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Oscillotherapeutics – Time-targeted interventions in epilepsy and beyond

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ABSTRACT

Oscillatory brain activities support many physiological functions from motor control to cognition. Disruptions of the normal oscillatory brain activities are commonly observed in neurological and psychiatric disorders including epilepsy, Parkinson's disease, Alzheimer's disease, schizophrenia, anxiety/trauma-related disorders, major depressive disorders, and drug addiction. Therefore, these disorders can be considered as common oscillation defects despite having distinct behavioral manifestations and genetic causes. Recent technical advances of neuronal activity recording and analysis have allowed us to study the pathological oscillations of each disorder as a possible biomarker of symptoms. Furthermore, recent advances in brain stimulation technologies enable time- and space-targeted interventions of the pathological oscillations of both neurological disorders and psychiatric disorders as possible targets for regulating their symptoms.

1. Introduction: oscillations and neuronal activities are self-organized

In contexts of the neuroscience field, oscillations are rhythmic neuronal activities (Buzsáki, 2006). They are typically measured as fluctuating extracellular potentials by using electroencephalography (EEG), electrocorticography (ECoG), intracranial local field potential (LFP) or read out with functional brain imaging techniques or magnetoencephalography (MEG) each offering different time and spatial resolutions (Hong and Lieber, 2019). The major source of oscillations is rhythmically synchronizing synaptic transmissions. The rhythmicity stems from network structures composed of distinct cell-types and the population activities inside the network (Buzsáki et al., 2012). For example, at mesoscopic network levels, inhibitory neurons are essential to generate oscillatory network activities; the interactions of excitatory pyramidal and inhibitory basket neurons via their reciprocal connections generate gamma band oscillations and sharp wave-ripples in the hippocampus (HPC) (Buzsáki and Watson, 2012; Stark et al., 2014). At macroscopic network levels (the interaction between brain regions), the medial septum (MS, a rhythmogenic basal forebrain nucleus) externally regulates theta band oscillations in the HPC (Kang et al., 2017). Emergent oscillations (the extracellular electrical field) then orchestrates neuronal activities (the ephaptic effects) (Anastassiou et al., 2011). Thus, oscillations and neuronal activities in the brain are interdependent and self-organized. Oscillations reflect functional network states, and they affect neuronal population activities in the network.

Abbreviations: 6-OHDA, 6-hydroxydopamine; AI, artificial intelligence; AD, Alzheimer's disease; AMY, amygdala; BDNF, brain-derived neurotrophic factor; CSFA, cross-spectral factor analysis; CSTC, corticostriatal-thalamocortical; DBS, deep brain stimulation; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; DSM-5, diagnostic and statistical manual of mental disorders; DSP, digital signal processor; DRT, dopamine replacement therapy; ECN, executive control network; ECoG, electrocorticography; ECT, electroconvulsive therapy; EEG, electroencephalography; FDA, food and drug administration; fMRI, functional magnetic resonance imaging; FPGA, field-programmable gate array; GAD, generalized anxiety disorder; GPU, graphical processing unit; HD-tACS, high definition transcranial alternating current stimulation; HD-tDCS, high definition transcranial direct current stimulation; HPC, hippocampus; ICA, independent component analysis; IoT, internet of things; ISP, intersectional-short pulse; LFP, local field potential; MAM, methylazoxymethanol acetate; MDD, major depressive disorder; MEG, magnetoencephalography; MS, medial septum; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NAc, nucleus accumbens; PCA, principal component analysis; PCP, phencyclidine; PD, Parkinson's disease; PFC, prefrontal cortex; PTSD, posttraumatic stress disorders; PTZ, pentylenetetrazole; PV, parvalbumine; REM, rapid eye movement; rTMS, repetitive transcranial magnetic stimulation; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; SUDEP, sudden unexpected death in epilepsy; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TES, transcranial electrical stimulation; tFUS, transcranial focused ultrasound stimulation; TI, temporal interference; TMS, transcranial magnetic stimulation.

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Many studies have revealed that oscillatory brain activities support various brain functions such as motor control and cognition including spatial memory (Girardeau et al., 2009), arbitrary representational spaces (Agarwal et al., 2014; Solomon et al., 2019), sleep (Watson and Buzsáki, 2015), and emotions (Karalis et al., 2016; Likhtik et al., 2014) via temporally coordinated interactions between multiple brain regions (Bonnefond et al., 2017). Therefore, if oscillations are disrupted (and the neuronal activity is consequently disrupted), normal brain functions are supposed to be disrupted. If oscillations reflect both normal and pathological brain states, they could be good biomarkers of symptoms or behavioral phenotypes of neurological and psychiatric disorders. Oscillations are the dynamics of macroscopic neuronal circuits, which is the closest to the behavioural phenotypes in the multiple levels of biological structure (Fig. 1) (Leuchter et al., 2015). Thus, it is not surprising that more-and-more studies show the coincidence of the temporal expression of pathological oscillations with that of the abnormal behavioral phenotypes of neurological and psychological disorders (see Section 2); these disorders are considered as 'Oscillopathies' (Mathalon and Sohal, 2015). Pathological oscillations possibly come with both a correlation and a causal relationship with abnormal brain states and functions. If this is the case, the pathological oscillations may be a therapeutic intervention or modulation target for the disorders using the recently emerged time- and space-targeted brain stimulation technologies (Berényi et al., 2012; Vöröslakos et al., 2018). We call this strategy 'Oscillotherapeutics'.

In the following sections, we provide overviews on 1) the phenomenology of oscillopathies, 2) how we find abnormality in oscillations in animal models and human subjects, 3) how pathological oscillatory states emerge mechanically, a strategy for its intervention, 4) the embodiments of oscillotherapeutics in distinct stimulation modalities, and 5) the engineering challenges of future clinical applications of oscillotherapeutics.

2. Oscillopathy – a phenomenological overview

Oscillopathy is defined as a neurological or psychiatric disorder in which abnormality in oscillatory brain activities is observed (Braun et al., 2018; Buzsáki and Watson, 2012; Mathalon and Sohal, 2015). We will briefly summarize abnormal oscillations of known oscillopathies which can be targeted by interventions.

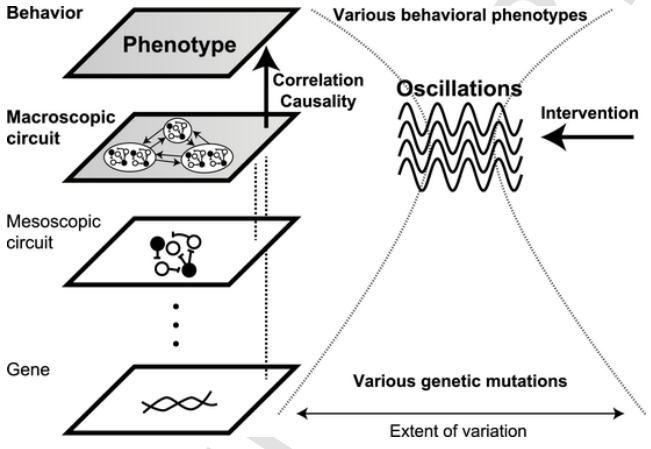

Fig. 1. The concept of oscillotherapeutics.A behavior is generated as a result of brain dynamics. Brain dynamics are determined by factors at various levels from genes to macroscopic network activity as a hierarchical system. The macroscopic circuit level is the closest to the behavior level. Therefore, oscillation (which reflects the dynamics of the macroscopic circuit level) supposes to have a close temporal correlation to (and an evident causal relationship to) behavioral phenotypes. There are huge variations at both the gene and subcellular levels of neurological and psychiatric disorders. In contrast, variations in the phenomenology of neurological and psychiatric disorders at the macroscopic circuit level (oscillation) are relatively minor. Therefore, time-targeted pathological oscillation intervention for neurological and psychiatric disorders (oscillotherapeutics) could be an effective strategy for regulating their behavioral phenotypes.

2.1. Epilepsy

Epilepsy is a neurological disorder characterized by an enduring predisposition to generate epileptic seizures (Fisher et al., 2014). An epileptic seizure is a transient behavioral change that might carry objective, overtsigns (e.g. convulsions) or subjective, covert symptoms (e.g. loss of consciousness). These changes are most probably caused by abnormally synchronous neuronal activities in the brain. The synchronized neuronal activity is quite evident in EEG measurements during seizures (ictal period) and the EEG synchronization is concomitant with behavioural manifestations such as tonic and clonic convulsions. Successful pharmaceutical and surgical treatments of epilepsy consistently reduce the frequency of electrographic and behavioural seizures (Glauser et al., 2006; Li and Cook, 2018). Furthermore, time-targeted intervention with the pathological neuronal oscillations of seizures or seizure predictions suppresses the behavioural manifestation of seizures (Morrell, 2011). This strongly suggests a causal relationship between the pathological oscillation of EEG measurements and the symptoms of epilepsy. Thus, epilepsy is a typical oscillopathy.

2.2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by tremor, rigidity, bradykinesia, and postural instability with the underlying loss of nigrostriatal dopaminergic neurons (Soileau and Chou, 2016). The pathological hallmark of PD is the finding of protein aggregates containing α-synuclein in neurons called Lewy bodies throughout brain. Symptoms of PD are thought to be caused by the dysfunction of the corticostriatal-thalamocortical (CSTC) loop due to decreased dopaminergic tone.

Dopamine replacement therapy (DRT) is typically used to ameliorate the associated motor disturbances. There are pathological oscillations of tremor (4–7 Hz), double tremor (10 Hz), and beta (15–30 Hz) frequencies in the CSTC loop of PD patients (Holt et al., 2019; Weinberger et al., 2009) and animal models (Deffains and Bergman, 2019; Heimer et al., 2006). Disruption of pathological oscillations by DRT (Heimer et al., 2006), the inactivation of the subthalamic nucleus (STN) (Wichmann et al., 1994), or deep brain stimulation (DBS) of the STN (Deuschl et al., 2006) consistently decreases the motor disturbances of PD. This suggests a causal relationship between the pathological oscillations and symptoms of PD (Bergman et al., 2015). The target of the STN stimulation may be the corticostriatal axons (Gradinaru et al., 2009). The intrinsic, slowly oscillating resting network activity, measurable by fMRI, is called default mode network (DMN) (Raichle, 2015). This network mostly consists of hub-like brain structures including the medial prefrontal cortex (PFC), the precuneus, and the posterior cingulate cortex (Hagmann et al., 2008). In PD patients, there are PD specific changes in the DMN (Delaveau et al., 2010; van Eimeren et al., 2009). These changes were restored by DRT (Delaveau et al., 2010) and possibly will also be restored by DBS in the future (Kringelbach et al., 2011).

2.3. Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by well-defined neurological features: neuronal loss, neurofibrillary tangle, and senile plaque. However, the clinical manifestations of AD as a major neurocognitive disorder are mainly psychiatric which include dementia, paranoia, depression and other cognitive defects: the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013).

Oscillopathic endophenotypes of AD are explored mainly phenomenologically yet, and are summarized below (Cassani et al., 2018): (1) Slowing. The power spectrum shifts from high-frequency components (alpha, beta, and gamma) toward low-frequency components (delta and theta) that are commonly seen in the resting-state EEG measurements of AD patients (Jeong, 2004). This shift is proportional to the progression of AD and is thought to appear due to the decrease of cholinergic tones. (2) Reduced complexity. A decrease in the complexity of the brain electrical activity has been observed in AD patients (Jeong, 2004). (3) Decrease in synchronization. Synchronization between brain regions in AD patients decreases (Babiloni et al., 2016; Wen et al., 2015). The synchronization was evaluated using the Pearson correlation coefficient, magnitude coherence, phase coherence, Granger causality, phase synchrony, global field synchrony, and cross-frequency coupling. (4) Long-range, effective EEG connectivity (functional coupling) decreases (e.g. front-parietal, front-temporal) (Babiloni et al., 2016). (5) The disruption of delta waves during slow wave sleep (Zott et al., 2018). These oscillopathic features were also reported with MEG and fMRI studies (Engels et al., 2017; Greicius, 2008). Amyloid-beta and tau protein pathologies are at least partially causal to these oscillopathic features of AD because amyloid-beta peptides and tau proteins affect excitatory and inhibitory synaptic transmissions and thereby memory functions in a concentration dependent manner (Gulisano et al., 2019; Roberson and Mucke, 2006). Amyloid-beta peptides are known to disrupt the excitatory/inhibitory balance by interfering with GABAergic interneurons as well (Mably and Colgin, 2018).

Furthermore, acute application of soluble amyloid-beta alone can acutely and reversibly disrupt synchronizing slow waves across the cortex, thalamus and HPC during non-rapid eye movement (REM) sleep-like anaesthetized mice (Zott et al., 2018). The reduction in gamma oscillations in AD animal models is commonly observed (Mably and Colgin, 2018). Inversely, the artificial induction of gamma oscillations in the brain decreases amyloid-beta depositions, prevents neuronal loss, and improves cognitive functions in AD animal models (Adaikkan et al., 2019; Iaccarino et al., 2016; Martorell et al., 2019). The introduction of high-frequency oscillatory activity into the brain via fornix DBS decreases amyloid-beta deposition in a rat AD model (Leplus et al., 2019) and improves cognitive functions in both AD animal models and patients (Mirzadeh et al., 2016).

2.4. Schizophrenia

Schizophrenia is a severe psychiatric illness characterized by positive symptoms including delusions, hallucinations, or paranoia, and negative symptoms including a loss of motivation, apathy, asocial behavior, loss of affect, and poor use and understanding of speech. Schizophrenia patients also have cognitive symptoms such as impaired working memory, dissociated thought processes, and impaired executive function (Sontheimer, 2015). Because of an absence of unequivocal biomarkers, schizophrenia is diagnosed entirely on the assessment of symptoms by a trained psychiatric doctor who bases his or her judgment on a number of features described in DSM-5 (American Psychiatric Association, 2013). Therefore, efforts have been made to find an appropriate biomarker using functional brain imaging techniques, EEG and MEG recordings etc. (Meyer-Lindenberg, 2010). For example, fMRI studies revealed that PFC activity was reduced in schizophrenia patients (Barch et al., 2001); the PFC governs executive function, task initiation, motivational drive, and working memory. Reduced activities have been reported on the amygdala (AMY) and the HPC (Meyer-Lindenberg, 2010), which could explain the flat affect of individuals of schizophrenia. Resting state networks have also been changed in schizophrenia patients (Alexander-Bloch et al., 2012; Cabral et al., 2012).

Gamma oscillations typically result from the fast, reciprocal interactions of excitatory glutamatergic neurons and inhibitory GABAergic neurons in the brain (Buzsáki and Wang, 2012). These oscillations are thought to support many cognitive functions including working memory in the PFC (Benchenane et al., 2011; Roux and Uhlhaas, 2014). Studies have found that gamma oscillations were disrupted in schizophrenia patients (Gonzalez-Burgos et al., 2015; Senkowski and Gallinat, 2015) and that this gamma disruption in the PFC presumably leads to disrupted intra-PFC and PFC-HPC communications (Moran and Hong, 2011). The decreased gamma oscillations are mediated by hypofunctional GABAergic networks in the PFC (Lewis et al., 2012). This finding is supported by evidence that the gene expression of 67-kD isoform of glutamic acid decarboxylase, the key enzyme in GABA synthesis, is reduced in the post-mortem brains of schizophrenia patients (Akbarian et al., 1995; Volk et al., 2000). It has been reported that repeated transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) restored gamma oscillations of schizophrenia patients and cognitive functions concomitantly (Farzan et al., 2012). This result suggests a possible causal relationship between the reduction in frontal gamma oscillation and cognitive deficit in schizophrenia (Pittman-Polletta et al., 2015).

2.5. Anxiety and trauma-related disorders

Generalized anxiety disorder (GAD) and post-traumatic stress disorders (PTSD) are characterized by chronic and exaggerated anxiety and fear (American Psychiatric Association, 2013). Conceptually, these disorders can be related to (1) the overgeneralization of perception, interpretation, and assessment of innocuous stimuli and (2) overexpression of anxiety and fear responses. The former is explained by the disruption of the PFC, pattern separation of the HPC, and intrinsic sensory hyperactivity in the primary sensory cortex. For example, resting EEG recordings from PTSD patients revealed that there was disrupted sensory processing with intrinsic sensory hyperactivity in the visual cortex (suppressed alpha power), decreased bottom-up alpha power-mediated inhibition to the frontal cortex, and increased frontal gamma band (30–50 Hz) power activated by the intrinsic sensation (Clancy et al., 2017). The latter can be explained by enhanced neural activity in the negative emotion networks. For example, Huang et al. (2014) found hyperactivities in the AMY, the HPC, and the insular cortex in resting MEG recordings of PTSD patients, which are supposed to positively correlate with their symptoms.

In addition, Qiao et al. (2017) found stronger functional connectivity with the AMY, insular cortex, putamen, thalamus, and posterior cingulate cortex (which are negative emotion circuits) in resting state fMRI recordings of GAD patients. In contrast, they found that weaker connections in the frontal and temporal cortices in GAD patients. Interestingly, they also found decreased effective connectivity (Granger causality) from the frontal cortexes to the AMY and basal ganglia (Qiao et al., 2017), which is the top-down inhibitory activity control of the subcortical networks. The MEG study also reported that the alpha (8–12 Hz) activity of PTSD patients decreased in the DLPFC and ventromedial PFC, and it also decreased the top-down alpha causality from these structures (Huang et al., 2014). Other resting state EEG studies support hypofunction of the frontal cortexes in GAD and PTSD patients (Crost et al., 2008; Eidelman-Rothman et al., 2016; Veltmeyer et al., 2006). Rodent studies have shown the role of the PFC in regulating the limbic system as a top-down control of fear expression and anxiety, which are mediated by theta or alpha range functional couplings (Dejean et al., 2016; Karalis et al., 2016; Likhtik et al., 2014). Therefore, on-demand modulation of the top-down control may be effective for supressing excessive anxiety and fear expression.

2.6. Major depressive disorder

Major depressive disorder (MDD) is a common and persistent psychiatric disorder characterized by extreme feelings of sadness and low mood disproportionate to any possible cause (American Psychiatric Association, 2013). MDD results in tremendous societal costs (Greenberg et al., 2003). Intracranial electrophysiological recordings from epilepsy patients indicate that mood can be decoded from multi-channel LFP recordings in the limbic system, including the orbitofrontal cortex, the cingulate cortex, the AMY, the HPC, the superior frontal cortex, and the middle frontal cortex (Reardon, 2017; Sani et al., 2018). Vulnerability to stress and susceptibility to depression have been decoded from multi-channel recordings in the limbic system in animal models of depression (Hultman et al., 2016, 2018). These models indicate the oscillopathic nature of depression.

The oscillopathic features of MDD are summarized as follows (Baskaran et al., 2012; Eidelman-Rothman et al., 2016; Fitzgerald and Watson, 2018): (1) elevated alpha band activity in the temporoparietal region; (2) elevated frontal theta band activity; (3) alpha frontal asymmetry (left hemispheric hypoactivity and right hemispheric hyperactivity represented as alpha, theta, and beta band activities); and (4) decreased gamma band activity. These features relate to MDD symptoms and predict the effectiveness of pharmacological treatment using tricyclic antidepressants and selective serotonin reuptake inhibitors and electroconvulsive therapy (ECT). This suggests their usefulness as a biomarker of depression disorder. In addition, fMRI studies suggest that the DMN, the cognitive control network, and the affective network were functionally hyperconnected in depression patients (Sheline et al., 2010). Functional decoupling of these networks by neuromodulation techniques may relieve depression symptoms (Fox et al., 2012; Liston et al., 2014).

Furthermore, there may be causal relationships between oscillation disturbances and depression symptoms. First, restoration of the frontal alpha symmetry using anodal transcranial direct current stimulation (tDCS) on the DLPFC (Loo et al., 2012) and specifically neurofeedback (Mennella et al., 2017) improved depression symptoms. In addition, subanaesthetic dose of ketamine (0.5 mg/kg) reduced delta oscillations (1–5 Hz) and increased gamma oscillations (45–85 Hz) in the human cortex and improved depressive mode of patients (Berman et al., 2000; Hong et al., 2010). Furthermore, high frequency rTMS on the left DLPFC increased resting state gamma oscillations in the frontal cortex and improved the depressed mood in patients (Noda et al., 2017). These pathological oscillations can be targeted using molecular (pharmacological), network (neuromodulation), and cognitive (behavioural) methods to interrogate depression symptoms (Leuchter et al., 2015).

2.7. Drug addiction

Drug addiction (also known as substance use disorder) is a chronically relapsing disorder characterized by persistent drug seeking and drug-taking behaviors despite significant negative physical, emotional, social and occupational consequences (Volkow and Morales, 2015). Drug addiction progresses from an impulsive to a compulsive intake in a collapsed cycle that consists of three stages: (1) preoccupation/anticipation, (2) binge/intoxication, and (3) withdrawal/negative affect (Koob and Volkow, 2010). At the beginning, the voluntary or impulsive intake induces euphoria during the binge/intoxication stage and positive reinforcement will drive the next intake. After establishment of maladaptation (addicted state), negative reinforcement caused by relief of anxiety, stress, and/or restlessness during abstinence will be a drive for further intake (Volkow et al., 2016). In the preoccupation/anticipation stage, patients have a craving, and obsession to get drugs.

In addicted brains, many neuroadaptations happen from epigenetic to neurocircuit levels. These neuroadaptations contribute to chronic, obsessive drug intake behaviors and impulsive decision-making in the preoccupation/anticipation stage. For example, the neural activity of the PFC is reduced (hypofrontality) in addicted patients (e.g. smokers) (Goldstein and Volkow, 2011; Zilverstand et al., 2018). This reduced activity would presumably be a cause of impulsive decision-making of addicted patients (Bechara, 2005) because the PFC governs analysis, prediction, and the executive control of reward seeking behaviors (Kennerley and Walton, 2011).

Abnormal frontal EEG measurements during the resting state are also observed in opioid users (Motlagh et al., 2017), alcohol abusers (Huang et al., 2018), tobacco smokers (Li et al., 2017), cannabis users (Prashad et al., 2018), and psychostimulant users (Newton et al., 2003), although their abnormalities are dependent on drug modalities (Newson and Thiagarajan, 2019). The oscillation abnormality in the frontal cortex is context dependent as well. For example, frontal asymmetry (left lateralization effects, less alpha oscillation in the left hemisphere) occurred in cocaine abusers in response to losing on their choice of immediate large rewards during the Iowa gambling task (Balconi et al., 2014). These disrupted frontal oscillatory activities are also represented by the reduction of the top-down inhibitory control called the executive control network (ECN), which for example controls the desire salience for drugs (Bechara, 2005). Together with the DMN and the salience network, the decreased ECN activity is a good predictor of the cravings of chronic tobacco smokers (Lerman et al., 2014; Sutherland et al., 2012). The restoration of the ECN by rTMS of the left DLPFC alleviated nicotine craving with significant EEG power changes (Pripfl et al., 2014).

Therefore, an obsessive drug taking habit driven by drug craving and impulsive decision-making during the preoccupation/anticipation stage may be treated with non-invasive or invasive stimulation (Dandekar et al., 2018; Diana et al., 2017), or cognitive interventions (Zilverstand et al., 2016) by modulating the oscillating networks where the PFC is central. Negative reinforcement during the withdrawal/negative affect stage (which can be mediated by delta and gamma band activities in the limbic system including the PFC and the nucleus accumbens (NAc) (Dejean et al., 2013, 2017)) may be intervened by DBS or non-invasive stimulation (Dandekar et al., 2018; Diana et al., 2017). Positive valence during the binge/intoxication stage (which is presumably mediated by delta-band activity in the NAc (Wu et al., 2018)) may be replaced by DBS of the NAc or the medial forebrain bundle (Dandekar et al., 2018). These facts indicate the oscillopathic features of drug addiction and the possible applications of oscillotherapeutics.

3. Mapping of oscillopathies

Appropriate animal models for each disease or disorder are required to facilitate development of oscillotherapeutics. Appropriate recording techniques for the oscillating neuronal activities of animal models and humans are indispensable, as are efficient analytical methods. Thus, here we provide an overview of how the pathological oscillations of neurological and psychiatric disorders are recorded and detected (the 'diagnostic' in research and clinics).

3.1. Animal models

3.1.1. Animal models for epilepsy

Animal models for epilepsy research are thoroughly summarized in the book of Pitkänen et al. (2017). Briefly, the epilepsy models are classified by seizure types (generalized or focal, petit mal or grand mal), animal species (mice, rats, cats etc.), whether *in vitro* or *in vivo*, whether genetic or acquired, whether acute or chronic, and how

each seizure is evoked (electrical, chemical, sensory inputs, spontaneous etc.).

Chronic spontaneous seizure models are typically employed for the development of time-targeted closed-loop interventions. Tottering (tg) and Stargazer (stg) mouse strains are available to study absence (petit mal) seizures with spike-and-wave discharges. These strains have known mutation on alpha and gamma subunits of voltage-dependent calcium channels, respectively (Upton and Stratton, 2003). Two inbred strains are for example available for rat experiments: the genetic absence epilepsy rats from Strasbourg (GAERS) and the Wistar Albino Glaxo strain (WAG/Rij) (Coenen and van Luijtelaar, 2003; Danober et al., 1998). The spike-and-wave discharges are seen in ordinal outbred laboratory rats and even in wild-caught rats as well (Taylor et al., 2019). Absence seizures can induced acutely by systemic administration of a single pharmacological compound [4,5,6,7 tetrahydroxyisoxazolo (4,5,c) pyridine 3-ol (THIP), low dose pentylenetetrazole (PTZ), or gamma-hydroxybutyrate] in rats (Fariello and Golden, 1987; Marescaux et al., 1984; Snead, 1988) and chronically by prepuberty systemic administration of AY-9944 or methylazoxymethanol acetate (MAM)-AY in rats (Cortez et al., 2002; Serbanescu et al., 2004).

The systemic injection of $GABA_A$ receptor antagonists (e.g. PTZ, bicuculline, picrotoxin) can induce acute generalized convulsion seizures in rodents (Mackenzie et al., 2002; Velisek et al., 1992; Velíšková et al., 1991). The systemic injection of glutamate receptor agonists (e.g. kainic acid and NMDA) or muscarinic receptor agonists (e.g. pilocarpine) can also induce acute, generalized, convulsive seizures in rodents (Ben-Ari et al., 1981; Mareš and Velišek, 1992; Turski et al., 1983). In addition, the inhalation of flurothyl can be used (Prichard et al., 1969), along with intracranial injections of bicuculline, picrotoxin, kainic acid and other drugs to induce acute convulsive seizures in rodents (Ben-Ari et al., 1980; Sierra-Paredes and Sierra-Marcuño, 1996; Velíšková et al., 1991). A chronic spontaneous, limbic seizure rodent model can be prepared by the repeated systemic injection of PTZ, kainic acid, or pilocarpine (Cain, 1981; Cavalheiro et al., 1991; Hellier et al., 1998), a single intrahippocampal injection of kainic acid (Bragin et al., 1999), or repeated daily electrical stimulation of the limbic structure (e.g. the AMY, HPC) (Goddard et al., 1969; McIntyre and Gilby, 2009). Genetic models for spontaneous convulsive seizures are available both in mouse and rat strains (e.g. weaver mice, NER/Kyo rats) (Serikawa et al., 2015; Upton and Stratton, 2003). Auditory stimulation can induce-convulsive seizures in the generically epilepsy-prone rats (GEPRs) and DBA/2 mice (De Sarro et al., 2017).

3.1.2. Animal models for Parkinson's disease

Animal models of PD are classified into neurotoxin models and genetic models (Gubellini and Kachidian, 2015). 6-OHDA (6-hydroxydopamine) and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) are typically used to mimic selective loss of nigrostriatal dopaminergic neurons via mechanism by which mitochondrial complex I is blocked (Tieu, 2011). Both neurotoxins are used in rodent and non-human primate experiments.

Systemically administered MPTP can easily cross the blood brain barrier whereas 6-OHDA should be stereotaxically injected into the target brain structure (usually the substantia nigra pars compacta (SNc), the medial forebrain bundle, or the striatum). 6-OHDA and MPTP administrations lead to significant PD-like motor symptoms including akinesia, freezing, bradykinesia, muscle rigidity, abnormal posture, stereotypy and tremor associated with significant degenerative loss of SNc dopaminergic neurons (Smeyne and Jackson-Lewis, 2005). Neither 6-OHDA nor MPTP administration induces Lewy body-like inclusions with alpha-synuclein (Cenci et al., 2002). Importantly, both the 6-OHDA rodent model and the MPTP-treated monkeys exhibit pathological oscillations in their basal ganglia as frequently observed in human patients: tremor (4–7 Hz), double tremor (10 Hz), and beta (15–30 Hz) (Deffains and Bergman, 2019; Heimer et al., 2006). Mutations of causal genes or genetic risk factors of Parkinson's disease are modelled in mice and rats including *SNCA* (alpha-synuclein), *PRKN* (parkin), *PINK1* (PTEN-induced putative kinase 1), *DJ-1* (PARK7) and *LRRK2* (leucine-rich repeat kinase 2). These models offer ways to study pathology as Lewy-body like inclusions, but they exhibit only mild motor symptoms. Pathological oscillations in the basal ganglia in these genetic models have not been studied well yet.

3.1.3. Animal models for Alzheimer's disease

Most AD patients are sporadic and there are some animal models for sporadic AD using metabolic and traumatic brain injury-induce damage etc. (Zhang et al., 2019). However, the vast majority of current AD animal models are transgenic rodents (mainly mice) and are based on the amyloid and tau hypotheses, and the genetics of the familial form of the disease (Mullane and Williams, 2019). Nearly 170 transgenic/knock-in/knock-out models of AD have been developed to date (ALZ FORUM Research Models Database; https://www.alzforum.org/research-models). They are principally focused on mutations in *APP* (Amyloid precursor protein), *PSEN1* (presenilin 1), *MAPT* (microtubule-associated protein tau), and *Trem2* (Triggering receptor expressed on myeloid cells 2), and *APOE* (apolipoprotein E), as well as the transfection of the amyloid processing enzyme, *BACE1* (Beta-Secretase 1) (Götz et al., 2018; Mullane and Williams, 2019). The model animals have single or multiple mutations of these genes. For example, 3×Tg mice, which have APP KM670671NL (Swedish), MARPT P301 L, and PSEN1 M146 V triple mutations, show amyloid beta plaque, hyperphosphorylated tau, and neurofibrillary tangle as pathological phenotypes and deficits in working, spatial, and fear conditioning memory (Oddo et al., 2003). 5 × FAD mice have three mutations on *APP* (Swedish, Florida, London) and two mutations on *PSEN1*, and they show amyloid-beta plaque and memory deficits as soon as two months old (Oakley et al., 2006). In the tau pathology model, rTg4510 mice with MAPT P301 L mutation have neurofibrillary tangle, neuronal loss and memory deficits as phenotypes (Santacruz et al., 2005). The overexpression of mutant human APOE4 protein (a risk factor of AD) in APOE4-KI mice results in significant memory impairment as well (Sullivan et al., 2004).

Importantly, all these AD models (3×Tg, 5 × FAD, rTg4510, APOE4-KI) consistently show a reduction of slow gamma oscillation in the CA1 of HPC (Booth et al., 2016; Gillespie et al., 2016; Iaccarino et al., 2016; Mably et al., 2017), which contributes to the encoding and retrieval of memory. CA1 place cell representations of space were unstable in these mice and the deficits in slow oscillations in the HPC were concomitant with spatial memory. Surprisingly, the optogenetic activation of parvalbumine (PV)-interneurons at slow gamma frequencies (or 40 Hz light flicker sensory stimulation) reduced amyloid-beta depositions in the brain and restored cognitive impairment of the AD mice model (Iaccarino et al., 2016; Martorell et al., 2019).

In the APP23 × PS45 mouse model (Busche et al., 2008), the coherence of slow waves between different cortical regions, the thalamus, and the HPC is completely disrupted in the light anesthesia condition (Zott et al., 2018). This resembles disrupted, slow-wave oscillations during natural non-REM sleep in AD patients (Winer et al., 2019). The coherent slow wave oscillations were transiently disrupted in wild-type mice by the application of soluble amyloid-beta, which suggests a causal relationship between amyloid-beta and the pathological oscillation pattern in AD (Busche et al., 2015).

3.1.4. Animal models for schizophrenia

Animal models of schizophrenia mostly fit into one of four different induction categories: developmental, drug-induced, lesion or genetic manipulation models (Jones et al., 2011). Examples of neurodevelopmental models include gestational MAM injections, bacterial or viral infections, and post-weaning social isolation; pharmacological models include amphetamine-induced psychosis, NMDA antagonist [phencyclidine (PCP), MK-801, ketamine)]-induced psychosis; lesion models include neonatal ventral HPC lesion; genetic models include various knock-out or mutant models of schizophrenia susceptibility genes, some of which were validated by genome-wide association studies (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

These models resemble various cognitive symptoms found in schizophrenia patients including deficits of sensorimotor gating, working memory, visio-spatial memory, and object recognition, as well as decreased social interaction, increased locomotion, and exaggerated sensation etc. The models also show cellular or circuit level alterations including decreased synaptic connections, and spine densities, the loss of prefrontal PV-positive interneurons, the loss of dendrites in cortical pyramidal neurons, and pathological oscillations (e.g. dysfunctional prefrontal gamma oscillations). The pathological oscillations tie the cellular or circuit level pathophysiology to alterations in local processing and large-scale coordination, and in turn may lead to cognitive and perceptual disturbances observed in schizophrenia (Pittman-Polletta et al., 2015; Senkowski and Gallinat, 2015).

A number of schizophrenia-susceptibility genes have been identified on chromosome 22. These include *DISC1* (disrupted-in-schizophrenia 1), *NRG1* (neuregulin 1) and its receptor *ERBB4* (erb-b2 receptor tyrosine kinase 4, erbB-4), and *COMT* (catechol-*O*-methyltransferase). DISC1 is a synaptic protein that plays a crucial role in synaptogenesis (Bennett AO, 2008). Mutations or the functional disturbance of DISC1 lead to the disruption of PV-positive interneuron cytoarchitecture and hypofunction in the cortex and HPC, which is critical for normal oscillatory activity in the brain (Koyama et al., 2013; Nakai et al., 2014). *NRG1* and *ERBB4* are also synaptogenic schizophrenia susceptible genes (Mei and Xiong, 2008). Their disruption resulted in abnormal gamma oscillations in the HPC and disrupted functional coupling between the ventral HPC and NAc (Koyama et al., 2013; Nason et al., 2011). Reduced dysbindin-1 (another synaptic protein from susceptible gene *DTNBP1* (Dickman and Davis, 2009)) is associated with reduced phasic activation of PV-positive interneurons and reduced gamma oscillations (Carlson et al., 2011).

One of the largest risk factors for schizophrenia is the microdeletion of chromosome 22q11.2 that wipes out up to 60 genes; the 22q11.2 deletion syndrome results in facial abnormalities, heart defects, and a number of neuropsychiatric conditions (Jonas et al., 2014). A quarter of the patients that have the microdeletion of this chromosome develop schizophrenia. Importantly, in the *Df(16)A*$^{+/-}$ mouse model of this micro delision, mice exhibited reduced PFC-HPC synchrony, represented by reduced phase-locking of PFC neurons to HPC theta oscillation and disrupted coherence across multiple frequency ranges (delta to gamma ranges) (Sigurdsson et al., 2010).

As pharmacological models, NMDA receptor blockers such as ketamine and PCP are known to induce delusions and hallucinations in otherwise healthy subjects (Krystal et al., 1994). Ketamine is known to attenuate both background and sensory evoked theta power in the CA3 in mice. It enhances both background and evoked gamma power, but it decreases relative-induced gamma power (Lazarewicz et al., 2010). This suggests that ketamine decreases the signal-to-noise ratio of gamma-band activity and possibly leads to disrupted pattern separation function in the CA3 region, contributing its dissociative feeling. Ketamine reduces NMDA receptor function preferentially on PV-positive interneurons, which impairs HPC synchrony, spatial representations, and working memory in mice (Korotkova et al., 2010). The NMDA hypofunction also reduces delta and theta activity in the cortex and HPC (Kiss et al., 2013). Ketamine also disrupts the theta modulation of gamma-band activity and reduces network responsibility to the environment in a computer model of HPC (Neymotin et al., 2011).

As a gene-environment interaction model, WISKET rats were reported as a selectively bred line with schizophrenia-like phenotypes (reduced sensorimotor gating, hyperalgesia, and memory deficit) after post-weaning social isolation and chronic ketamine treatment over 15 generations (Büki et al., 2018). The WISKET rats showed increased theta, alpha, and beta-band activities and reduced gamma-band activities in ECoG recordings (Horvath et al., 2016).

3.1.5. Animal models for anxiety and trauma-related disorders

Animal models for anxiety and trauma-related disorders are classified into five models: experience-based, pharmacologic, pharmacological lesion, selectively bred genetic, and specific transgenic (Hoffman, 2016). Examples of experience-based models include fear conditioning and extinction, pre-weaning stress, and maternal deprivation. Pharmacologic models include yohimbine (alpha-2 adrenergic receptor antagonist), CCK tetrapeptide (CCK-4, an anxiogenic neuropeptide), caffeine (adenosine receptor antagonist), *m*-chlorophenylpiperazine (serotonin 5-HT_{2C} receptor antagonist), and FG7142 (benzodiazepine partial inverse antagonist). Pharmacological lesion models include the chronic infusion of L-allylglycine (an inhibitor of glutamic acid decarboxylase) into the dorsomedial/perifornical region of the hypothalamus (DMH/PeF) in rats (Johnson and Shekhar, 2012). Selectively bred genetic models include Roman High and Low Avoidance rats (Escorihuela et al., 1999), Sardinian alcohol-preferring rats (Colombo et al., 1995), High anxiety behavior and Low anxiety behavior rats (Yilmazer-Hanke et al., 2004), Floripa H and L rats (Ramos et al., 2003), Ultrasonic rats (Brunelli and Hofer, 2007), and High anxiety behavior mice (Erhardt et al., 2011). Specific transgenic models include 5-HT transporter knockout mice, brain-derived neurotrophic factor (BDNF) Val66Met mice, COMT and monoamine oxidase A deficient mice, 5-HT_{1A} knockout mice, corticotropin-releasing hormone overexpression mice, and neuropeptide Y-knockout mice.

Their endophenotypes can be measured as startle reactivity, behavioral inhibition (via the open field and elevated plus mazes, as well as the light/dark, social interaction, and punished conflict tests), carbon dioxide sensitivity (avoidance of a CO_2-enriched environment, exploratory behavior after exposure to CO_2-enriched air, tidal respiratory volume during exposure to CO_2-enriched air), and fear over-generalization (discrimination of CS+ and CS− stimuli after fear conditioning). Recent studies have revealed that distinct oscillatory activities in specific PFC-AMY-HPC networks are related to both fear/anxiety expression and its regulations (Çalışkan and Stork, 2019; Dejean et al., 2016; Karalis et al., 2016; Likhtik et al., 2014).

3.1.6. Animal models for depressive disorders

Animal models for depressive disorders are classified into five models: experience-based, pharmacologic, lesion, genetic, and gene-environment interaction (Hoffman, 2016). Experience-based models include learned helplessness, chronic adult stress (e.g. overnight illumination, water or food restriction, tilting cages, social isolation or crowding etc.), early life stress (e.g. maternal separation), and social stress (e.g. chronic social defeat). Pharmacological models include withdrawal from psychostimulant use. Lesion models include bilateral olfactory bulbectomy. Genetic models include selectively bred lines (e.g. the Rousen depressed mouse line, Flinders Sensitive Line rats, Wister Kyoto rats, Fawn Hooded rats, SwLo/SwHi rats, cLH rat lines) (El Yacoubi et al., 2003; Henn and Vollmayr, 2005; Overstreet and Wegener, 2013; Rezvani et al., 2007; Will et al., 2003), and specific trans-

genic lines (e.g. 5-HT transporter knock-out rats and mice, BDNF promoter IV-mutant mice, BDNF Met mice) (Chen et al., 2006; Sakata et al., 2010; Wisor et al., 2003). Their cognitive/behavioral phenotypes such as anhedonia can be measured using the sucrose preference test, conditional place preference, intracranial self-stimulation, variable progressive ratio reinforcement, and response bias probabilistic reword task; they can be measures as negative processing bias using increased reactivity to aversive stimuli, probabilistic reversal learning, and reactivity to emotionally ambiguous cues. Some physiological endophenotypes (e.g. sleep pattern changes) are recapitulated as well in these rodent models.

Recently, stress vulnerability and depression susceptibility were successfully decoded from large-scale electrophysiological recordings as distinct oscillation patterns in freely moving mice (Hultman et al., 2018). The specific oscillation patterns for the vulnerability and susceptibility are consistent with the results of pharmacological (interferon administration) and early life stress (maternal separation).

3.1.7. Animal models for drug addiction

Animal models for drug addiction can be classified into models for the three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect stages (Koob and Volkow, 2010).

Animal models for the preoccupation/anticipation stage fit into two categories: extinction-based and abstinence-based relapse models (Venniro et al., 2016). Extinction-based relapse models include drug-, cue-, context-, stress-, and withdrawal state-induced relapses (Alleweireldt et al., 2001; Shaham et al., 2003), reacquisition (Bouton et al., 2012), and resurgence (Winterbauer and Bouton, 2011). Abstinence-based relapse models include forced abstinence and drug craving incubation (Fuchs et al., 2006), adverse consequences-imposed abstinence (Cooper et al., 2007), and voluntary abstinence induced by introducing non-drug rewards (Caprioli et al., 2015). In addition, risky and gambling choice tasks and those with reward/aversion conflicts can be used to study the pathological oscillations underlying inappropriate, impulsive and executive decision making in addicted states (Passecker et al., 2019; Verharen et al., 2018).

Animal models of the binge/intoxication stage consist of intravenous and oral drug self-administration (Ahmed and Koob, 1998), intracranial self-stimulation (Markou and Koob, 1992), conditional place preference (Sanchis-Segura and Spanagel, 2006), drug discrimination (Stolerman et al., 2011), and genetic models of high addiction susceptibility (Quintanilla et al., 2006). In addition, the drug taking in the presence of aversive consequences model can be used to find pathological oscillations governing compulsive drug taking behavior (Vendruscolo et al., 2012).

Animal models of the withdrawal/negative affect stage include intracranial self-stimulation (reward decreases), conditional place aversion (Hand et al., 1988), measures of anxiety-like responses (e.g. the open field and elevated plus mazes), and drug self-administration with extended access or in dependent animals (Ahmed et al., 2000).

3.2. Neural activity recordings

3.2.1. For animal research

Large-scale brain dynamics recordings as LFPs are very powerful for investigating oscillatory activities across multiple brain regions (Hong and Lieber, 2019; Pesaran et al., 2018). Beyond single site recordings, multi-site recordings with silicon probes have allowed the geometry of oscillatory activities in the brain to be studied (Wise and Najafi, 1991). Linear 16–32 ch recording probes have been used to map layer specific oscillations for example in the cortex (Minlebaev et al., 2011). Recent CMOS-based probes (Neuropixel) enable up to 960 ch high-density recordings on a single shank (Jun et al., 2017). Multi-shank linear silicon probes (e.g. buz256) can capture two-dimensional spatiotemporal structure of oscillations in a brain region (Agarwal et al., 2014; Berényi et al., 2014). For example, Oliva et al. found that sharp-wave ripple in the CA2 subregion precedes those in the CA1 and CA3 subregions in the rat HPC (Oliva et al., 2016).

The insertion of multiple silicon probes and/or wire electrodes into distinct brain regions allowed oscillatory interactions between brain regions to be explored during spatial navigation (Fernández-Ruiz et al., 2017), goal-directed behaviors (Fujisawa and Buzsáki, 2011), epileptic seizures (Berényi et al., 2012), anxiogenic conditions (Girardeau et al., 2017), depression (Hultman et al., 2018), and drug addiction (Sjulson et al., 2018). Matrix silicon probes can be used to obtain high-density three-dimensional oscillation activities in the brain (Rios et al., 2016), and flexible mesh electronics used instead of rigid electrodes enable year-long stable recordings (Hong et al., 2018). Two-dimensional electrodes on flexible polymer sheets enable potential recordings from the cortical surface (Khodagholy et al., 2015). Simultaneous recording of brain and other physiological oscillations (e.g. electrocardiogram, electromyogram, and breathing) from freely-moving animals is an important technique to study pathophysiological representations of neuropsychiatric disorders (Sasaki et al., 2017).

3.2.2. For clinical practice

The international 10–20 or 10–10 EEG recording systems are widely used for standard diagnosis or study of a variety of neuropsychiatric disorders, including epilepsy (Nuwer et al., 1998). One of the advantages of EEG recordings is its time resolution. This enables fast oscillatory activities to be analyzed (typically 0.3–300 Hz). MEG recordings have an even higher time resolution (in milliseconds). The frequency spectrum density in each recording site and the relationships between the recording sites (coherency, connectivity, causality etc.) are typically analyzed. High-density EEG recordings (64–256 ch) increase spatial resolution and allow source imaging with even sub-lobar precision (Seeck et al., 2017). This enables better spatial resolution for seizure focus prediction with tomography. fMRI recordings give higher spatial resolution (in millimeters) but lower time resolution (in seconds) compared to EEG recordings; they primarily utilize the blood-oxygen-level dependent contrast, which is complementary to EEG recordings. fMRI recordings can be used to investigate very slow oscillatory activities within and between brain regions. Invasive electrophysiological recordings on or in the brain are required to find the seizure focus much more precisely or the optimal location of DBS electrodes in the basal ganglia of PD patients.

3.3. Machine learning-mediated approaches for analysis

It is challenging to find disease or disorder-specific oscillation patterns in large-scale neuronal activity data. For example, unsupervised learning techniques have been used to find significant coherent resting-state fluctuations and functional connectivity of resting-state fMRI data (Khosla et al., 2019). Unsupervised methods like independent component analysis (ICA) and principal component analysis (PCA) decomposition are also used to find latent variable models in fMRI data. Deep learning methods such as convolutional neural networks and feed-forward neural networks were used to successfully discriminate the fMRI data of AD and schizophrenia patients from those of healthy control patients with 96.85 % and 85.8 % accuracy, respectively (Wen et al., 2018). These machine learning methods can also be applied for electrophysiological data to find disease-specific oscillation patterns in EEG or intracranial LFP data from humans and experimental animals (Reardon, 2017). However, if the disease-specific oscillation model is extracted by PCA, the model is so abstract that it cannot be interpreted well enough to develop an intervention based on the analysis.

Recently, Gallagher and others successfully developed a new modeling algorithm for multi-region LFP recordings (cross-spectral fac-

tor analysis, CSFA). This algorithm breaks the observed signal into factors defined by unique spatiotemporal spectral properties (a power or cross-spectral densities) (Gallagher et al., 2017). The critical thing is that the factors are interpretable. Combined with a supervised-learning algorithm, CSFA has revealed symptom specific oscillation patterns in depression (Hultman et al., 2018).

4. Oscillopathy – the realistic view of pathological oscillatory states and a strategy for oscillotherapeutics

Here we describe the pathophysiology of oscillopathies with an emphasis on epilepsy as a system of multistable dynamic oscillatory states. We also provide a conceptual overview on how to intervene with pathological oscillations focusing on the control of epilepsy and epileptic seizures in a time-targeted closed-loop manner.

4.1. Bistable or multistable circuit states

4.1.1. Modelling concept and example of seizure model

Epilepsy is a network disorder which can be characterized by bistable or multistable oscillatory states (e.g. interictal and ictal states) and the transitions between them (Kalitzin et al., 2019). Circuit-state dynamics are determined by the stability of each state and probability of transition between stable oscillatory states, which are supposed to be affected by the following factors: (1) network resonance, (2) resilience, (3) perturbation, sensory inputs (e.g. a well-timed pulse input), (4) neuromodulatory inputs, and (5) time spent in the state (Chang et al., 2018).

Stable oscillatory states include at least normal (interictal) and hypersynchronous ictal states. This concept has been validated in *in vivo* animal and human recordings and *in silico* modelling studies. For example, theta frequency MS stimulation stabilized oscillatory activity in the septo-hippocampal axis and decreased seizure susceptibility whereas over 20 Hz MS stimulation induced transition from normal to ictal oscillatory state in rats (Fisher, 2015; Miller et al., 1994). Modelling studies have successfully established realistic behaviors of epileptic networks, which resemble network states including, normal states, pre-ictal recruitment, epileptic seizures, and post-ictal suppression (Bauer et al., 2017; Jirsa et al., 2014). The seizure models can recapitulate oscillatory state transitions including the onset, evolution, and termination of epileptic seizures. They help to explain mechanisms underlying the state transitions and they may enable upcoming seizures to be predicted. They may also enable secondary generalization and possibly sudden unexpected death in epilepsy to be explained (Kuhlmann et al., 2018). Modeling studies have also explained the pathological oscillations of PD (Pavlides et al., 2015; Shouno et al., 2017).

4.1.2. Generation of hypothesis and quantification of circuit states

Modelling studies are not merely explanatory tools but also an instrument to generate a hypothesis. They can also provide readouts of otherwise complex state indicators (Kalitzin et al., 2019). For example, CSFA (Gallagher et al., 2017), machine learning-assisted modelling of multi-site oscillatory networks, has revealed previously unknown pathological oscillations for depression (Hultman et al., 2018). In a multistate model study, the seizure susceptibility of an instantaneous network state can be readout as a' separatrix proximity' for the closeness to ictal transition (Petkov et al., 2018). This is measure of instantaneous distance between the current network state and the threshold for the ictal (hypersynchronous state). Using this possible biomarker of seizure susceptibility, epilepsy is considered as a state where the average network oscillatory state is close to the ictal threshold. Physicians or researchers can estimate the effectiveness of treatments or new intervention technique with this biomarker. This strategy is quite effective for predicting upcoming seizures, and for developing a new therapeutic technology in a very time-efficient manner. Seizure susceptibility is not currently titrated directly but estimated by seizure occurrence frequency, which is time consuming and has high uncertainty due to sparseness. CSFA can be used instead to instantly quantify it once the pathological pattern has been modelled; instantaneous amount of a disease-specific oscillation pattern is quantified as a spectral factor score (Gallagher et al., 2017; Hultman et al., 2018).

Given the hypothesis and the quantitative measure of pathological oscillatory network states, the following oscillotherapeutic strategies would be effective to control epileptic seizures: (1) introducing oscillatory activity which resonates with and stabilizes non-seizure states (e.g. theta oscillation in the HPC), (2) reducing the normal to ictal transition rate by reducing seizure susceptibility, especially during a seizure prediction period, (3) inducing immediate transition from ictal to normal states by introducing a huge oscillatory disturbance on ictal hypersynchronous oscillations, (4) intervening to prevent or any intermittent pathological oscillations which would induce maladaptation in neural networks. These strategies could be effective for intervening in other oscillopathies with fast oscillatory state transitions, including PD and possibly for the psychotic attack of schizophrenia, for impulsive and addicted drug intake, and for an attack of PTSD.

For other oscillopathies with much slower underlying state transitions (e.g. GAD, depression, addiction craving, and AD), long-lasting plastic changes in oscillating network dynamics would be required to be induced by external oscillatory interventions. For example, on-demand deletion and the continuous introduction of oscillations for negative and positive feelings might improve depression symptoms.

4.2. Stimulation strategies

Pathological oscillations are intervened in an open- or closed-loop manner in terms of how the stimulation is temporally delivered. Intrinsic structure of the neuronal networks can be utilized to maximize the effect of stimulation.

4.2.1. Open-loop interventions

Open-loop intervention in the oscillotherapeutic context means introduction of external stimulation without the feedback of internal oscillatory activity (Fig. 2**A**). The external stimuli can be a sinusoidal waveform or pulse trains. The open-loop intervention can be non-invasive (e.g. transcranial electrical stimulation: TES) or invasive (e.g. DBS). The open-loop stimulation with a sinusoidal stimulus waveform can interact with ongoing intrinsic network activities if appropriate stimulus intensity is provided (Fig. 2**B**). For example, transcranially applied alternating electrical stimulation can modify and entrain the membrane potentials of cortical neurons in rats (Ozen et al., 2010). Furthermore, intense TES at 1 Hz sinusoidal wave can phase-specifically enhance alpha-band activity in the parietal cortex of healthy human subjects (Vöröslakos et al., 2018). If properly applied, these resonance approaches can modulate the cognitive functions of humans (e.g. enhancement of memory) (Hanslmayr et al., 2019; Reinhart and Nguyen, 2019). The continuous application of high-frequency pulse trains to the STN and the anterior nucleus of the thalamus (conventional DBS) successfully improved symptoms of PD and drug-resistant epilepsy, respectively (Deuschl et al., 2006; Li and Cook, 2018). However, open-loop interventions are less flexible in terms of temporal structure compared with closed-loop interventions, which are discussed below.

4.2.2. Closed-loop interventions

Closed-loop interventions for oscillotherapeutics are brain stimulations based on intrinsic physiological signal feedback (e.g. LFP, EEG) (Fig. 2**A**). The feedback information allows the stimulation to be time-targeted and on-demand stimulation. It also avoids overstimulation and prevents unwanted out-of-phase interactions.

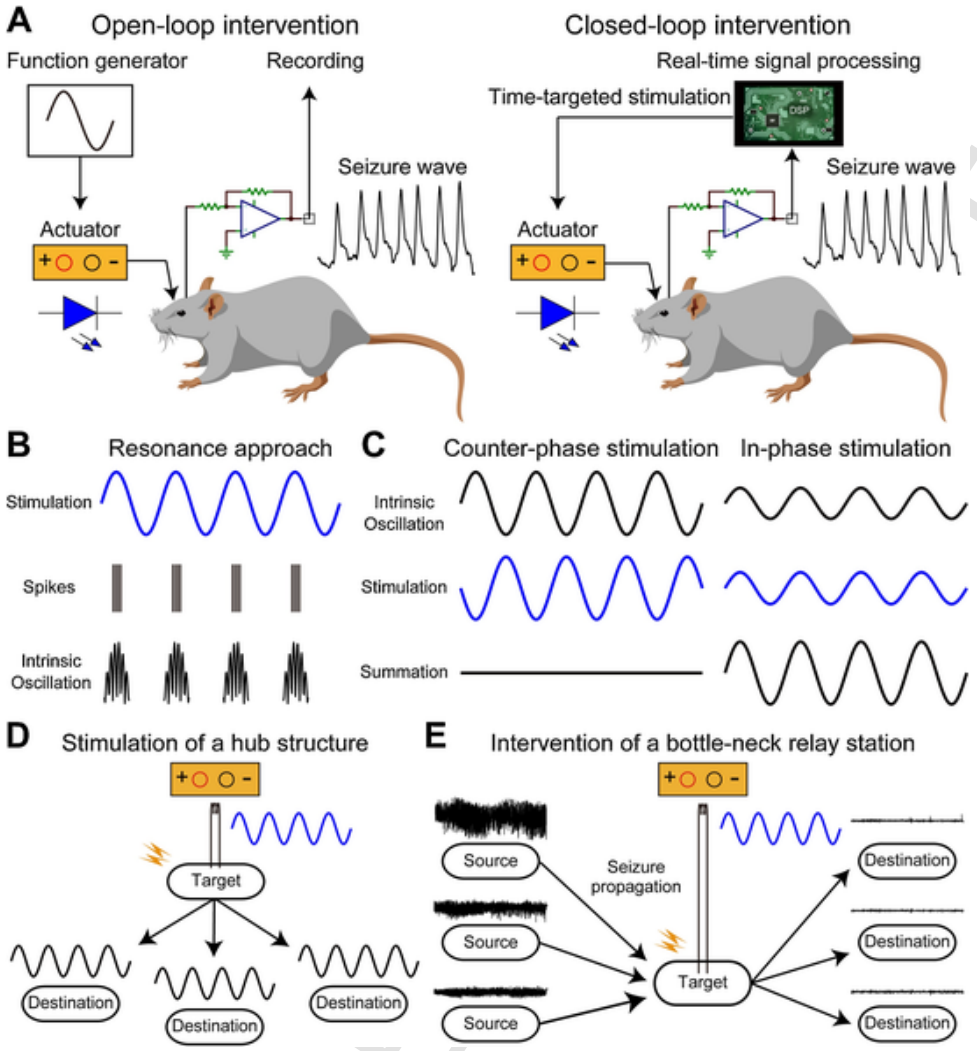

Fig. 2. Brain stimulation techniques for intervening with pathological oscillations.(**A**) Schemas of open-loop and closed-loop interventions with epileptic seizures (pathological oscillation). Open-loop intervention provides pre-determined stimulus waveforms without processing recorded brain activities (e.g. EEG). Recorded brain activities for closed-loop intervention are processed in rea-time, and the parameters of stimulus waveforms (timing, intensity, frequency etc.) are determined online. (**B**) A schematic showing of sinusoidal stimulation in an open-loop manner and the typical responses of neural firing and intrinsic oscillations. Neural firings (spikes) and intrinsic oscillations are entrained to the externally applied stimulus frequency (resonance approach). (**C**) Conceptual examples of closed-loop interventions for the destruction and restoration of intrinsic oscillations. Counter-phase stimulation (e.g. electrical stimulation) provides the opposite effect of intrinsic oscillation to destroy an arbitrary oscillation. In contrast, in-phase stimulation can restore decreased oscillation by enhancing the summation of intrinsic oscillation. (**D**) A stimulation strategy for providing a widespread oscillatory effect externally by stimulating a target brain structure that provides diffuse axonal projections with fast synaptic transmissions (e.g. the medial septum). (*E*) A stimulation strategy for intervening with a huge internal oscillation (e.g. epileptic seizures). Stimulation of a bottleneck structure (choke point) of the internal oscillation can effectively intervene with it (e.g. the entorhinal cortex).

Closed-loop stimulation can reduce the side effects of excessive and unnecessary stimulus delivery. Chronic stimulation in a non-responsive, open-loop manner may be unnecessarily excessive. Unnecessary stimulation can introduce adverse effects by disturbing physiological oscillations in the brain both by spatial on and off target effects. For example, chronic stimulation of the HPC may disrupt normal physiological oscillation and thereby cognitive functions including learning and memory. Continuous strong electrical stimulation on the scalp can introduce pain sensations via peripheral nerve stimulation. In addition, chronic electrical stimulation of the limbic structures (including the HPC and AMY) could induce pro-seizure effects called kindling (McIntyre and Gilby, 2009). Importantly, an excessive continuous stimulus could induce accelerated habituation or rebound symptoms in patients (Pilitsis et al., 2008; Shih et al., 2013). Patients instructed to turn on DBS in an on-demand manner for essential tremor had longer effects than open-loop continuous stimulation (Kronenbuerger et al., 2006).

Closed-loop stimulation could introduce much higher therapeutic effects for neurological and psychiatric disorders. The first closed-loop configuration is 'closed-loop responsive' stimulation, in which pre-determined stimulus pulses are delivered only when the stimulus is necessary (on-demand stimulation). In this configuration, physiological signals are continuously monitored to automatically trigger stimulation in an on-demand manner. For on-demand control of epileptic seizures, we have revealed that transcranial applied electrical stimulation triggered by electrographically monitored seizures can effectively shorten the duration of petit mal seizures in rats (Berényi et al., 2012). The closed-loop seizure suppression remained effective at least for months (Kozák and Berényi, 2017). Responsive neurostimulation (the RNS system) is approved for human application by the U.S. Food and Drug Administration (FDA) as an adjunctive therapy for medically intractable partial seizure patients (Morrell, 2011). Seizure or seizure-predicting neuronal activity is monitored via depth and/or subdural strip leads

and electrical stimulation is delivered through these leads in an on-demand manner in the RNS system. For example, HPC and cortical activities are monitored and intervened via the depth and strip leads, respectively. Closed-loop responsive stimulation can be controlled by behavioural oscillations as well. Koganemaru and others have reported that walking rhythm triggered TES of the primary motor cortex in stroke patients could improve their gain disturbance (Koganemaru et al., 2019).

The second closed-loop configuration for brain stimulation is 'closed-loop adaptive' stimulation, in which input physiological variables gate output variables for stimulation. For example, the power of beta oscillation in STN LFP determines the intensity of DBS on the STN for PD patients (Bouthour et al., 2019). The relationship between input and output variables is fixed or programable. Adaptive closed-loop brain stimulation has been suggested for controlling neurological and psychiatric disorders (epilepsy, movement disorders, AD, depression, and obsessive-compulsive disorders) (Hoang et al., 2017; Provenza et al., 2019).

The third important nature of closed-loop stimulation is 'phase-targeting' stimulation. Theoretically, phase-targeting electrical stimulation is very effective in the destruction of pathological oscillations and in the restoration of reduced physiological oscillations (Fig. 2**C**). Counter-phase stimulation destructs pathological oscillations and in-phase stimulation restores reduced physiological oscillations. Practically, precisely-timed phase-targeting stimulus delivery over ongoing pathological oscillations has been proved to be essential for the closed-loop intervention of epilepsy and PD (Berényi et al., 2012; Holt et al., 2019). In addition, HPC LFP phase-specific fornical stimulation has been proposed to improve the cognitive functions of AD patients (Senova et al., 2018). This is because temporal organization of theta and gamma oscillations in the HPC are thought to be important in memory encoding and retrieval (Colgin, 2016). Dejean and others have shown that the phase-specific optogenetic excitation of PV-positive interneurons in the PFC over frontal 4 Hz oscillation bidirectionally controls fear behavior of auditory cue conditioned mice (Dejean et al., 2016).

4.2.3. How to effectively introduce or disturb oscillatory activities

Introducing or disturbing oscillatory brain activities in an effective way is essential for oscillotherapeutics. Utilizing intrinsic circuit structures in the brain is an important factor for effective interventions. Stimulation of a hub-like structure is effective upon introducing widespread oscillatory activity into the brain (Fig. 2**D**). If the target brain region has diverging projections to several destination brain regions, oscillatory activity applied to the target region can spread to the destination brain regions via axonal projection and synaptic transmissions. The applied stimulation frequency should be within the frequency properties of the neuronal circuits. For example, the MS is in the midline of the basal forebrain and projects to the bilateral HPC in a diverging way. This pathway is mainly mediated by fast GABAergic synaptic transmissions (Dutar et al., 1995). The MS and HPC are highly coherent in both physiological and pathophysiological conditions. The electrical or optogenetical stimulation of the MS is transmitted to the bilateral HPC at exactly the same frequency that is applied within the delta to gamma-band range (Sinel'nikova et al., 2009; Zutshi et al., 2018). For human application, the thalamic stimulation for refractory epilepsy, the fornical stimulation for AD, and the medial forebrain bundle stimulation for depression all utilize this principle for DBS (Dandekar et al., 2018; Li and Cook, 2018; Mirzadeh et al., 2016). In addition, both TES and transcranial magnetic stimulation (TMS) of the PFC for treatment of depression and drug addiction also utilize this principle, because the PFC has widespread synaptic connections to the limbic brain structures (Ferenczi et al., 2016; Loo et al., 2012; Noda et al., 2017).

The intervention of a bottle-neck relay station in the brain is effective for intervening with the propagation of huge oscillatory activity like epileptic seizures. For example, partial seizures in the HPC occasionally secondary generalize, which may be a cause of sudden unexpected death in epilepsy (SUDEP) (Bone et al., 2012; Massey et al., 2014). The subiculum and the entorhinal cortex are bottleneck structures (choke points) from the HPC to the neocortex. Interventions on these structures can effectively suppress the secondary generalization of HPC-origin seizures (Lu et al., 2016; Wang et al., 2017). The thalamus and the STN are choke points in post-stroke epilepsy and absence epilepsy, respectively (Paz and Huguenard, 2015).

5. Oscillotherapeutics – embodiment for distinct modalities

Here we provide an overview of several brain stimulation technologies with different modalities that can be employed for oscillotherapeutics. In addition to the time-targeting nature of closed-loop configurations, brain stimulation technologies offer space-targeting. Combining less aversive time- and space-targeting enables oscillotherapeutics to provide therapeutic options distinct from pharmacological treatments, which are easier in terms of their application but have sustained and off target effects. We discuss deep brain stimulation (DBS), transcranial electrical stimulation (TES), transcranial magnetic stimulation (TMS), transcranial focused ultrasound stimulation (tFUS), and optogenetic stimulation for the space-targeting.

5.1. Deep brain stimulation

The main advantages of DBS for oscillotherapeutics are its focality and efficacy (Kringelbach et al., 2007). Stimulus leads are directly inserted into the brain. Electrical stimulation can be limited to the target structure and the stimulation energy directly activates nearby neurons and axonal fibers without shunting via the skull. However, one of drawbacks of DBS is its invasiveness. There are risks of infection and bleeding because of the electrode insertion. Although DBS is basically reversible, the insertion causes microlesion along the electrode track from the surface to the target region. Thus, if the target region is superficial, transcranial stimulation may be considered.

DBS electrodes are precisely located with stereotaxic surgery while stimuli are delivered to validate its effects on symptoms especially for motor disorders. DBS stimulation can be provided in a closed-loop responsive manner to achieve time-targeting (Bouthour et al., 2019). DBS stimulations are usually provided as pulse trains and they can be delivered chronically, intermittently, or precisely synchronized with electrophysiological or behavioural signals in a closed-loop manner. The stimulus parameters include frequency, pulse width, pulse amplitude etc. These parameters have been titrated by physicians empirically, but they can be guided by pre-clinical studies using optogenetics (Creed et al., 2015). The stimulation parameters can be updated online using closed-loop adaptive techniques. For example, dynamic changing of amplitude in response to beta-band power in the STN for PD (Bouthour et al., 2019; Provenza et al., 2019). DBS has already been used for PD, drug-resistant epilepsy, treatment resistant depression, and drug addiction (Deuschl et al., 2006; Li and Cook, 2018). DBS for AD, schizophrenia, GAD, and PTSD are under investigation (Bina and Langevin, 2018; Krack et al., 2010). DBS acts rapidly for movement disorders but it takes time for depression treatment.

5.2. Transcranial electrical stimulation technologies

TES is a non-invasive brain stimulation technique. It is a safe and reversible adjunctive therapy because its stimulus electrodes are located outside the skull. TES technologies are classified into ECT and non-convulsive therapy. Although ECT on the PFC is one of the effective therapies for depression (and is still used for schizophrenia in developing countries), we focus here on non-convulsive TES. This is because of its therapeutic potential for the on-demand control of

many symptoms of neurological and psychiatric disorders, combined with closed-loop time-targeting nature. The focality of TES is not as good as DBS or TMS because of its transcranial nature. However, its diffuse mild modulation over the cortex may be an advantage for intervention (e.g. desynchronization) of pathological oscillations in widespread cortical regions for example absence seizures (Berényi et al., 2012; Kozák and Berényi, 2017). Furthermore, the focality of TES has improved via recent advances in the technologies we discuss below. Traditionally, the stimulus intensity of non-convulsive TES has been limited to up to 2 mA and it has been used for neuromodulation.

However, we recently found that this amount of stimulus intensity is not enough to directly induce large enough electrical fields (1 mV/mm) that in turn reliably induce action potential in the intracranial space, because of the shunt effect of the skull and skin (Liu et al., 2018). Thus, we have developed a new TES technology (Intersectional-Short Pulse (ISP) stimulation) by which electrical stimulation can be transcranially focused in any intracranial space, enabling much higher electrical currents (Vöröslakos et al., 2018). Wearable or implantable devices for closed-loop, focused TES intervention will be available in the future because TES device can be implemented in smaller devices than TMS and tFUS technologies (see Section 6).

5.2.1. High definition transcranial direct current stimulation

tDCS is used for inducing plastic changes by introducing subthreshold membrane potentials in the neurons in the cerebral cortex. Classical tDCS employs two large electrodes (25–35 cm^2) for the stimulation. tDCS induces subthreshold depolarization of cortical neurons below the anodal electrode, and hyperpolarization below the cathodal electrode. Repeated tDCS conducted once a day for five or more consecutive days, can induce long-lasting effects on motor performance, depressed mood, and other functions for one month or more after stimulation (Buch et al., 2017; Loo et al., 2012). Efforts have been made to increase the focality of tDCS by reducing the size of the relatively large stimulus electrode placed over the target area, by increasing the size of the return electrode, and/or by placing the return electrode at another location other than the scalp (for example, the neck, shoulder, and arms, or knee).

Alternatively, an electrode configuration has been developed to optimize stimulation focality on the basis of the modelling of electrical field strength. The so-called high definition tDCS (HD-tDCS) is one of these approaches (Nitsche et al., 2015). Relatively small electrodes are placed in the vicinity of the stimulation electrode for this approach (Datta et al., 2009). Since the distance between the respective electrodes is relatively short, shunting is enhanced relative to the more conventional electrode arrangements. Therefore, current density has to be relatively high to obtain similar effects as large electrode pads. Studies have revealed that HD-tDCS treatment has alleviated symptoms of epilepsy and pain perception (Castillo-Saavedra et al., 2016; Meiron et al., 2019).

5.2.2. High definition transcranial alternating current stimulation

Transcranial alternating current stimulation (tACS) is relatively a newly developed stimulation technique that non-invasively modulates cortical excitability and activity. While tDCS induces neuroplasticity via the constant polarization of neuronal membrane potentials with the application of a tonic subthreshold direct current, tACS is thought to affect neuronal membrane potentials by oscillatory electrical stimulation with a specific frequency (Nitsche et al., 2015). The stimulation used for tACS and its duration are quite similar to tDCS. tACS at a normal stimulus frequency (1–100 Hz) does not induce any plasticity but it interacts with the intrinsic oscillatory activities in the brain (Antal et al., 2008). However, tACS at a much higher frequency (140 to low kHz range) may induce neuroplastic excitability alterations (Antal et al., 2017).

Recently, a new tACS configuration has emerged, the so-called high-definition (HD-tACS). Stimulus focality is dramatically increased in HD-tACS via having one stimulating electrode on the target structure surrounded by several anti-phase returning electrodes. Several cortical regions can be independently stimulated with distinct oscillatory stimulus waveforms by using this stimulation technology. Reinhart has artificially synchronized and desynchronized the human medial frontal cortex and the lateral PFC in theta-band frequency, and successfully modulated executive functions using HD-tACS stimulation (Reinhart, 2017). Reinhart and Nguyen also found that the forced coupling of the PFC and the temporal cortex in theta frequency improved working memory task performance in aged adults (60–76 years of age) (Reinhart and Nguyen, 2019). HD-tACS can be delivered in a closed-loop manner.

5.2.3. Temporal interference stimulation

Temporal interference (TI) stimulation is a newly developed TES technique that enables deep brain stimulation without electrode insertion (Grossman et al., 2017). TI stimulation utilizes the temporal interference between two electrical fields with alternating vectorial directions in similar but slightly different, over-kilo Hertz frequencies. For example, Grossman and others applied 2 kHz (f_1) and 2.01 kHz (f_2) alternating current stimulations on the heads of mice. Depending on the alignment of the electrodes, the superposition of the two electric fields inside the brain resulted in an electrical field at the average frequency of f_1 and f_2, whose envelope was modulated at the frequency of delta f (10 Hz). The 10 Hz modulated envelope entrained the action potentials of the neurons inside the brain, whereas the very high frequency oscillating (>2 kHz) electrical fields did not cause any changes in the membrane potentials of cortical neurons because of intrinsic low-pass filtering properties of the neuronal membrane. They also showed that TI stimulation could transcranially induce cFos (immediate early gene) expression in the hippocampal neurons of mice, but not in neurons in the overlaying cortex.

The TI stimulation is an innovative technique, but only its proof of concept has been established so far, especially because it does not address the bottleneck of intensity dependent peripheral side-effects establishing its efficacy with non-human primates or healthy human volunteers is required before possible clinical application. The spatial resolution and maximal depth for effective stimulation will be dependent on the number and alignment of electrodes on the scalp. One issue could be the possible off-target effects of very high frequency electrical fields over large brain areas. Strong kHz-frequency electrical fields can block the propagation of compound action potential in peripheral nerves (Kilgore and Bhadra, 2014). In their experiments, the 2 kHz electrical stimulation with hundreds microampere order did not induce any acute physiological effects on the brain. Further experiments will be necessary for determining the upper limit of the electrical field to ensure that any conduction block on axons in the brain is not induced. Chaieb and others have reported that very high frequency electrical fields (1–5 kHz) could induce neural plasticity similar to that which can be evoked by anodal direct current stimulation (Chaieb et al., 2011). The long-term effects of kHz stimulation of TI should be studied in future. Temporal resolution of TI simulation has a limitation because the introduction of kHz electrical fields in short ramp-up times induces the transient non-spatially focused activation of neurons, whereas slow ramp-up does not. Because of this limitation, closed-loop TI with time precision (e.g. phase-targeting stimulation) is not feasible. Therefore, TI stimulation seems preferable to applications for inducing plasticity in non-cortical deep brain regions.

5.2.4. Intersectional short pulse stimulation

We have recently developed a new TES technology, by which stimulus induced electrical fields can be focused in any region of the

brain (Vöröslakos et al., 2018). The spatially-targeted TES has been achieved by spatiotemporally rotating Intersectional Short Pulse (ISP) stimulation (2.5–10 μs duration, 5–50 μs pause, depending on the number of electrode pairs) (Fig. 3**A**). This method exploits the integration time constant of the neuronal membrane (5–20 ms), a mechanism that can temporally integrate multiple consecutive electrical gradients with similar vector directions (Fig. 3**A**). Because of this, ISP stimulation could transcranially focus a strong enough electrical field on a target brain region to directly induce or inhibit action potentials (> 1 mV/mm) without placing too much current densities on the scalp (i.e. it is less painful). Spikes of HPC neurons could successfully be modulated in a hemisphere specific manner with ISP stimulation. Furthermore, the 1 Hz ISP stimulation phase- and hemisphere-specifically modulated amplitude of alpha-band activities of EEG in healthy volunteers.

The major advantages of ISP stimulation are: (1) Focality. ISP stimulation can focus on a small brain region. This focus can be further improved by placing a number of electrode pairs on the scalp; (2) Time-resolution. It can be easily implemented with a closed-loop configuration with millisecond precision. Phase-targeted closed-loop stimulation is possible; (3) Intensity. Currents as high as ten-sixteen mA can be used (an order of magnitude larger than conventional TES) because the current density on each electrode is similar to that of conventional TES; (4) Bilateral stimulation. The same effects (excitation or inhibition) can be applied on both hemispheres simultaneously by aligning electrodes (unlike conventional TES, which induces opposing anodal-cathodal effects). This is because direction of electrical fields along dendrite-axon axis on neurons determines whether the electrical fields activate or inhibit the target neurons (Liu et al., 2018), and ISP can induce symmetrically directed electrical fields on the both hemispheres (Fig. 3**B**); (5) Versatility. Several distinct stimulus waves can be employed independently for example to introduce distinct stimulus phase difference to different brain regions (Fig. 3**B**). ISP stimulation can be combined with tDCS, tACS, and even TI stimulation in principle; and (6) Simplicity. The ISP stimulation device can easily be miniaturized to be implantable or wearable. This enables the long-term control of neurological and psychiatric disorders, even for domiciliary care (Fig. 4**B**). ISP stimulation could enable non-invasive on-demand closed-loop control with space- and time-targeted brain stimulation for neurological and psychiatric disorders.

5.3. Transcranial magnetic stimulation

TMS is non-invasive brain stimulation technique that has been used for modulating symptoms of depression, schizophrenia, addiction etc. (Diana et al., 2017; Farzan et al., 2012; Fox et al., 2012). TMS employs the principle of electromagnetic induction, in which a changing magnetic field gives rise to a companion electric field that induces electric currents in nearby conductive structures (Hamada and Rothwell, 2015). A large pulse of current in the external stimulating coil generates a rapidly changing magnetic field that rises to (and falls from) 1 T or more within 1 ms. The design of the external stimulating coil affects the distribution of the induced field in the brain; the spread and depth of conventional figure-8 stimulating coils are 5 cm^2 and 1.0–3.5 cm, respectively (Deng et al., 2013). The main target of TMS is the cortex, but H-coil and double cone coils also enable the stimulation of deeper structures.

The main advantage of TMS is its high titer stimulation. Its inducted currents in the intracranial space are strong enough to directly evoke the action potentials of cortical neurons without resonance (stimulation of the motor cortex can evoke muscle movements). rTMS of the PFC achieves better or comparable efficacy than ECT for depression and it has less cognitive side effects. The time-resolution of TMS is good enough to be combined with closed-loop configurations. Major drawbacks of TMS are its cost and size. Due to the physical constrains of coil size, TMS instruments cannot be implanted or wearable. TMS treatments can only practically be possible in hospitals.

5.4. Transcranial focused ultrasonic stimulation

Low-intensity tFUS is an emerging brain stimulation technology that modulates mammalian brain activity (Fomenko et al., 2018). Relatively low intensity (< 3 W/cm^2) and low frequency (0.25–0.5 MHz) ultrasound stimulation is used for human neuromodulation studies. Stimulation parameters (e.g. sonication duration) and intensity determine whether a stimulus has excitatory or inhibitory effects. The mechanisms by which low-intensity ultrasonic stimulation modulates neuronal activity have been poorly understood. Thermal and non-thermal mechanisms have been proposed, but thermal mechanisms are negligible because low-intensity tFUS does not cause a significant rise in tissue temperature during sonication (< 0.1 °C). Direct effects on neuronal membrane and ion channels have been suggested as non-thermal mechanisms (Plaksin et al., 2014).

The major advantage of tFUS is its focality even for deep brain structures (however, compensation of bone scattering is challenging). Human and non-human primate studies have shown that the stimulus focus can be as small as 2–5 mm and tFUS can focus on (for example) the basal ganglia without affecting the cortex (Legon et al., 2014). In addition, tFUS can be delivered in a closed-loop manner (Fig. 4**A**). Miniaturization of the transducer and amplifier will be required for implantable or wearable devices. Implantable transcranial ultrasonic devices for mice have been reported, but none for humans yet (Li et al., 2019). tFUS can transiently open the blood brain barrier and it can

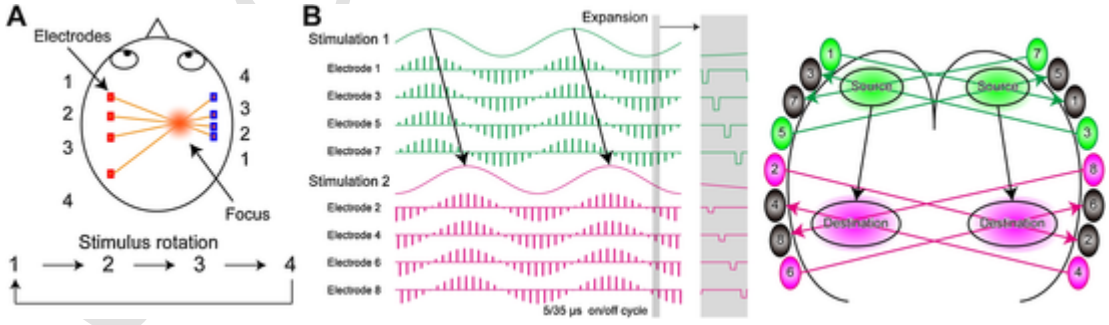

Fig. 3. Intersectional Short Pulse stimulation: a focused transcranial electrical stimulation technology.(**A**) Principle of Intersectional Short Pulse (ISP) stimulation. Multiple anodal and cathodal electrode pairs are located on the skull or scalp. Electrical stimulation was temporally interleaved at 5–25 μs and rotated within the electrode pairs. The electrical field generated by the stimulation is focused to an arbitrary region of the brain. (**B**) Expansion of ISP technology for multiple focusing points with two distinct stimulus waveforms (green and magenta in the left). Depending on electrode alignment and stimulus polarity, multiple brain regions can be stimulated using distinct stimulus waveforms causing the same effect (excitatory or inhibitory) on both hemispheres (right). Green and magenta arrows indicate current flows from anode to cathode. Black arrows indicate phase differences (temporal shifts) between the distinct stimulus waveforms.

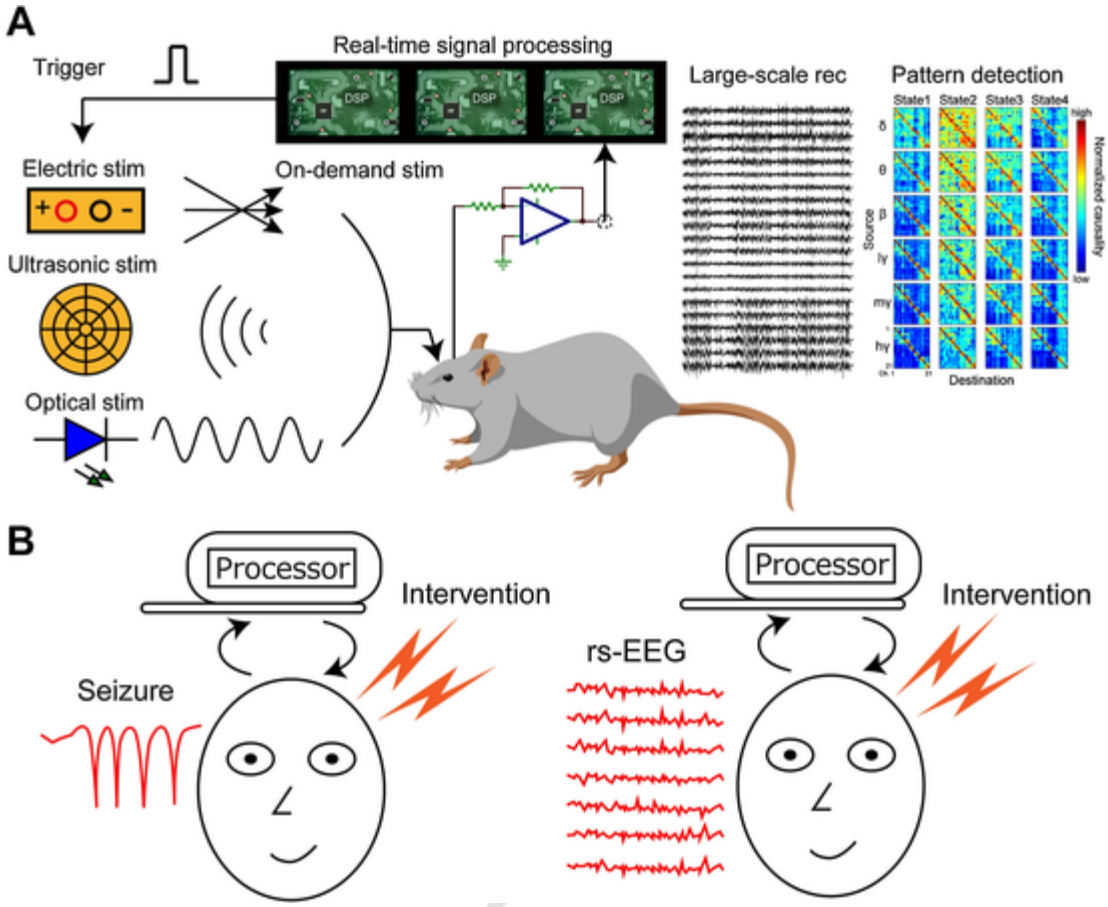

Fig. 4. Future direction and engineering challenges.(**A**) Pre-clinical research and development of closed-loop interventions for neurological and psychiatric disorders in the near future. Efficient algorithms should be developed for real-time detection of specific pathological oscillation patterns with large-scale data streams. Several brain stimulation modalities (e.g. electrical, ultrasonic, and optical) are investigated for efficient transcranial stimulation. (**B**) The development of wearable devices for the closed-loop intervention of neurological and psychiatric disorders. The real-time decoding of specific features of chronic symptoms from resting state EEG (rs-EEG) will be much more demanding on computation. Parallelization of processing units will be necessary for faster computation and lower power consumption. The devices need to be miniaturized to become wearable or implantable.

be used for both time- and space-targeted drug delivery for the central nervous system following intravenous administration of nanoparticle- or microbubble-caged drugs (Landhuis, 2017).

5.5. Optogenetics

Optogenetics is an innovative technology for the cell-type-specific manipulation of neuronal excitability with millisecond precision. Causal relationships between neuronal activities and natural behaviors have been extensively explored in neuroscience fields using optogenetics (Grosenick et al., 2015). The major advantages of optogenetics as a brain stimulation technique come with the genetically coded nature of its actuators (opsins). This genetic nature combined with various promoters and viral vector-mediated gene transduction enables cell-type- and neural pathway-specific, and even activity-dependent opsin expression in arbitrary brain regions (Kim et al., 2017). Opsin expression can be pharmacologically controlled via the Cre-estrogen receptor or Tet on/off system. The manipulation of neuronal excitability can be bidirectional with fine temporal resolution. For example, channelrhodopsin-2 and iC++ can respectively be used for blue light-mediated excitation and inhibition with millisecond precision.

The pathophysiology of neurological and psychiatric disorders and possible intervention strategies for them have been explored using animal models with closed-loop optogenetics. For example, Krook-Magnuson and others showed that seizure-triggered on-demand optogenetic inhibition of HPC pyramidal neurons suppresses HPC electrographic seizures in mice (Krook-Magnuson et al., 2013). Carlson and others showed that cortical slow oscillation-timed gamma frequency optogenetic activation of the PFC to thalamic pathway alleviated depression-like behavior in mice (Carlson et al., 2017). Major drawbacks of optogenetics as a brain stimulation technique for humans are gene introduction and invasiveness. Virus-mediated gene transduction and the insertion of optical fibers into the brain is not easily justified in terms of risk versus benefit. Magnet or radio-wave sensitive genetically coded actuators may enable the transcranial manipulation of defined neural circuits without optical fiber insertions, but gene manipulation is still required. However, Optogenetics is a very powerful and useful technique for basic oscillopathy research.

6. Engineering challenges and future directions

In addition to the pathophysiological aspects of oscillopathies and brain stimulation technologies themselves, technical implementation challenges the clinical applications of closed-loop brain stimulation should be addressed. Here we focus on the challenges of implementing closed-loop ISP stimulation for the real-time control of refractory epilepsy and beyond.

6.1. Recording and real time processing of pathological oscillations

Pathological oscillations need to be intervened in real-time for the online control of neurological and psychiatric disorders. At basic research levels, we previously developed an analog electrical circuit sys-

tem for the real-time detection and phase-specific intervention of epileptic seizures (Berényi et al., 2012). This system is very fast and has virtually no delay. However, an analog electrical circuit system is not flexible enough to be the best solution for developing new algorithms or even for tuning the detection parameters of existing algorithms. Analog electrical circuit systems are not even size efficient.

Therefore, we have developed a digital seizure detection system using a real-time digital signal processor unit and a 256 ch multiplexed biosignal amplifier (Berényi et al., 2014; Kozák and Berényi, 2017). Harnessing its 100 MHz digital signal processors (DSPs), we could implement a 24 h real-time closed-loop TES system with up to eight subjects (rats). Each subject has 30 ch recording sites. The time resolution of the system is 2 ms, but it is configurable with a trade-off between the number of recording sites and the number of calculations for each subject. The graphical programing environment for the system enabled us to utilize many digital signal processing functions (arithmetic, filtering, root-mean-square, power spectrum and coherency calculation, timer, counter, logic gates etc.) to implement virtually any simple detection algorithm from multi-dimensional time series. While a closed-loop control program is running in the system, any parameters in a detection program can be turned via any external programming environment that supports ActiveX™ controls including MATLAB, Visual Basic, Visual C++, LabView, Python etc. Other groups have also reported seizure detection systems; for example, Armstrong and others reported a MATLAB-based system (Armstrong et al., 2013). The Open Ephys-based closed-loop system is also getting popular in field in systems neuroscience (Siegle et al., 2017). There is some intervention delay for closed-loop in the system because signal processing calculations are conducted in the host PC. They are dependent on the data transfer speed of serial ports (means of 11 ms via USB2.0 and 8 ms via USB3.0). This delay is planned to be reduced to be less than 1 ms by developing a PCIe acquisition board in future (https://open-ephys.atlassian.net/wiki). Phase-locked (targeting) stimulation is essential for efficient intervention in pathological oscillations. New algorithms (for instantaneous phase-calculation, for example) will be useful and can be implemented in the above mentioned closed-loop system for efficient pathological oscillation intervention (Mansouri et al., 2017).

The real-time prediction of seizures is more demanding than detecting seizures themselves because of smaller signal-to-noise ratios and untypical feature changes, but prediction is more valuable than detection as it enables prevention (Kuhlmann et al., 2018). Recruiting larger number of time series data for analysis, calculating coherence or causality matrices, entropy, phase-amplitude coupling, and/or loss of resilience could all be useful to increase detection power and decrease false positive detections. They could enable the detection of a seizure predictor specific network activity pattern as three-dimensional template matching (Fig. 4**A**) (Chang et al., 2018). The real-time detection of the symptom-specific network activities of psychiatric disorders can be as (or more) demanding as seizure prediction because its oscillatory representations are not supposed to be as evident as epileptic seizures. They are typically subtle and distributed to many brain regions (Fig. 4**B**) (Carlson et al., 2017; Hultman et al., 2016, 2018). This means that much faster algorithm and computation may be required for psychiatric disorders than for epilepsy.

Another possible issue related to interventions for predicted seizures and psychiatric disorders is that their specific oscillatory patterns are so complex. It would not be very efficient to find these patterns via exploratory analyses by the researchers themselves. As we have already discussed earlier in this paper, machine learning-mediated modelling of oscillatory network activities (e.g. CSFA) would be useful to identify them instead. Although precise offline modelling is a time-consuming process even with powerful computers, online detection of specific oscillatory patterns based on the established model (real-time brain state classification) would be feasible because it does not require intensive calculations as the modelling process. A reduction in the dimension and complexity of the established model may be required for online intervention. Superfast, massively parallelized graphical processing unit (GPU) computing would be useful to implement real-time online closed-loop interventions for research purposes.

6.2. Stimulation: precise localization for targeting a seizure (or symptom) focus in the brain

Increase of number of pairs of stimulus electrode pairs is important for further improvement of spatial resolution of ISP stimulation (and this is the case for TI stimulation and tFUS as well). A specialized headset with multiple EEG and stimulus electrodes is required for transcranial closed-loop intervention with ISP stimulation (Fig. 4**B**). Intracranial implantation of the stimulus electrodes will increase the efficacy and focality at the expense of non-invasiveness. The alignment of stimulus electrodes should be tailored for the individual needs of each patient, especially for focal seizures. The target brain region should be determined via high-density EEG-mediated functional tomography and the long-term video monitoring of seizures. Brain structure imaging will be also required for designing of the ISP stimulation target. Although electrical artifacts of ISP stimulation are smaller than those of conventional TES, feedforward removal of gross artifacts from applied currents is required (Kohli and Casson, 2019; Vöröslakos et al., 2018). Ready-to-use simulation environments for electrode alignments and artifact predictions should be developed for the clinical application of ISP stimulation.

The optimization of stimulation parameters (stimulus frequency, duration, intensity etc.) is critical for alleviating symptoms effectively. This optimization has been conducted by physicians empirically, but it is time-consuming. Deep learning technology is suggested to find optimal DBS stimulus parameters for movement disorders for the effective real-time classification of brain states (a closed-loop intelligent implementation of adaptive DBS) (Neumann et al., 2019). This approach could be implemented in future for optimizing closed-loop ISP stimulation to control epilepsy and psychiatric disorders as well. Supervised and reinforced learning would be useful for initial parameter settings and dynamic optimization during ongoing intervention treatments, although artificial intelligence (AI) medicated brain stimulation is currently cleared by the FDA

6.3. Device implementation- miniaturization, power supply, and IoT in the 5 G era

The implementation of ISP stimulation for implantable or wearable devices requires the miniaturization of each unit for recording, processing, and stimulation, which we are working on. Detection algorithms should be simplified and optimized to be implemented into a micro processing unit for example a field-programmable gate array (FPGA), although it requires low-level programming skills of experienced engineers. Massive parallelization will be required to ensure real-time computation in a small device with limited clock rate without significant delay. This will also improve power efficiency (Hirano et al., 2015). The use of bionic chips optimized for machine learning with neuronal data (Qiao et al., 2015) would be useful for much faster mobile devices as implemented in iPhone X (Apple A11) or Intel's Nervana Neural Network Processors. Even quantum computing processors (e.g. Google's Sycamore processor) might be implemented in medical devices in the future (Arute et al., 2019). Many implantable or wearable medical devices will be always connected via the Internet of Things (IoT) in the 5 G or 6 G era. They will have large highly reliable data transfer capabilities with negligible delay. Computation for closed-loop interventions may be outsourced to external supercomputer servers via highly reliable bidirectional data streams in those eras.

The power supply for implantable or wearable devices needs to be addressed. Miniaturized rechargeable batteries with large capacities are required. Contactless recharge stations (via magnetic induction for example) may be available everywhere in the future at least in big cities (Mickle et al., 2019).

Author Contributions

Y.T. and A.B. conceived the idea. Y.T. wrote the original draft and A.B. reviewed and edited it. Y.T. prepared the figures and A.B. supervised this work.

Declaration of Competing Interest

A.B. is the owner of Amplipex Llc and Neunos Ltd in Szeged, Hungary, manufactures of signal-multiplexed headstages and neurostimulator devices.

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