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ORIGINAL PAPER

Neuronal Network Oscillations in Neurodegenerative Diseases

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Abstract Cognitive and behavioral acts go along with highly coordinated spatiotemporal activity patterns in neuronal networks. Most of these patterns are synchronized by coherent membrane potential oscillations within and between local networks. By entraining multiple neurons into a common time regime, such network oscillations form a critical interface between cellular activity and large-scale systemic functions. Synaptic integrity is altered in neurodegenerative diseases, and it is likely that this goes along with characteristic changes of coordinated network activity. This notion is supported by EEG recordings from human patients and from different animal models of such disorders. However, our knowledge about the pathophysiology of network oscillations in neurodegenerative diseases is surprisingly incomplete, and increased research efforts are urgently needed. One complicating factor is the pronounced diversity of network oscillations between different brain regions and functional states. Pathological changes must, therefore, be analyzed separately in each condition and affected area. However, cumulative evidence from different diseases may result, in the future, in more unifying "oscillopathy" concepts of neurodegenerative diseases. In this review, we report present evidence for pathological changes of network oscillations in Alzheimer's disease (AD), one of the most prominent and challenging neurodegenerative disorders. The heterogeneous findings from AD are contrasted to Parkinson's disease, where motor-related changes in specific frequency bands do already fulfill criteria of a valid biomarker.

Keywords Oscillations · Alzheimer's dementia · Biomarker · Neurodegenerative diseases · Parkinson's disease · EEG

Introduction

Oscillating electrical activity is a prominent feature of most neuronal networks. This is no surprise for rhythmic behaviors like breathing or walking which must be driven by rhythmic nerve pulses from synchronously oscillating nuclei (Grillner 2006). However, since the discovery of the electroencephalogram (Berger 1929), we have learned that almost all brain regions express coherent electrical oscillations, whether or not their output is rhythmic. These patterns are state-dependent; i.e., they differ in amplitude, frequency, and spatial extent depending on the organism's vigilance and behavior.

While many studies have correlated network oscillations (EEG rhythms) with defined cognitive or behavioral states, causal relationships have remained elusive for a long time. However, combined experimental and theoretical work during past decades has led to considerable mechanistic insight, at least in selected functional systems like those

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responsible for memory formation (Düzel et al. 2010; Fell and Axmacher 2011), perception (Engel et al. 2001), or motor activity (Schnitzler et al. 2006). Causal links between network oscillations and systemic functions have been recently highlighted by targeted interventions (i.e., electric stimulation), causing selective effects at the behavioral level (Girardeau et al. 2009; Ego-Stengel and Wilson 2010; Polanía et al. 2012; Fell et al. 2013; Lee et al. 2013; Lozano and Lipsman 2013).

Despite many unsolved problems and open debates, some unifying features of neuronal network oscillations can be identified (Buzsáki and Draguhn 2004; Traub and Whittington 2010). One important example is the crucial role of inhibitory synaptic transmission in the temporal organization of neuronal activity (Mann and Paulsen 2007; Whittington and Traub 2003). Many inhibitory interneurons have widespread axonal plexus which allow for synchronous inhibition of multiple neurons within their local circuits. In many networks, interneurons are mutually interconnected by chemical or electrical synapses which synchronize their activity—as a result, phasic synaptic inhibition transmits a powerful and synchronous rhythmic signal throughout entire networks, defining cyclic changes between increased and decreased spike probability, respectively (Schmitz et al. 2001; Traub et al. 2002). On the other hand, interneurons are highly diverse, and detailed analysis of specific networks shows that different subtypes of interneurons support different features and patterns of network oscillations. Interneurons can be classified by several features, including the expression pattern of calcium-binding proteins and peptides (Kawaguchi and Kondo 2002). Parvalbumin (PV)-expressing interneurons and cholecystokinin (CCK) interneurons are particularly relevant subtypes contributing to the modulation of network oscillations. Investigating the functional anatomy of interneurons within their network context has become a highly active and fruitful field in neuroscience (Freund and Buzsáki 1996; Klausberger and Somogyi 2008). Each pattern of network activity results from the specific functional architecture of the local circuit which defines the contributions of synaptic inhibition, synaptic excitation, electrical coupling, and intrinsic neuronal discharge properties. These properties differ between networks and functional states, thereby accounting for the diversity of observable spatiotemporal patterns (Buzsáki 2006; Traub and Whittington 2010).

Neurodegeneration goes along with changes in oscillatory activity, most prominent at the level of slower waveforms [delta (1–3 Hz), theta (3–8 Hz), and alpha (8–12 Hz)], but also including faster oscillations [gamma (30–100 Hz)]. Slow oscillations like delta extend over larger brain regions, while high-frequency oscillations occur typically in smaller networks (Buzsáki and Draguhn 2004). Importantly, such fast oscillations can synchronize between different local networks, a mechanism that has been suggested to underlie several cognitive functions (Engel et al. 2001; Fell and Axmacher 2011). Disruption of gamma oscillations is a prominent feature in different neurodegenerative diseases and may, therefore, directly contribute to the associated cognitive deficits. The molecular-, cellular-, and network-level processes mediating different types of oscillations have been subject to intense research over the past decades. It turns out that the enormous variety of patterns in different regions, behavioral states, and developmental stages requires individual case-to-case analyses. On the other hand, some general principles have emerged. With respect to neurodegenerative diseases, two properties of oscillating networks are particularly important: (1) The functional state of networks is often defined by neuromodulatory systems—changes in activity or integrity of such systems will, therefore, affect the occurrence, strength, and coherence of rhythmic brain activity; (2) synchronization of neuronal networks at a given frequency depends on the recruitment of specific neuronal subtypes, often highly specialized inhibitory interneurons—selective loss of a given cell type may, therefore, cause selective disruption of specific oscillating activity patterns. However, this rule is not without exceptions: Delta oscillations may recruit the entire neocortex through activity in large thalamocortical feedback loops (Steriade 2003). Interestingly, this type of oscillations remains intact, or is even enhanced, in different neurodegenerative diseases (Rodriguez et al. 1999; Babiloni et al. 2004). Other types of oscillations do depend on the function of specific subtypes of inhibitory interneurons and are, therefore, selectively vulnerable to loss of these cells. As a highly simplified and global rule, it can be said that in these patterns recurrent cycles of phasic inhibition and post-inhibitory increase in firing probability entrain principal neurons into a common oscillating regime (Mann and Paulsen 2007; Whittington and Traub 2003). Theta oscillations, which occur prominently in the hippocampus (Buzsáki 2002), are modulated by CCK-expressing perisomatically inhibiting interneurons and by several types of dendrite-targeting GABAergic cells (Klausberger 2009; Klausberger and Somogyi 2008). Gamma oscillations, on the other hand, depend more strongly on perisomatic inhibition by parvalbumin-expressing basket cells and do not require rhythmic activity of distal-dendrite-targeting cells (Cardin et al. 2009; Klausberger and Somogyi 2008; Lasztóczi and Klausberger 2014). Interestingly, loss or reduced activity of parvalbumin-expressing basket cells may play a major role in dysfunctional cognition in schizophrenia (Curley and Lewis 2012; Lewis et al. 2012). A very fast class of oscillations is sharp wave-related ripples in hippocampal networks which occur during slow-

wave sleep or behavioral inactivity (Buzsáki et al. 1992). These oscillations comprise frequencies around 200 Hz in rodents and 80–120 Hz in monkeys and humans, and they do also involve, among others, activation of fast-spiking parvalbumin-expressing interneurons (Bähner et al. 2011; Klausberger and Somogyi 2008; Schlingloff et al. 2014; Stark et al. 2014). However, the precise mechanisms underlying ripple oscillations are still subject to debate, mostly because multiple lines of evidence indicate that ripple-entrained firing of pyramidal cells is critically dependent on axo-axonic gap junctions (Draguhn et al. 1998; Schmitz et al. 2001; Simon et al. 2014; Traub et al. 2002) and can occur in the absence of inhibition, at least in vitro (Nimmrich et al. 2005).

In any case, a reduction in oscillatory activity in the frequency domains of theta, gamma, or above indicates loss or dysfunction of specific types of interneurons in the respective diseases. Indeed, there is evidence that a dysfunction of parvalbumin-positive interneurons contributes to AD-related functional impairments (Verret et al. 2012), consistent with a reduction in gamma activity in AD (Herrmann and Demiralp 2005). The highly complex cytoarchitecture of the brain requires that multiple cell types interact for the generation of network activity, and this implies that also other cell types, including pyramidal cells, glial cells, or distant projection neurons, are involved in disturbed oscillatory activity. For example, as described below, slower cortical waveforms in AD are probably related to a reduced cholinergic input from the nucleus basalis of Meynert.

The increasing knowledge about patterned network activity suggests that dysfunctions of the nervous system cannot be understood without analyzing the respective (oscillating) network activity patterns. Surprisingly, however, the pathophysiology of network oscillations is much less understood than molecular and cellular changes. Only recently, we begin to see how disturbed network functions may affect motor activity, perception, or more complex cognitive functions like memory formation or decision-making. The emerging concept of neurological and psychiatric disorders as "oscillopathies" may provide a useful new perspective toward these insufficiently understood conditions. The best-established example for this approach is Parkinson's disease (PD). We will therefore start by summarizing the concept of PD as an oscillopathy before turning to the more heterogeneous and less complete knowledge about disturbed network oscillations in AD.

Network Dysfunction in Parkinson's Disease

In Parkinson's disease (PD), rhythmic patterns are prominent, and they even constitute one of the most relevant clinical symptoms, tremor. PD can, therefore, arguably be conceptualized as an "oscillopathy" (Schnitzler and Gross 2005). PD is a neurodegenerative disorder characterized by loss of pigmented cells in the substantia nigra pars compacta and other brainstem nuclei. Histologically, PD is characterized by intracellular inclusions of the protein synuclein (termed Lewy bodies). Consequently, the dopaminergic nigral fibers innervating the striatum strongly decline. As a result, patients exhibit a spectrum of movement and posture abnormalities including hypokinesia, rigidity, tremor at rest, masked face, stooped posture, and gait problems. Pharmacological treatment involves replenishment of dopamine by oral administration of L-DOPA. Co-morbidity with other neurodegenerative disorders like AD or Lewy body disease is frequent and causes dementia.

Computer simulations suggest that reduced dopaminergic input to the basal ganglia results in emergent oscillatory phenomena within several nuclei including the subthalamic nucleus (Terman et al. 2002; Frank 2006). Indeed, pathological neural oscillations have been identified in the basal ganglia of Parkinson's disease patients (Brown and Williams 2005; Hammond et al. 2007; Schnitzler and Gross 2005). Specific symptoms have been linked to specific pathological increases in neuronal synchronization (Timmermann and Florin 2012). The causal relevance of pathological hypersynchronization in the beta frequency range was demonstrated by studies showing that stimulation of the subthalamic nucleus at 20 Hz (i.e., within the beta frequency range) impairs grip force in Parkinson's disease (Chen et al. 2007, 2011). By contrast, slower frequencies affect the rate and—specifically—the precision of finger tapping, a different, coordinated motor pattern (Eusebio et al. 2008). Clinically, dopamine treatment and deep brain stimulation to the subthalamic nucleus improve motor deficits, and the degree of improvement directly correlates with a reduction in beta oscillations (Ray et al. 2008). In fact, the magnitude of beta power allows one to predict the rate of stimulation-induced improvement. Discharge of neurons in the subthalamic nucleus is time locked to beta oscillations, suggesting that synchronous neural activity in this area in PD causes field potential oscillations (Kühn et al. 2005).

Besides beta frequencies, gamma oscillations have also been recorded in the subthalamic nucleus in PD. Gamma oscillations are enhanced during periods of tremor, and the ratio of beta-to-gamma oscillations seems to correlate with the strength of the tremor (Weinberger et al. 2009). Neuronal discharges are also time locked to gamma frequency oscillations, indicating that gamma oscillations may represent synchronous activity of neuronal assemblies (Trottenberg et al. 2006). An emerging treatment for gait impairment in PD is the stimulation of the pedunculopontine nucleus (Gregory 2008), which is part of the reticular

formation. Alpha oscillations can be recorded in the pedunculopontine nucleus in patients with PD, and they correlate with gait speed. Accordingly, gait freezing is accompanied by a reduction in alpha activity (Thevathasan et al. 2012). Finally, recordings during deep brain stimulation in patients also suggest that the absence of a 300-Hz component in the subthalamic nucleus may contribute to the pathophysiology of PD (Foffani et al. 2003). Dopamine treatment restores the 300-Hz component, and so does deep brain stimulation at high frequencies, improving symptomatology. Further evidence indicates that the temporal coupling of this high-frequency oscillation and the phase of an underlying beta frequency rhythm correlates with symptoms of PD (López-Azcárate et al. 2010). Thus, higher-order phenomena such as cross-frequency coupling may be promising candidates for biomarkers of neurodegenerative diseases.

Apart from these alterations of oscillatory activity within the basal ganglia, PD patients also show oscillatory changes at the level of the neocortex. Whole-head MEG recordings have revealed a slowing of brain activity during resting state in PD patients, especially in the theta and slow alpha range, with reduced activity in the fast alpha and gamma domains (Bosboom et al. 2006; Stoffers et al. 2007). These impairments in oscillatory activity could be reversed by the cholinesterase inhibitor rivastigmin, indicating that cholinergic degeneration may contribute to altered waveforms in PD (Bosboom et al. 2009). It is presently unclear how this slowing of neocortical—mostly frontal—oscillations relates to the observed increase in faster rhythms within the basal ganglia. Interestingly, studies in rodents revealed that degeneration of cholinergic cortical projections from the basal nucleus of Meynert is also associated with an increase in slow activity, suggesting that similar network phenomena may also be relevant to other neurodegenerative syndromes (Ray and Jackson 1991).

To summarize, these studies show that the PD-associated reduction in dopaminergic input to the basal ganglia results in pathological increases in oscillations in the theta, slow alpha, beta, and gamma frequency range and a reduction in high-frequency oscillations at 300 Hz. Changes in beta oscillations appear to be most directly related to clinical symptoms of the disease.

Network Dysfunction in Alzheimer's Disease

Alzheimer's disease (AD) is the leading cause of dementia, affecting 5–10 % of the population over the age of 65, and over 30 % after 85 years of age. Neuropathological hallmarks of the disease are the presence of senile plaques, mostly composed of amyloid-β (Aβ) peptide, as well as neurofibrillary tangles and synaptic loss. Another feature is cortical and subcortical atrophy, causing a ventricular enlargement. Cholinergic neurons of the basal forebrain are particularly vulnerable in AD, leading to cholinergic hypofunction and associated cognitive deficits. Genetic linkage of mutations in the amyloid precursor protein (APP) and presenilin genes to rare familial forms of AD have led to the proposal that Aβ formation is causal to the disease, initiating further pathological cascades (Hardy and Higgins 1992; LaFerla 2010; Zempel and Mandelkow 2012, but see Swaab et al. 1998). APP is cleaved by enzymes, yielding several Aβ species of different lengths and toxicities. The 42-amino acid peptide $A\beta_{42}$ is elevated in AD and is prone to aggregate to oligomeric forms as well as amyloid plaques. A vast number of publications from the last two decades revealed that in particular small oligomeric aggregation states of $A\beta_{42}$ are pathologically relevant and directly affect the synaptic machinery (Selkoe 2002; Walsh and Selkoe 2007).

The cellular pathology leading to network dysfunction is currently a matter of exciting investigations and not yet well understood. It has been suggested that changes in the calcium homeostasis cause an increase in neuronal excitability, subsequently leading to synaptic degeneration. Multiple publications of the last two decades indicate that Aβ peptides increase the influx of calcium (Dougherty et al. 2003; Kelly and Ferreira 2006; Hermann et al. 2013; Ramsden et al. 2002; reviewed by Yu et al. 2009). Such influx may increase cellular excitability, although this has not yet been shown experimentally. Pre- and postsynaptic modifications have been described as a result of Aβ exposure (reviewed by Nimmrich and Ebert 2009). Other studies point toward an impairment of interneuron activity of the parvalbumin-positive type via an Aβ-mediated decrease in sodium channel activity in these cells, leading to epileptic seizures (Verret et al. 2012). In addition to these effects of Aβ, recent reports also indicated that abnormal tau protein in AD impairs proper synaptic functioning (Pooler et al. 2014).

Findings in Patients

Local EEG Synchronization and Oscillations

The cortical EEG of AD patients is altered over a wide range of frequencies. A shift from fast to slow waves is typically observed in spontaneous EEG recordings, i.e., an increase in the delta and theta frequency range, and a decrease in alpha and beta power (e.g., Besthorn et al. 1997; Jeong 2004; Rodriguez et al. 1999; see Fig. 1). The slow component of evoked and event-related electrographic responses shows more heterogeneous changes of both, amplitude and frequency range, and has been suggested as a

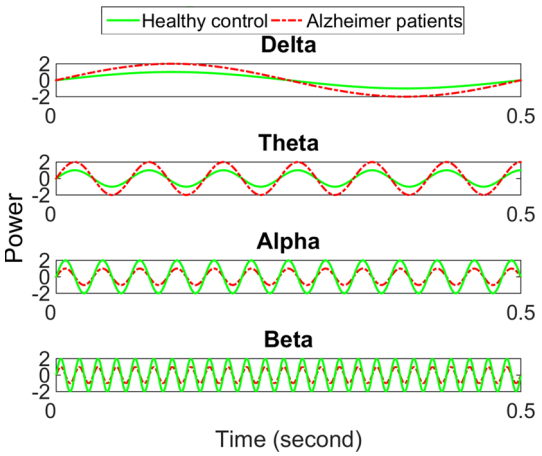

Fig. 1 Schematic overview of EEG abnormalities in Alzheimer's disease

functional marker of early Alzheimer's disease (Yener et al. 2008, 2015). Babiloni et al. (2004) analyzed mild cases of AD in a multicenter EEG trial and modeled EEG sources by low-resolution brain electromagnetic tomography (LORETA). They found an increased power of delta band activity in occipital, temporal, and limbic brain regions, and a reduction in central, parietal, temporal, and limbic alpha rhythms. Theta waveforms were unaffected. Unlike the decrease in alpha, which was specific to AD, the increase in delta power was also observed in vascular dementia. The decrease in alpha power with disease progression was related to the decline of cognitive performance as assessed by the Mini-Mental State Examination (MMSE) test. A correlation of alpha waves to disease severity was also observed by others (Chiaramonti et al. 1997; Rodriguez et al. 1999). Slowing of EEG waveforms is positively correlated to tau protein concentrations in the cerebrospinal fluid (Jelic et al. 1997). The latter is used as a biomarker to support diagnosis and clinical studies of AD (Table 1).

A number of studies have reported AD-related alterations of faster brain waves such as gamma oscillations, which are involved in long-term memory formation in humans (Fell et al. 2002; Gruber et al. 1999, 2002; Kaiser et al. 2003) and contribute to several further cognitive domains, including attention and working memory (Jensen et al. 2007). Ribary et al. (1991) analyzed the thalamocortical coherence of 40 Hz oscillations by magnetic field tomography in AD patients. They observed a reduction in this rhythmic activity in the cortex. Using MEG in patients, Stam et al. (2002) reported a loss of gamma band synchronization in AD. AD-related changes of oscillations may have some similarity to EEG changes during normal aging, as the amplitude of evoked gamma activity is decreased in aged healthy individuals (Böttger et al. 2002).

To summarize, these studies show that AD is associated with reduced amplitudes of EEG oscillations in the alpha and gamma frequency range, and enhanced amplitudes of delta oscillations. It should be noted, however, that some authors observed an increase in gamma band power in EEG recordings from AD patients (van Deursen et al. 2008). MEG (Osipova et al. 2006) as well as EEG recordings (van Deursen et al. 2011) also revealed an increased gamma steady-state response in AD. It has been argued that these divergent findings are due to methodological differences (van Deursen et al. 2009). This issue clearly needs further investigation before allowing clear statements about network-level biomarkers for the disease.

Global EEG Synchronization

Successful cognitive processing requires a functional integration of activity within large-scale networks (Fell and Axmacher 2011; Fries 2005; Siegel et al. 2012). Cognitive impairment in AD may thus not only be related to alterations of local network oscillations, but could also involve a failure of functional interactions between multiple brain areas (Bokde et al. 2009). In principle, this alteration would be detectable as a pathological reduction in coherence between brain regions in the EEG of AD patients. A number of studies described diminished coherence of the alpha band in AD (Cook and Leuchter 1996; Locatelli et al. 1998). Using MEG in patients with early AD, Montez et al. (2009) reported an impaired synchronization in the alpha frequency range. In this respect, it is an interesting observation that apolipoprotein epsilon4 (APOE4), the most important genetic risk factor for late-onset AD, decreases cortical coherence at alpha frequency in AD patients (Jelic et al. 1998). Reduced coherence has also been observed for other frequency bands such as delta, theta, and beta (Wada et al. 1998).

Prominent alterations of EEG activity in AD patients are observed during sleep. The sleep structure is disturbed in AD patients, with shortened REM sleep episodes, and this has been related to a reduced cholinergic input. Slowing of the EEG seems more prominent in REM sleep than in wakefulness (Petit et al. 1993), and the ratio of slow to fast frequencies during REM sleep was suggested as a biomarker for AD (Montplaisir et al. 1998). The cholinesterase inhibitor donepezil, which is clinically used for symptomatic treatment of AD, enhances REM sleep and reduces the power of slow EEG oscillations during REM sleep (Moraes Wdos et al. 2006), supporting the view that cholinergic deficits cause this phenotype. To summarize, these studies show that not only the local power but also the interregional synchronization of EEG oscillations is reduced in AD.

Table 1 Overview of AD-related oscillatory changes in different frequency bands

Recording technique	AD related waveform changes					Reference
	Delta	Theta	Alpha	Beta	Gamma	
EEG						Besthorn et al. (1997) Chiaramonti et al. (1997) Rodriguez et al. (1999) reviewed by: Jeong (2004)
EEG						Babiloni et al. (2004)
EEG		ATR↓	ATR↓			Jelic et al. (1998)
MEG					Coh	Ribary et al. (1991)
MEG			Sync	Sync	Sync	Stam et al. (2002); Montez et al. (2009)
EEG						van Deursen et al. (2008)
MEG					SSR	Osipova et al. (2006)
EEG					SSR	van Deursen et al. (2011)
EEG			Sync			Cook and Leuchter (1996); Locatelli et al. (1998)
EEG	Sync	Sync		Sync		Wada et al. (1998)
EEG						Petit et al. (1993)

Green fields indicate increases, red fields indicate decreases, and yellow fields indicate no changes

ATR alpha/theta ratio, *Coh* coherence, *SSR* steady-state response, *Sync* synchronization

Default Mode Network Activity in AD

As outlined above, cognitive dysfunction in AD appears to be related to disturbed integrity of large-scale networks. Disturbed large-scale activity has been confirmed in neuroimaging studies (Seeley et al. 2009), especially with respect to a reduced deactivation of the "default mode network" during resting periods following cognitive tasks (Lustig et al. 2003; Rombouts et al. 2005). Impaired deactivation in the parietal lobe (with increased activation in the temporal lobe) directly correlates with reduced performance during an episodic memory task (Pihlajamäki et al. 2008), indicating that memory impairment in AD can be related to the failure to deactivate cortical networks. Deactivation is already impaired in patients with a low degree of mild cognitive impairment (MCI) and increases in MCI patients with greater impairments and even more in mild AD (Rombouts et al. 2005; Celone et al. 2006). Furthermore, studies on young (Filippini et al. 2009) as well as old (Persson et al. 2008) APOE4 carriers revealed changes in the default network. These data indicate a potential use of default mode network analysis for the identification of patients at risk of AD. The use of such high-level functional alterations has also been suggested as a

biomarker of early AD (Sperling et al. 2010). In the future, it will be interesting to investigate whether AD-related alterations of resting-state BOLD activity are associated with changes in EEG connectivity patterns during rest.

Hyperexcitability and Epileptic Seizures

AD-pathology-related cortical hyperexcitability has been reported in AD patients following magnetic stimulation of the cortex (Di Lazzaro et al. 2004). PET studies, in which regional cerebral blood flow was estimated by measurement of radioactivity counts after injection of oxygen-15-labeled water, also showed increased activity in prefrontal regions of AD patients during memory tasks (Grady et al. 2003). Consequently, AD patients are particularly susceptible to seizures (reviewed by Larner 2010). The prevalence of seizures in AD varies between studies, but is in the range of 10–22 % (Mendez and Lim 2003). Seizure susceptibility increases with progression of the disease (Romanelli et al. 1990), and seizures are more frequent in patients with early disease onset (Amatniek et al. 2006). Amnestic episodes in patients are associated with seizures recorded by EEG, indicating that seizures not only are a concomitant phenomenon of AD, but may actually contribute to the symptoms of dementia (Rabinowicz et al. 2000). It has therefore been proposed that non-convulsive seizures may underlie disorientation and some cognitive disabilities in AD (Palop and Mucke 2009).

Animal Studies

EEG Oscillations

What are the reasons for those alterations of oscillatory activity in AD? Lesioning the nucleus basalis magnocellularis is often used to mimic a major pathological finding in AD—the loss of cholinergic fibers originating in the nucleus basalis of Meynert (Wenk et al. 1997; Bartus et al. 1982). Lesions of these neurons in the rat forebrain lead to the generation of delta waves (Buzsáki and Gage 1989), indicating that the prominent cholinergic input from this brain region maintains desynchronized EEG activity. Indeed, projections from basal forebrain neurons phasically activate cortical neurons and provide the major pathway for cholinergic modulation of cortical activity (Détári et al. 1999). As an effect, stimulation of the nucleus basalis changes cortical oscillations to higher frequencies via activation of muscarinic acetylcholine receptors (Metherate et al. 1992). Cholinergic alteration of cortical and hippocampal network activity is at least in part brought about by muscarinic modulation of inhibitory interneurons (Blatow et al. 2003; Cea-del Rio et al. 2011). Together, these findings have led to the suggestion that cognitive symptoms and slowing of the EEG in AD are both causally related to the degeneration of cholinergic neurons in the nucleus basalis (Dringenberg 2000). It should be mentioned, however, that synchronization of the EEG may also be brought about by alterations of other neuromodulators, especially by the serotonergic system (Dringenberg 2000) which is also affected in AD pathology (Cross 1990; Yamamoto and Hirano 1985). Furthermore, as described above, EEG slowing is by no means specific for AD but can also be observed in vascular dementia (Babiloni et al. 2004) or even in PD (Bosboom et al. 2006; Stoffers et al. 2007).

Important information is also provided by studies in rats following exposure to Aβ. Focal injection of Aβ into the rat hippocampus reduces theta frequency oscillations in association with a decline in cognitive performance (Villette et al. 2010). At the same time, rhythmic activity of GABAergic neurons in the medial septum-diagonal band, which are phase-locked to theta oscillations, was shown to be impaired. Septohippocampal projections are of particular importance for hippocampal theta oscillations (Buzsáki 2002), indicating that suppression of septohippocampal GABAergic cells by Aβ may be one underlying cause for hippocampal network alterations in AD. There was no detectable loss of GABAergic neurons in these studies, pointing toward a functional, rather than structural deficit in inhibition following Aβ exposure. Recently, another study examined the effect of oligomeric Aβ on sensory-induced theta rhythms (Peña-Ortega and Bernal-Pedraza 2012). Aβ was injected intraventricularly and slowed the oscillatory activity induced by sensory stimulation, in analogy to an alteration of evoked theta oscillations in patients (Cummins et al. 2008).

In several transgenic mouse models of AD, electroencephalographic activity is altered. For example, hippocampal theta oscillations are disrupted in APP-overexpressing mice (Scott et al. 2012). Increases in delta power were observed in a transgenic mouse model of AD with both Aβ and tau pathology (Platt et al. 2011). Electrophysiological changes preceded cognitive impairment, suggesting that EEG changes may be indicative for preclinical stages of the disease. In another APP-overexpressing mouse model, EEG changes (delta frequency and theta frequency) occurred at pre-plaque stages (Jyoti et al. 2010), which may indicate a causal relationship of the electrophysiological changes and non-fibrillar amyloid.

In some rodent AD models, fast waveforms have also been studied. Precise synchronization of gamma oscillations is required for the generation of long-term memories not only in humans, but also in rats (Igarashi et al. 2014). In slices from APP-transgenic mice, hippocampal gamma oscillations are strongly suppressed (Driver et al. 2007). A loss of gamma oscillations was also observed in another

Aβ overexpressing mouse strain, and this was related to dysfunctional parvalbumin-expressing interneurons (Verret et al. 2012). Administration of Aβ oligomers to hippocampal slices impairs kainate-induced fast waveforms mainly in the beta frequency range (Adaya-Villanueva et al. 2010). These data indicate that Aβ can cause an impairment of faster EEG frequencies. Consistent with findings in humans, hippocampal gamma oscillations are also decreased in mice during aging (Vreugdenhil and Toescu 2005). Interestingly, high-frequency ripple oscillations are not altered in APP-transgenic mice. When hippocampal slices of APP-overexpressing mice were analyzed at different ages for spontaneously occurring sharp wave ripple complexes, both sharp waves and ripples were similar to wild-type slices (Hermann et al. 2009).

Hyperexcitability and Epileptic Seizures

AD-related alterations of network activity have been studied in APP-transgenic mice carrying one or several mutations which increase cleavage of APP and Aβ production. Neurotransmission is impaired at pre-plaques stages, indicating that soluble Aβ, not amyloid plaques, affects glutamatergic synaptic transmission in vivo (Hermann et al. 2009). Perhaps the most severe change in network function is the generation of epileptiform activity. Seizures have been observed in several APP-transgenic mouse strains (LaFerla et al. 1995; Moechars et al. 1999; Kumar-Singh et al. 2000; Lalonde et al. 2005), indicating a relative excess of excitatory neurotransmission. Electrophysiological recordings from brains of several APP-transgenic mouse strains confirmed the occurrence of epileptiform activity (Minkeviciene et al. 2009; Palop et al. 2007). Hypersynchronous discharges were even present when mice did not exhibit any behavioral phenotype (Palop et al. 2007). Increase in neuronal activity in turn enhances the production of Aβ, suggesting that Aβ may promote its own production (Kamenetz et al. 2003). Work on transgenic mice overexpressing mutated APP or presenilin revealed an early-onset increase in activity in hippocampal neurons, whereas later disease stages were accompanied by a bimodal distribution of hyper- and hypoactive hippocampal and neocortical neurons (Busche et al. 2008, 2012). These findings may indicate that local changes in the balance of excitation and inhibition are an early network-level marker of AD, especially in the hippocampus. Whether or not this notion can be translated into a clinically detectable macroscopic marker remains open (Goutagny and Krantic 2013).

These findings have led to three hypotheses: First, Aβ may preferentially impair inhibitory neurotransmission, thereby leading to over-excitation. Second, Aβ may itself facilitate excitatory neurotransmission, and constant elevation of synaptic activity may subsequently lead to a compensatory growth of synaptic connections (Palop and Mucke 2010). Third, oscillations may be altered in AD due to a direct effect on synaptic connections. At the molecular level, there is support for all three hypotheses. Consistent with the hypothesis of preferentially impaired inhibition, it was recently shown that parvalbumin-positive inhibitory interneurons are selectively impaired in APP-transgenic mice (Verret et al. 2012). In accordance with the view of facilitated excitatory neurotransmission, Wu et al. (1995) reported a facilitation of NMDA receptor-dependent neurotransmission by Aβ. Finally, supporting the hypothesis of synaptic dysfunction, several groups have recently reported that $A\beta_{42}$ oligomers impair NMDA receptor function in vitro (Lacor et al. 2007; De Felice et al. 2007; Shankar et al. 2007; Snyder et al. 2005). Using a different preparation, Kelly and Ferreira showed that $A\beta_{42}$ oligomers cause synaptic dysfunction by depletion of the readily releasable pool of presynaptic vesicles (Kelly and Ferreira 2007). Aβ has been found to either enhance (Abramov et al. 2009) or impair (Nimmrich et al. 2008) synaptic vesicle release in hippocampal neuronal cultures. We reported that $A\beta_{42}$ oligomers suppress P/Q-type calcium currents in cultured hippocampal neurons (Nimmrich et al. 2008) and enhance calcium currents in heterologous expression systems (Mezler et al. 2012; Hermann et al. 2013). Further work is necessary to understand whether these effects selectively affect inhibitory or excitatory neurotransmission, or whether both are equally altered.

Altered Network Oscillations in AD: Clinical Implications

In the last decades, there have been extensive attempts to develop a causal therapeutic strategy for the treatment of AD. Lowering the level of amyloid (in particular through vaccinations or gamma secretase inhibitors) seemed promising, but the outcome of clinical trials has been disappointing. It has been argued that these trials included patients that already had irreversible neuronal damage and that treatments should be initiated before the manifestation of the disease (Kotzauer and Katz 2013). It is therefore fundamental to identify prodromal stages of the disease in order to initiate a therapy before irreversible degeneration has taken place. This, however, was so far hampered by the lack of a reliable biomarker that would identify patients who are prone to develop AD in future.

The required preselection of high-risk patients, however, seems principally possible as shown by recent MRI studies. For example, Sperling et al. (2010) showed an increase in cortical activity in prodromal AD or in patients at risk.

MRI studies in patients with mild cognitive impairment showed increased hippocampal activation during cognitive tasks (i.e., less deactivation), and the degree of activation was correlated with the degree of cognitive decline (Miller et al. 2008). FDG-PET analysis revealed increased cortical activity in patients with Down syndrome (Haier et al. 2003). These patients have three copies of chromosome 21, which carries the gene coding for APP, resulting in an increased risk of Aβ pathology and dementia. Asymptomatic carriers of a mutation in the presenilin 1 gene were examined by fMRI (Mondadori et al. 2006). Those carriers develop a familiar form of AD with early onset. Increased cortical activity (during memory tasks) was detected around 30 years before onset of the clinical disease. During the approximate age of clinical manifestation, brain activity was decreased, indicating that cortical hyperactivity may precede a hypoactive state, perhaps as a result of compensatory mechanisms. Sperling et al. (2010) hypothesized an "inverse U-shaped curve" of cortical excitation during the course from prodromal AD to manifest AD. As data on decreased cortical activity in manifest AD seem to be more robust than those of decreased activity in patients at risk (Sperling 2007), the diagnostic value for prodromal AD is still questionable, and additional studies are urgently required to assess the predictive value of such functional tests. It should be noted that radiotracers to predict pre-AD stages are also in use and have some predictive value for the conversion into AD, like [11C]-PIB PET (Hatashita and Yamasaki 2013; Zhang et al. 2012). Radiotracers for tau imaging are also emerging (Shah and Catafau 2014).

In addition to patient identification, drug development lacks a reliable biomarker that would allow following the progress of the disease. Although certain clinical tests, including the Mini-Mental State Examination (MMSE), are helpful tools for the diagnosis of AD, an exact diagnosis can—if at all—only be made by neuropathological analysis of brain sections. A translational approach would ideally reveal a sensitive and reliable biomarker in animal experiments which can then be translated to humans. For AD, several molecular liquor biomarkers are clinically used, but sensitivity and specificity are still unsatisfying for predictions in individual patients. EEG has the advantage of being inexpensive, noninvasive, and easily available in small clinical units. In light of the fact that parts of the EEG spectrum are specifically modified in AD, it has been suggested to use EEG as a tool for the diagnosis of AD (Claus et al. 1999). Novel quantitative EEG (qEEG) recording techniques may be particularly promising to yield a high predictive value for dementia (Prichep 2007). It has also been suggested to use EEG recordings obtained during REM sleep as a possible biomarker for AD (Montplaisir et al. 1998).

Recent studies indicate that some of the abnormal network activity in AD can be treated and that such treatment indeed leads to improved cognitive function. In a preclinical study, Sanchez et al. (2012) used the antiepileptic drug levetiracetam to diminish cortical hyperexcitability in mice overexpressing human amyloid-β. Chronic treatment with levetiracetam reverses memory deficits and normalizes long-term potentiation in these animals. Similar findings were observed in humans: In MCI patients, levetiracetam treatment diminishes hippocampal task-related hyperexcitability and improves memory (Bakker et al. 2012).

In summary, multiple lines of evidence suggest that coordinated network oscillations are pathologically altered in AD, similar to other neurodegenerative or neuropsychiatric diseases. While our knowledge is still far from complete, the observed changes give hope that changes in state-dependent oscillations can be developed into reliable biomarkers in the future. They may be of diagnostic and predictive value in early stages of AD; they may help to understand the pathophysiological processes linking neuronal loss and synaptic dysfunction to the cognitive deficits which constitute the most severe clinical symptoms of the disease. First studies to correct network dysfunction in AD are promising.

Network Dysfunction in Frontotemporal Dementia

Frontotemporal dementia (FTD) is a neurodegenerative disorder affecting prefrontal and anterior temporal cortices. In conjunction with temporal lobe symptoms, it is referred to as frontotemporal lobar degeneration (FTLD; Rosen et al. 2002). FTD may account for as many as 15 % of all degenerative dementias. Although the clinical distinction from AD is often difficult (van der Zee et al. 2008), episodic memory is usually not affected at early stages of the disease. Instead, behavioral problems and progressive loss of speech are dominating the clinical symptomatology. In contrast to AD, the EEG recordings of FTD patients are often normal upon visual inspection (Neary et al. 1998; Pijnenburg et al. 2008). However, quantitative EEG analysis revealed that FTD patients did show abnormalities as compared to control participants, although the results are currently still inconclusive. In one study, it was found that FTD patients exhibit a tendency for a decrease in fast activities (alpha and beta), whereas slow activities (delta and theta) were similar to controls (Lindau et al. 2003). The discrimination of FTD from AD could thus be via the analysis of slow activities, in particular in the delta band (Lindau et al. 2003). A decrease in EEG power in the alpha band in FTD patients was confirmed by Nishida et al. (2011) by global field power analysis. Using LORETA,

these authors also showed reduced alpha activity in frontal lobes. In contrast to Lindau et al. (2003), however, they observed an increase in beta activity. Finally, Caso et al. (2012) used quantitative EEG and LORETA to compare brain activities of patients with frontotemporal lobe dementia and AD. They found that FTD patients exhibit a widespread increase in theta power and a lower delta power relative to AD patients. There was no difference in fast activities between FTD and AD.

Seizures seem to be rare events in FTD and occur in advanced stages, although they have also been described to be a principal phenotype of an early-onset form of FTD (Sperfeld et al. 1999). In a genetic model of frontotemporal dementia with parkinsonism (FTDP-17), spontaneous epileptiform activity was recorded (García-Cabrero et al. 2013). Epileptiform activity included both interictal activity and generalized tonic–clonic seizures. This pathology is reminiscent of the seizure phenotype observed in many APP-transgenic models.

Network Dysfunction in Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disease that is characterized by progressive impairments of muscle coordination, dementia, and behavioral disturbances. It is genetically linked to an expansion of a trinucleotide motif, resulting in an expansion of the amino acid sequence of the huntingtin protein. Numerous studies report abnormal EEG in HD patients, and a common observation is a reduction in alpha amplitude (Bylsma et al. 1994; de Tommaso et al. 2003; Scott et al. 1972). Reduction in alpha activity was also observed in preclinical stages of the disease (de Tommaso et al. 2003; Ponomareva et al. 2014; van der Hiele et al. 2007). A decrease in EEG alpha power was confirmed by LORETA in a large study with 55 HD patients (Painold et al. 2011). Whereas some studies report a positive correlation of reduced alpha activity with cognitive performance (Bylsma et al. 1994; Painold et al. 2011), other studies did not find such a relationship (de Tommaso et al. 2003). Several authors link the alpha band modulation to a dysfunction of cortico-striato-thalamocortical circuits, as HD involves strong striatal atrophy (van der Hiele et al. 2007; Painold et al. 2011). Alterations of other waveforms have also been described in the literature (e.g., increase in delta activity, decrease in theta activity), but less consistently than the reduction in alpha activity.

Seizure activity also occurs in HD, although this seems to be restricted to juvenile forms (JHD). At least 38 % of JHD patients exhibit seizures, and multiple seizure types may occur in the same patient (Cloud et al. 2012). Epileptiform activity was also observed in mouse models of HD (Pignatelli et al. 2012).

Conclusions

Neuronal network dysfunction is common to all major neurodegenerative disorders. It may be a direct consequence of the spatial disintegration of highly organized neuronal networks. Subtle changes in waveform activities are often detectable by cortical EEG recordings, although the precise nature of such alterations is often not understood. Severe disturbances are sometimes present in the form of seizure activity, which probably originate from an imbalance of excitatory and inhibitory inputs. Currently, these alterations are not sufficient for a clinical discrimination between neurodegenerative disorders. Rapid advancements in high-resolution recording technologies may improve the diagnostic value of network analyses in the future.

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