facilitates normal SP. As rodent studies increasingly implicate the involvement of HPC-mPFC pathways 352 353 in modulating SP, future work in humans is warranted to elucidate distinct oscillatory contributions across the HPC-mPFC network in response to various stimuli. 354

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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**.

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364 Abnormal HPC-mPFC Circuit Dynamics in Neurodevelopmental Disorders

Abnormal brain development affects the structural and functional connectivity across the HPC-365 mPFC circuit, resulting in alteration at different spatial scales from cellular levels to network 366 level. Neurodevelopmental disorders have been associated with maladaptive formation of 367 cortical networks and faulty programming of synaptic connections, as neural oscillations and 368 synchrony may have crucial roles in synaptic modifications (Galuske et al., 2019; Zarnadze et 369 al., 2016). In this section, we highlight aberrant oscillations within and across the HPC-mPFC 370 network associated with a variety of cognitive and behavioural deficits in several 371 372 neurodevelopmental disorders.

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374 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by 375 376 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 377 range $(\delta, \theta, \alpha, \beta)$ and short range (β, γ) connectivity (Simon and Wallace, 2016). Altered neural 378 circuitries in numerous brain regions including the orbitofrontal and sensory-motor networks 379 are observed in ASD individuals, suggesting that cortical asynchronization during sensory and 380 381 perceptual processing is a pathological hallmark of ASD (Hull et al., 2017; Oldehinkel et al., 2019; Xu et al., 2019b). 382

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,

387 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 388 excitatory transmission and disturb the balance of excitation/inhibition (E/I) signals that 389 support social behaviour. A study found reduced θ synchronization between the vHPC-mPFC 390 and loss of excitatory signalling from the vHPC to prefrontal GABAergic interneurons in mice 391 392 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 393 in aberrant social behaviour (Sun et al., 2020), where dysfunctional interactions across this 394 circuit may alter GABAergic circuits and impair long-range communication between the HPC 395 396 and mPFC in the pathophysiology of ASD (Nelson and Valakh, 2015; Sohal and Rubenstein, 397 2019; Zhao et al., 2022).

398 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 399 in a mouse model of Rett syndrome (classified as an ASD disorder) (Phillips et al., 2019). 400 401 Another study revealed monosynaptic connections from HPC pyramidal neurons to mPFC GABAergic neurons, and inhibition of this pathway negatively impacted social behaviour in 402 mice (Sun et al., 2020). Importantly, activation of mPFC parvalbumin-positive (PV+) neurons 403 404 rescued social memory impairments caused by inhibition of vHPC (Sun et al., 2020). Deficits 405 in hippocampal PV+ interneurons, circuit changes (altered y oscillations, sharp wave-ripples, and θ -y coupling), and impaired spatial discrimination were further found in a mouse model of 406 ASD, *Cntnap2* mice (Paterno et al., 2021). Altered oscillatory θ and α activity associated with 407 increased memory load have also been demonstrated in individuals with ASD (Larrain-408 Valenzuela et al., 2017). In addition, studies have shown substantially reduced hippocampal 409 functional connectivity with frontal regions during episodic memory retrieval (Cooper et al., 410 2017), as well as rest-associated functional abnormalities in the mPFC correlating with social 411 impairment in individuals with ASD (Kennedy et al., 2006). 412

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.

418

419 Fragile X Syndrome

420 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 421 422 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 423 FMRP is concurrent with characteristic social impairments, learning disabilities and cognitive 424 425 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 426 impairments have been linked to changes in synaptic plasticity and circuitry involving 427 excitatory and inhibitory activity in Fmr1-KO mice (Gibson et al., 2008; Morin-Parent et al., 428 2019; Sidorov et al., 2013; Contractor et al., 2015). Evidence from rodents and humans 429 suggest that abnormal HPC-mPFC oscillatory dynamics are associated with FXS. Major 430 electrophysiological observations from recordings in the HPC CA1 pyramidal cell layer 431 included abnormally greater power of θ oscillations associated with increased slow y, and 432 decreased spike-count correlations of interneurons hyper-synchronized with θ and slow y 433 oscillations in the FXS mouse model (Fmr1-KO) during free exploration (Arbab et al., 2018). 434

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 442 crucial time points of postnatal development (Kramvis et al., 2020). At prepubescence, there 443 was increased inhibition of the mPFC with decreased inhibitory synaptic depression. This 444 445 contrasted prolonged synaptic kinetics with reduced inhibition of the mPFC at adolescence, 446 and dynamic changes to mPFC pathways in Fmr1-KO during development is functionally 447 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 448 449 basolateral amygdala (BLA) to the mPFC (Yang et al., 2021), these abnormalities reflect an imbalance in GABAergic signalling persisting throughout development with consequential 450 phenotypes in FSX (Van der Aa and Kooy, 2020). D'Hulst et al. (D'Hulst et al., 2015) 451 demonstrated an average of 10% reduction in GABA_A receptor availability and binding 452 potential throughout the brain in FXS patients. Using FXS human pluripotent stem cells 453 (hPSCs), Zhang et al., (Zhang et al., 2022) further found delayed maturation of human 454 455 GABAergic neurogenesis in hPSCs, and at later stages of GABAergic neurogenesis, including (1) increased neuronal networks activity, (2) increased proliferation of neuroblast progenitors 456 457 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 458 GABAergic system in FXS patients (Van der Aa and Kooy, 2020), resulting in altered inhibitory 459 signals and abnormal homeostatic development of excitatory/inhibitory circuits (Paluszkiewicz 460 et al., 2011). Consequently, altered local and long-range GABA-dependent HPC-mPFC 461 interactions expressed in the θ and γ ranges (Molen et al., 2014; Wulff et al., 2009; Contractor 462 463 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 464 al., 2009). Future work exploring how GABAergic circuit impairments influence oscillations at 465 various frequency bands across the HPC-mPFC network will provide insight into mechanisms 466 linking circuit level to behavioural changes in FSX. 467

468

469 Down Syndrome

470 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, 471 2012; Witton et al., 2015; Zorrilla de San Martin et al., 2020). We have previously 472 demonstrated in DS mouse models atypical neural circuitry involving altered θ frequency, 473 474 altered hippocampal phase-amplitude coupling, modulation of hippocampal high y, and altered HPC-mPFC 0 coherence (Chang et al., 2020). These abnormalities were segregated with 475 476 behavioural changes associated with impaired spatial working memory and prolonged decision-making (Chang et al., 2020). Recent evidence further demonstrates increased 477 478 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-479 Rs are coupled to cortical networks including the mPFC to facilitate cognitive processes 480 481 (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 482

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).

486 Abnormal brain synchrony is well established in people with DS. Notably, enhanced synchronization between adjacent brain regions and widespread alterations in default mode 487 network (DMN) connectivity including weakened long range connections are largely 488 characterized (Anderson et al., 2013; Rosas et al., 2021; Wilson et al., 2019). Recently, 489 reduced long-range DMN connectivity associated with cognitive decline were found in DS 490 individuals, providing evidence that altered connectivity between the HPC and prefrontal 491 cortices underlie cognitive impairments in DS (DiProspero et al., 2022). In addition, the 492 493 attenuation of early exploratory behaviour associated with developmental delays in DS (Fidler 494 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 495 disinhibitory HPC microcircuits to facilitate object-related spatial encoding and exploratory 496 497 behaviours (Malik et al., 2022). Long-range GABAergic projections promoted network oscillations that facilitate object exploration such as increased PFC-HPC low-y synchrony and 498 greater high-y and θ power (Malik et al., 2022). These findings implicate that dysfunctional 499 GABAergic innervation may alter HPC-mPFC oscillatory synchrony and mediate cognitive and 500 501 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 502 503 to Alzheimer's Disease (AD) in people with DS (DiProspero et al., 2022; Koenig et al., 2021; 504 Liang et al., 2020).

505

506 Abnormal HPC-mPFC Circuit Dynamics in Neurological Disorders

507 Aging is associated with alterations in cognitive processing and brain neurophysiology. 508 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). 509 Pathological changes of synaptic integrity and coordinated network activity has been 510 associated with neurodegenerative and age-related neural disorders. Recent research further 511 suggests that altered oscillatory activity in the brain may be an early warning sign of age-512 related neurological diseases (Murty et al., 2021). As the HPC and mPFC have well-513 established roles in cognitive and memory functions, we discuss relevant age-related 514 515 neurological disorders that have aberrant HPC-mPFC circuitry.

516

517 <u>Alzheimer's Disease</u>

Alzheimer's Disease is a progressive neurodegenerative disorder with widely characterized 518 abnormalities in neural oscillations and cognitive deficits (Byron et al., 2021; Hamm et al., 519 2015; Isla et al., 2021; Kitchigina, 2018). It has been shown that prominent neural HPC-mPFC 520 oscillations, particularly slow-frequency θ and fast-frequency y, are significantly altered in 521 mouse models of AD (Kitchigina, 2018; Mehak et al., 2022) and in patients with early and late 522 stage AD (Başar et al., 2017; Goodman et al., 2018; McDermott et al., 2018). Additionally, 523 524 abnormal oscillations across the HPC-mPFC circuit are associated with AD pathology such as extracellular insoluble β -amyloid (A β) plaques, intracellular neurofibrillary tangles (NFTs), 525 and tau aggregation (Ahnaou et al., 2017). A study found that A β significantly reduces synaptic 526 inputs of hippocampal fibres to the PFC at different frequencies (5–50 Hz) measured by mean 527 amplitudes of field excitatory postsynaptic potentials (fEPSPs) in vitro (Flores-Martínez and 528 Peña-Ortega, 2017). Intracranial recordings from the HPC and mPFC of TgF344-AD rats 529

530 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, 531 Tanninen and colleagues revealed a significant attenuation of inter-region θ and y phase-532 phase and amplitude-amplitude oscillatory coupling between the HPC and prelimbic mPFC 533 during associative learning (Tanninen et al., 2017). Notably, these changes in neural 534 535 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 536 coupling with hippocampal ripples (Maingret et al., 2016; Zhurakovskaya et al., 2019). 537

The significance of HPC-mPFC in AD is further understood through studies of memory. 538 Episodic memory is one of the first systems to decline in AD, and affected individuals show 539 540 deficits in object and spatial recognition memory consolidation (Tromp et al., 2015). These 541 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 542 543 demonstrates that CA1 and mPFC θ sequences are temporally coordinated to support 544 memory-guided decision-making processes in rats (Tang et al., 2021), and synchronization of θ and y oscillations regulate HPC-mPFC communication during cognitive processes 545 particularly learning and memory (Colgin, 2011; Hyman et al., 2005; Wirt et al., 2021; Buzsáki 546 547 and Draguhn, 2004). Low levels of θ -y coupling associated with working memory deficits are 548 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 549 550 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, 551 552 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). 553

554

555 <u>Epilepsy</u>

Epilepsy is a common neurological disorder that is characterized by frequent seizures. It 556 affects nearly 1% of the population with substantial morbidity and mortality (Fiest et al., 2017) 557 There is increasing interest to study the pathophysiological mechanisms underpinning seizure 558 generation in epilepsy, particularly abnormal connectivity in certain brain regions (Engel et al., 559 2013; Englot et al., 2016; Jiruska et al., 2013). Studies in patients with focal epilepsy showed 560 widespread network alterations that extend beyond the epileptogenic zone (Braakman et al., 561 2013; Luo et al., 2012; Widjaja et al., 2015). In rodent and human studies, altered connectivity 562 between the HPC and mPFC has been correlated with epilepsy conditions (Englot et al., 2015; 563 Jin and Maren, 2015). Individuals with temporal lobe epilepsy (TLE) show HPC-mPFC 564 hypersynchrony and abnormally greater coherence in θ bands (Holmes, 2015), suggesting 565 that epileptiform events are facilitated by the slow oscillation state biasing hippocampal 566 pathways towards hyperexcitability and enhancing hypersynchrony across HPC and cortical 567 networks (Nazer and Dickson, 2009). In a rat model of TLE, coherence in θ band synchrony 568 between the dHPC and mPFC was further found to be increased in the pre-ictal period 569 preceding seizures, suggesting that altered HPC-mPFC connectivity may promote seizure 570 571 generation (Broggini et al., 2016).

572 Further evidence revealed that prolonged or recurrent seizures can cause or exacerbate 573 cognitive impairments (Blake et al., 2000; Butler and Zeman, 2008; Butler et al., 2009). 574 Numerous studies suggest that altered HPC-mPFC connectivity may be related to 575 neurocognitive deficits in patients with epilepsy (Doucet et al., 2013; Voets et al., 2014). One 576 study found fewer physiological hippocampal ripples, greater spontaneous HPC interictal 577 epileptiform discharges (IEDs), and impaired spatial memory consolidation associated with 578 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 579 in regions distinct from the epileptic network were further observed to alter spatiotemporal 580 oscillatory properties and mediate abnormal patterns of brain connectivity (Dahal et al., 2019). 581 It is becoming increasingly clear that precisely coordinated HPC IEDs-prefrontal cortex 582 583 spindles exacerbate aberrant HPC θ -y coupling during rapid eye movement (REM) in the epileptic brain (Jansen et al., 2021; Mendes et al., 2021). Consequently, the generation of 584 pathological HPC oscillations and IED-mediated abnormal coupling of oscillations may alter 585 HPC-mPFC network activity and disrupt normal HPC ripples-mPFC spindles coupling crucial 586 587 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 588 589 endeavours that may lead to improved strategies for localization epileptogenic area, aid surgical intervention and facilitate outcome prediction in epilepsy. 590

591

592 Therapeutic Strategies for Targeting HPC-mPFC Circuit Dynamics

593 Medical treatments and neural substrates for therapeutic approaches can be guided by the 594 study of brain oscillations. Oscillotherapeutics is an exciting area of therapy that uses 595 oscillations as biomarkers or therapeutic targets to treat disorders with brain network 596 dysfunction (Takeuchi and Berényi, 2020). Here, we discuss advancements in brain 597 stimulation, gene therapy, and pharmacotherapy, highlighting evidence for the use of 598 oscillotherapeutics to treat disorders with aberrant HPC-mPFC circuit dynamics.

599

600 Brain Stimulation

An emerging application in brain stimulation therapy is the use of neuromodulation to restore network abnormalities in cognitive disorders such as AD (<u>Chan et al., 2021a</u>). 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 y brain activity has well-established roles in cognition, y entrainment therapy has been 608 explored for neurological disorders such as AD (Adaikkan and Tsai, 2020; Traikapi and 609 Konstantinou, 2021). Visual GENUS at 40 Hz entrained y oscillatory activity in the HPC and 610 prefrontal cortices and enhanced inter-regional y oscillatory activity in mouse models of 611 neurodegeneration (Adaikkan and Tsai, 2020; Adaikkan et al., 2019). Auditory and audiovisual 612 GENUS at 40 Hz further reduced amyloid load in the HPC and mPFC respectively, and 613 hippocampal-dependent recognition and spatial memory tasks were also improved by auditory 614 GENUS at 40 Hz in the neurodegeneration mouse model, 5XFAD mice (Martorell et al., 2019). 615 These findings demonstrate the potential for GENUS to ameliorate AD pathology and improve 616 617 cognitive function (laccarino et al., 2016).

618 Preliminary data from human studies highlights its potential application in treatment for AD. 619 Chan et al. (Chan et al., 2021b) conducted a randomized, placebo-controlled trial in 620 participants with mild AD dementia and found that one-hour daily treatment of audio-visual 621 GENUS at 40 Hz delivered over 3 months improved memory performance and reduced brain 622 atrophy in the active group. Fatemi et al. (2022) employed simultaneous auditory and visual 623 stimulation in cognitive healthy participants and found significantly enhanced θ-γ phaseamplitude 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 based on the hypothesis that 628 DBS can modulate oscillations in these regions (Cervera-Ferri et al., 2016; Muthuraman et al., 629 630 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 631 modulate oscillatory rhythms is actively explored in diseases with pathological brain circuitries 632 633 (Herrington et al., 2016; Lozano et al., 2019). DBS of the subthalamic nucleus (STN) and 634 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 635 rhythms (Müller and Robinson, 2018). Central thalamus-DBS (CT-DBS) increased 636 hippocampal θ oscillations and improved SWM in SD rats (Chang et al., 2019), and ventral 637 638 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., 639 2019). Recent work further demonstrated that acute DBS in the mPFC with 130 Hz improved 640 mPFC-vHPC θ and γ coupling in a rat model of developmental schizophrenia (Lippmann et 641 642 al., 2021).

643 Insight from DBS for epilepsy further implicates its beneficial impact in treating disorders with 644 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 645 effects in patients with temporal lobe epilepsy (TLE), (Wang et al., 2021). In another large, 646 647 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 648 649 et al., 2017). Given that prominent oscillations regulate communication between the HPC and 650 mPFC, the ability for DBS to entrain oscillations in the HPC may restore normal HPC-mPFC 651 oscillatory coupling disturbed in neurological disorders with global network dysfunction such as epilepsy. With increasing evidence that IED-spindle coupling is associated with aberrant 652 653 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. 654 Further studies examining the ability for DBS to alter HPC-mPFC oscillations at different 655 frequencies will significantly contribute to advancing progress in using DBS to treat 656 neurological disorders with aberrant HPC-mPFC circuitry. 657

658

659 Gene Therapy

The use of gene therapy to modulate HPC-mPFC circuit dynamic is a relatively new area of 660 research. However, preliminary findings from clinical trials suggest that gene therapy can 661 target diseases like AD that have aberrant neural circuitries. There are over 40 ongoing clinical 662 trials in treatment for neurodegenerative diseases (Sun and Roy, 2021) and for example, 663 currently, much optimism surrounds the Phase 1 clinical trial of the AAV2-Brain Derived Nerve 664 Growth Factor (BDNF) gene therapy to treat AD or MCI (National Institute of Health (NIH), 665 NCT05040217). Since BDNF regulates key memory circuits involving the HPC and mPFC 666 (Rosas-Vidal et al., 2014), AAV2-BDNF gene therapy represents a promising therapeutic 667 approach to treating neurodegenerative diseases like AD by targeting the modulation of 668 synaptic signalling (Gao et al., 2022); National Institute of Health (NIH), NCT05040217). A 669 recent study further demonstrated that SynCav1 gene therapy may also be a promising 670 therapy for AD. First, the authors demonstrated that PSAPP AD model mice at 9 and 11 671

672 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, 673 they found that delivery of SynCav1 to the HPC at 3 months using adeno-associated virus 674 serotype 9 (AAV9) improved memory and improved morphological changes including a 675 greater number of CA1 dendritic spines and dendritic arborization which support important 676 677 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 678 the role of this novel gene therapy for later stages of neurodegeneration where there may be 679 high levels of amyloid deposition (Wang et al., 2021). 680

The application of gene therapy for neural circuit disorders is further highlighted in its potential 681 682 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 683 technologies including chemogenetics (Sternson and Bleakman, 2020), optogenetics (Mirzayi 684 et al., 2022) and CRISPR-based gene editing (Heidenreich and Zhang, 2016) are viable tools 685 686 for dissecting and restoring neuronal circuits fundamental to developmental and neurological diseases. In a recent study, adeno-associated viruses (AAV)-mediated expression of human 687 FMRP isoform 17 orthologs corrected abnormal y activity and autism-related behaviours in 688 689 Fmr1 KO rodents (Hooper et al., 2021), and AAV-FMRP-injected mice demonstrated the ability 690 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 691 692 to restore cellular changes (e.g. GABAergic deficits) and correct circuit imbalances (neuronal hyperexcitability) associated with learning disabilities, sensory hypersensitivities, and social 693 694 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 695 remains unclear and clinical trials are warranted. Future work to improve gene delivery and 696 increase understanding of post-transcriptional regulation systems will further optimize gene 697 therapy to correct aberrant HPC-mPFC circuitry associated with developmental and 698 neurological disorders (Ingusci et al., 2019). 699

700

701 Pharmacotherapy

In pharmacotherapy for AD, there is an emerging paradigm shift from solely targeting 702 pathological hallmarks like amyloid plaques to modulating neural circuitries. Considerable 703 704 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; 705 Traikapi and Konstantinou, 2021). Several AD drugs have been shown to modulate these 706 rhythms (Isla et al., 2021). Notably, the AChE inhibitor donepezil was found to increase 707 stimulation-induced hippocampal θ oscillation power, enhance θ phase to γ amplitude 708 coupling, reduce cortical hyperexcitability and reduce occurrences of high-voltage spindle 709 activity in a transgenic AD mouse model (Stoiljkovic et al., 2018). In addition, current drugs 710 approved for the symptomatic treatment of dementia (rivastigmine, tacrine, galantamine and 711 memantine) have been shown to enhance cortical slow θ (4.5-6 Hz) and y (30.5-50 Hz) 712 713 oscillations (Ahnaou et al., 2014; Drinkenburg et al., 2015). Recently, the histone deacetylase 714 inhibitor (HDAC) suberoylanilide hydroxamic acid (SAHA), was found to rescue impairment of 715 hippocampal y (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 716 findings implicate the ability for SAHA to modulate hippocampal y oscillations through its effect 717 718 on fast-spiking PV+ GABA-containing interneurons (Bartos et al., 2007). Since PV+ interneurons mediate crucial HPC-mPFC interactions underlying memory consolidation 719

(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. Schizophrenia is 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 (Stepnicki et al., 2018), demonstrated evidence for stabilizing the aberrant increase and accelerating the resynchronization of hippocampal y 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 longterm 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 HPCmPFC circuit dynamics like AD and schizophrenia to restore normal function (Canter et al., 2016).

760 **Table 2** Overview of neurodevelopmental and neurological disorders associated with

abnormal hippocampus-medial prefrontal cortex circuit dynamics. For a more thorough

discussion, refer to text. (AD=Alzheimer's Disease; dHPC=dorsal hippocampus;

763 DMN=default mode network; HPC=hippocampus; HPC-mPFC=hippocampal-medial

764 prefrontal cortex; human pluripotent stem cells=hPSCs; interictal epileptiform

discharges=IEDs; MCI=mild cognitive impairment; mPFC=medial prefrontal cortex;

766 PV+=parvalbumin-positive; SPW-Rs=sharp wave-ripples; vHPC=ventral hippocampus)

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

Fragile X Syndrome	Rodent and Human	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)
	Rodent	Oscillatory changes in the HPC that potentially disrupts HPC-mPFC circuitry:	(Arbab et al., 2018)
		 (1) Abhormally greater power of θ associated with increased slow γ. (2) Decreased spike-count correlations of interneurons hyper-synchronized with θ and slow γ. 	
	Human	Evidence suggesting impaired GABAergic HPC-mPFC signalling in FXS patients: (1) A 10% reduction in GABA _A receptor availability. (2) Reduced GABA binding potential	(D'Hulst et al., 2015)
		throughout the brain.	
	Human	Evidence suggesting impaired HPC-mPFC local and long-range GABA-dependent interactions:	(Zhang et al., 2022)
		 (1) Delayed maturation of GABAergic neurogenesis in hPSCs (2) Increased neuropal patworks 	
		activity. (3) Increased proliferation of	

		neuroblast progenitors. (4) Downregulation of proteins associated with GABAergic neuronal maturation.	
Down Syndrome	Rodent	 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)
	Rodent	Reduced HPC SPW- Rs coupling with cortical networks and impaired working memory.	(Alemany- González et al., 2020)
	Rodent	Altered GABAergic signalling; loss of fast- spiking phenotypic PV+ cells and increased excitability.	(Zorrilla de San Martin et al., 2020)
	Rodent and Human	Abnormal coordination of θ oscillatory activity across the HPC and mPFC.	(Goodman et al., 2018; Wirt et al., 2021)
	Human	Widespread alterations in DMN connectivity and weakened DMN- frontal cortices connectivity	(Anderson et al., 2013; Wilson et al., 2019)
	Human	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	Rodent and Human	Abnormal mPFC spindle-band coupling with HPC ripples.	(Maingret et al., 2016; Zhurakovskay a et al., 2019)
		Rodent	Inactivation of the dHPC and mPFC impaired object and spatial recognition memory consolidation.	(Tuscher et al., 2018)
		Rodent	Altered CA1 HPC- mPFC θ temporal synchronization.	(Tang et al., 2021)
		Rodent	HPC-mPFC hypersynchrony associated with cognitive impairments.	(Holmes, 2015)
		Human	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	Rodent	Increased coherence at θ band synchrony between the dHPC and mPFC in pre-ictal seizure periods.	(Broggini et al., 2016)
		Rodent and Human	 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)
		Rodent and Human	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)

769 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 is 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.

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815 **References**

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