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What Happens with the Circuit in Alzheimer's Disease in Mice and Humans?

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Abstract

A major mystery of many types of neurological and psychiatric disorders, such as Alzheimer's disease (AD), remains the underlying, disease-specific neuronal damage. Because of the strong interconnectivity of neurons in the brain, neuronal dysfunction necessarily disrupts neuronal circuits. In this article, we review evidence for the disruption of large-scale networks from imaging studies of humans and relate it to studies of cellular dysfunction in mouse models of AD. The emerging picture is that some forms of early network dysfunctions can be explained by excessively increased levels of neuronal activity. The notion of such neuronal hyperactivity receives strong support from in vivo and in vitro cellular imaging and electrophysiological recordings in the mouse, which provide mechanistic insights underlying the

change in neuronal excitability. Overall, some key aspects of AD-related neuronal dysfunctions in humans and mice are strikingly similar and support the continuation of such a translational strategy.

Contents

INTRODUCTION

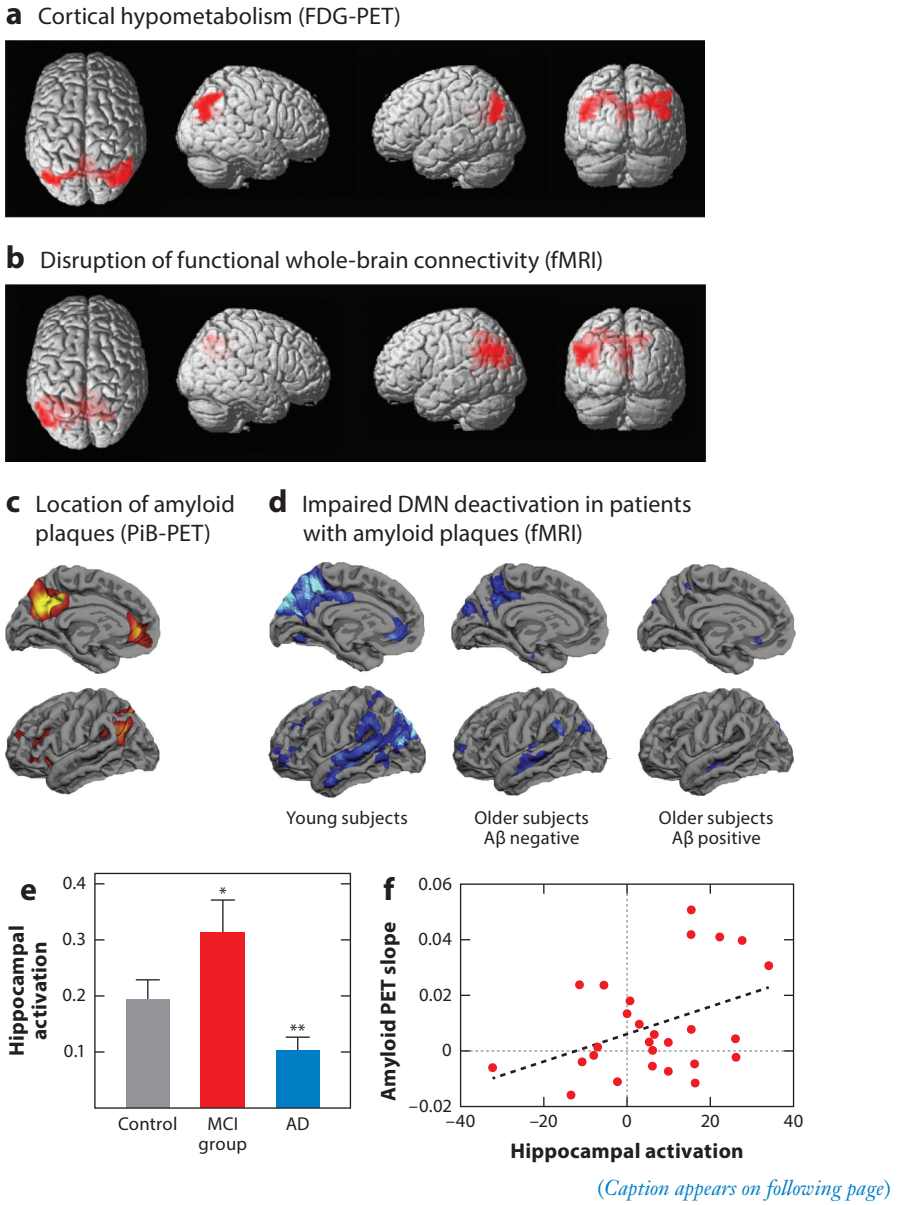
In 1907, the psychiatrist Alois Alzheimer reported postmortem pathological changes in the brain of a patient with a peculiar dementia (Alzheimer 1907, Alzheimer et al. 1995). These brain alterations, which would later be known as Alzheimer's disease (AD), included miliary foci and changes to the neurofibrils, which were later identified as amyloid-β (Aβ) plaques and neurofibrillary tangles, respectively (see Serrano-Pozo et al. 2011). Aβ peptides are derived from the neuronal amyloid precursor protein (APP) following enzymatic cleavage by β- and γ-secretases (Hardy & Selkoe 2002, Selkoe & Hardy 2016). In AD, Aβ peptides accumulate extracellularly and form soluble oligomers, fibrils, and finally amyloid plaques. Although the plaques were at first considered the primary cause of the disease, many recent studies have emphasized the potential toxicity of soluble oligomers (Barry et al. 2011, Borlikova et al. 2013, Freir et al. 2001, Jin et al. 2011, Klyubin et al. 2008, Li et al. 2009, Shankar et al. 2008, Yang et al. 2017). In addition to Aβ, other cleavage products of APP, such as the APP intracellular domain, the soluble APP, and eta-amyloid (Aη), might play a role in AD (Müller et al. 2008, 2017; Willem et al. 2015).

Because pathological brain changes and clinical symptoms are often not directly related, modern definitions make a conceptual distinction between AD, which refers to patients with neuropathological changes but without overt clinical symptoms, and full-blown Alzheimer's dementia (Jack et al. 2011). The most striking clinically observed symptom is memory loss. Brain regions prominently involved in the processing of memory, such as the hippocampus and the neocortex, are affected very early by the disease pathology (Braak & Braak 1991, Buckner et al. 2005). Accumulating evidence indicates that the neuropathological changes are paralleled by distinct changes in brain function, such as changes in neuronal plasticity and excitability and the disruption of large-scale neuronal circuits.

IMPAIRED LARGE-SCALE CIRCUITS

Early efforts to detect alterations in functional brain networks in patients living with AD used EEG recordings (reviewed in Jeong 2004). However, EEG recordings could not provide unambiguous pathophysiological information. The situation had changed decisively with the implementation of brain-imaging methods, primarily MRI and positron emission tomography (PET). In the 1970s and early 1980s, PET studies demonstrated a decreased level of brain metabolism in patients with

Alzheimer's dementia by using radiolabeled fluorodeoxyglucose (FDG) (Ferris et al. 1980), among other techniques. The main conclusion of these studies was that neurons display a pronounced decrease in their activity in AD. Since then, other researchers have confirmed this observation repeatedly (see **Figure 1*a***), and the reduced metabolism of specific brain areas, including the posterior cingulate cortex and precuneus, in FDG-PET is now used as a staging tool for the progression of AD (Dubois et al. 2014, McKhann et al. 2011). In parallel to the use of PET imaging, MRI became available for the analysis of brain changes in patients with AD and demonstrated marked brain atrophy, especially in the hippocampus, validating earlier pathological observations of postmortem brain sections (Seab et al. 1988).



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Circuit disruptions in AD—evidence from human studies. (*a*) FDG-PET imaging reveals cortical areas with decreased glucose metabolism (*red*). (*b*) Resting-state fMRI indicates disrupted cortical hubs. Voxel-based statistical group comparisons between MCI and PiB-negative healthy controls. Panels *a* and *b* adapted from Drzezga et al. (2011) with permission from Oxford University Press. (*c*) Cortical distribution of Aβ plaque load in PiB-positive subjects. Group-wise comparison with PiB-negative older subjects. (*d*) fMRI cortical maps of task-specific DMN deactivation (*blue*) in young (*left*), older Aβ-negative (*middle*), and older Aβ-positive subjects (*right*). Panels *c* and *d* adapted from Sperling et al. (2009) with permission from Elsevier. (*e*) Task-related hippocampal activation is increased in the MCI group compared with controls and patients with AD. Group mean fMRI activation data; activation is reported as the number of voxels within each region of interest that shows task-specific activation (*, $P < 0.03$; **, $P < 0.005$). Panel *e* adapted from Dickerson et al. (2005) with permission from Wolters Kluwer. (*f*) Graph of the PiB-PET imaging–derived slope of Aβ plaque accumulation versus fMRI-determined hippocampal activation at baseline. Panel *f* adapted from Leal et al. (2017). Abbreviations: Aβ, amyloid-β; AD, Alzheimer's disease; DMN, default mode network; FDG, fluorodeoxyglucose; fMRI, functional MRI; MCI, mild cognitive impairment; PET, positron emission tomography; PiB, Pittsburgh compound B.

In addition to structural MRI, functional MRI (fMRI), which measures changes in the blood-oxygen-level-dependent (BOLD) signal, became increasingly popular for the analysis of changes in the function of neurons and circuits in patients with AD. Thus, Lustig et al. (2003) and Greicius et al. (2004) were able to relate AD pathology to changes in neuronal activity in certain cortical regions. In later studies, fMRI was frequently used to investigate impaired functional connectivity between different regions of the brain. The imaging palette was completed when a variety of PET tracers for Aβ, including the widely used PET tracer Pittsburgh compound B (PiB) (e.g., Klunk et al. 2004; for review see Morris et al. 2016) and, more recently, tau (Chien et al. 2014, Johnson et al. 2016), were developed.

A widely studied network considered to be impaired in AD is the default mode network (DMN). The DMN spans different cortical areas, including the precuneus, the posterior cingulate cortex, and the lateral and inferior parietal cortices, as well as regions of the temporal and medial prefrontal cortices (Raichle et al. 2001). These brain regions are functionally strongly connected and can be further divided into subnetworks (see Uddin et al. 2009). The DMN is usually active by default, especially during internal processes such as daydreaming, introspection, and mind wandering (Buckner et al. 2008). It becomes deactivated when the attention of the subject is shifted to outwardly directed tasks such as learning new information (Daselaar et al. 2004). Whether the hippocampus is part of the DMN (Buckner et al. 2008, Ward et al. 2014) remains controversial. Therefore, we review AD-related defects in the hippocampal network separately below. The DMN is a highly conserved circuit in different mammalian species, including human and nonhuman primates and even rodents (see Buckner et al. 2008, Lu et al. 2012). The DMN is of particular interest for the study of AD. First, it includes many areas affected by the hypometabolism detected through FDG-PET (**Figure 1*a***). Second, it widely overlaps with areas of early Aβ plaque deposition (**Figure 1*c***). Additional relevance of the DMN for AD results from its role in memory encoding and retrieval. Indeed, various alterations in the DMN directly correlate with the corresponding memory impairments. Finally, fMRI studies revealed striking functional impairments in wide parts of the DMN (**Figure 1*b*,*d***), which are discussed in more detail in the following section.

A striking impairment of the DMN in AD is its decreased functional connectivity, which is revealed by resting-state fMRI. Accumulating evidence suggests that the functional disruption of DMN circuits occurs much earlier than the onset of clinical symptoms or obvious memory impairments. A decline in functional connectivity can be encountered in patients with normal

cognition but distinct Aβ plaque deposition, as indicated by PiB-PET (Hedden et al. 2009, Sheline et al. 2010b). Similarly, there is evidence that the DMN connectivity is defective in carriers of familial early-onset Alzheimer's disease (FAD) mutations at time points when cognition is still normal (Chhatwal et al. 2013). A disrupted connectivity in parts of the DMN can be observed in carriers of the apolipoprotein E (APOE) ε4 allele, the most important genetic risk factor for development of late-onset AD, even before detectable plaque deposition, cognitive impairment, or both (Sheline et al. 2010a). A recent study reported that the disrupted cortical connectivity can already be observed during the earliest accumulation of Aβ in the brain (Palmqvist et al. 2017).

AD is a neurodegenerative disease that develops slowly over several decades, and determining the relationship between the impaired connectivity and the cognitive decline is often challenging. Some studies suggest an AD-state-dependent correlation between impaired memory function and the increasingly impaired connectivity in parts of the DMN (Bai et al. 2011, Dillen et al. 2017, Liu et al. 2014). Other studies report a link between the extent of cognitive decline and the level of hyper- or hypoconnectivity in different parts of the DMN, implying that different subnetworks fail at different times during the disease (Damoiseaux et al. 2012). That parts of the DMN show pathologically increased connectivity at the beginning of the disease compared with that of healthy controls might indicate that these parts are in fact compensating for the failure of other parts of the circuit before they themselves eventually degenerate (Jones et al. 2016). Recent work suggests that poor DMN connectivity is a predictor of subsequent cognitive decline in the setting of elevated Aβ among clinically normal older individuals (Buckley et al. 2017).

Another major functional impairment of the DMN in AD, which parallels the disrupted functional connectivity, is the perturbed activity pattern of the DMN. More specifically, in contrast to the DMN activity in healthy young adults, which is high at rest and deactivates when the subjects successfully perform a task such as face-name matching (Sperling et al. 2009), the deactivation is reduced in healthy elderly people and largely absent in patients with AD (Lustig et al. 2003) (**Figure 1*d***). Such DMN-specific deficits can be detected by fMRI well before symptom onset. Indeed, deactivation deficits are already present in cognitively normal APOE ε4 carriers (Persson et al. 2008, Pihlajamäki et al. 2010) as well as in subjects with Aβ plaques but without cognitive impairment (Sperling et al. 2009). During the progression of AD, the deactivation deficits of the DMN become gradually more pronounced and can switch occasionally into a paradoxical task-specific hyperactivation of the DMN (Sperling et al. 2009). The positive correlation between the connectivity and the activity of the DMN becomes visible in memory tests. In healthy subjects there is a high correlation between task-specific DMN deactivation and memory performance (Miller et al. 2008), whereas in patients with AD memory-related DMN deactivation is impaired (see Sperling et al. 2010).

Among the widely distributed cortical areas of the DMN, the posterior parietal cortex (PPC) and the precuneus, as well as parts of the prefrontal cortex, have a particularly high degree of susceptibility to early Aβ plaque deposition (**Figure 1*c***) (Palmqvist et al. 2017). Intriguingly, these are also the cortical areas that are particularly strongly connected to many brain regions within the DMN (Buckner et al. 2008, Utevsky et al. 2014) and express strong levels of activity at rest (Buckner et al. 2005, Lustig et al. 2003). These findings might indicate that the combination of these factors predispose those areas to vulnerability for AD pathology. Independent evidence for these conclusions comes from PET imaging demonstrating decreased cortical glucose metabolism at sites with a strong decrease of connectivity, as illustrated in **Figure 1*a*,*b***(Drzezga et al. 2011).

In conclusion, PET and fMRI results provide evidence for the disruption of neuronal circuits in AD, but we are still faced with the question of whether the circuit disruption is a cause or a consequence of the disease. A related question is whether Aβ plaques are directly responsible for the AD pathophysiology. Here, it is noteworthy that the DMN dysfunction can occur before

Aβ plaque formation (Sheline et al. 2010a) or when plaques just start to form (Palmqvist et al. 2017). However, the absence of detectable Aβ plaques does not exclude increased concentrations of soluble Aβ oligomers or fibrils in those subjects. Another relevant observation may be that Aβ plaques are likely to cluster in cortical hubs with a particularly high functional connectivity (Myers et al. 2014). Finally, the increased task-specific DMN activity might directly determine an increased deposition of Aβ plaques. This hypothesis is supported by evidence from studies of mouse models suggesting a link between an increased level of neuronal activity and Aβ plaque deposition (reviewed in more detail below).

In summary, although changes in DMN connectivity and activity are now widely accepted as a useful diagnostic tool, a better understanding of the pathophysiology underlying circuit disruption in AD is needed.

HIPPOCAMPAL HYPERACTIVITY: CAUSE OR CONSEQUENCE?

The hippocampus is a brain region that has a key role in many forms of learning and memory (see Eichenbaum 2017) and, perhaps not surprisingly, is especially prone to various pathological changes in AD, including early formation of tau tangles and brain atrophy as well as, later, Aβ plaque deposition (Braak & Braak 1991, Devanand et al. 2007, Thal et al. 2002; see Serrano-Pozo et al. 2011). In line with the early onset of the structural changes, evidence exists for hippocampal dysfunction at the early stages of AD and a perturbation of the functional connections between the hippocampus and other brain regions.

There are indications that early stages of AD are characterized by increased or decreased functional connectivity between the hippocampus and other brain areas (Wang et al. 2006). In patients with AD and mild cognitive impairment (MCI), the most robust finding is decreased connectivity between the hippocampus and the PPC and precuneus regions (Allen et al. 2007, Tahmasian et al. 2015, Zhou et al. 2008). Also, studies using MRI and the diffusion tensor imaging method revealed that the structural connectivity between the hippocampus and other brain regions is significantly decreased in patients with AD (Fletcher et al. 2013, Nir et al. 2013). Together, these data support the notion of increasing functional and structural decoupling of the hippocampus that disrupts memory circuits.

What is the activity status of the hippocampus in AD? In healthy subjects, hippocampal activity increases during memory encoding of associative memory tasks such as face-name matching (Sperling et al. 2003, Zeineh et al. 2003), and memory deficits correlate especially with increased activation of the dentate gyrus and the CA3 area (Yassa et al. 2011). During the progression of AD, there seems to be a bimodal distribution of the hippocampal activity levels in memory tasks (**Figure 1*e***). Thus, early in the disease or even before symptom onset, there is pronounced hippocampal hyperactivity. For example, subjects at risk for developing AD such as APOE ε4 carriers (Bookheimer et al. 2000) as well as patients carrying mutations associated with FAD (Quiroz et al. 2010) showed increased task-specific activity of the hippocampus before symptom onset. In addition, hippocampal hyperactivity was observed in subjects with Aβ plaque deposition but without memory impairment (Mormino et al. 2012). During disease progression, which is associated with an early decline of cognitive performance, patients suffering from relatively mild memory loss usually still exhibit increased task-related hippocampal activity (Dickerson et al. 2005, Huijbers et al. 2015). However, as the cognitive decline worsens, in the stage of AD, there is evidence for a strong reduction in task-related hippocampal activity (Pariente et al. 2005) (**Figure 1*e***). The time course of the changes in the levels of hippocampal activity with the progression of the disease was confirmed in a prospective study. Patients with MCI that initially had increased hippocampal activity at baseline developed a decrease in hippocampal activation over time. Notably, the speed of

the decrease in hippocampal activity correlated with the rate of worsening memory performance (O'Brien et al. 2010). In summary, the hypothesis of the inverse U-shaped trend (Sperling et al. 2010) (**Figure 1*e***), in which initial hyperactivity is followed by a gradual switch to hypoactivity, is receiving increasing support.

The molecular and cellular mechanisms for these changes in AD were recently studied in mouse models of AD. In these mice, neuronal hyperactivity in the hippocampus occurs before the formation of amyloid plaques (Busche et al. 2012) (see section titled Analysis of Synaptic and Cellular Impairments). Moreover, other studies of mice provided evidence that higher firing rates can promote the production of Aβ (Cirrito et al. 2005, Dolev et al. 2013, Kamenetz et al. 2003, Yuan & Grutzendler 2016). Brain areas that are more active seem to be more prone to Aβ plaque deposition (Bero et al. 2011). Hyperactive neurons in the vicinity of newly formed amyloid plaques (Busche et al. 2008) could then close the vicious circle of hyperactivity and amyloid accumulation. Such a possible link between hyperactivity and Aβ plaque deposition finds support in human studies. Recent reports of patients with MCI indicated that hippocampal activity is associated with subsequent amyloid plaque deposition as well as hippocampal atrophy and memory decline (Huijbers et al. 2015, Leal et al. 2017). Most remarkably, the level of hippocampal hyperactivity predicted the slope of further amyloid plaque accumulation (**Figure 1*f***). Furthermore, the slope of Aβ plaque accumulation indicates the magnitude of cognitive decline during the next three to four years (Leal et al. 2017). In line with these observations, the pharmacological treatment of excessive hippocampal activity can ameliorate memory deficits. Recently, two studies indicated that the treatment of hippocampal hyperactivity, as monitored in the dentate gyrus and CA3 hippocampal regions, with the antiepileptic drug levetiracetam can partially restore memory performance in patients with MCI (Bakker et al. 2012, 2015). Studies of mice are consistent with these observations and suggest a causal link between hippocampal hyperactivity and memory impairment. Two studies reported a partial restoration in cognitive function upon treatment of rodent disease models with levetiracetam (Koh et al. 2010, Sanchez et al. 2012).

In conclusion, accumulating evidence from studies of humans and mice suggests a causal role of hippocampal hyperactivity at the early stages of AD. However, the establishment of hippocampal hyperactivity as a viable target for disease-modifying interventions requires more validation and additional translational efforts.

SLEEP, BRAIN OSCILLATIONS, AND MEMORY CONSOLIDATION

Sleep disturbances represent a prevalent symptom in many patients with AD (Zhao et al. 2016). Remarkably, sleep disturbance can be an early symptom in individuals with Aβ plaque deposition, or other pathological markers of the disease, precede pronounced memory decline (Spira et al. 2013, Sprecher et al. 2017) and become worse as the disease progresses (Liguori et al. 2014). Most intriguingly, the magnitude of the sleep deficits is correlated with memory loss, both in healthy adults and in patients with AD, suggesting a direct link between sleep quality and memory performance (Ficca et al. 2000, Westerberg et al. 2010). Importantly, not only is sleep disturbance a passive symptom of AD but increasing evidence indicates it can influence disease progression and worsen the symptoms, such as impaired memory consolidation. Thus, sleep times of less than 6.5 h per night increase the risk for cognitive decline in healthy patients (Keage et al. 2012). Also, higher sleep fragmentation is associated with a higher risk for developing AD (Lim et al. 2013a). In APOE ε4 carriers, subjects with better sleep quality are less likely to develop AD (Lim et al. 2013b). Finally, patients with sleep disturbances have abnormal levels of Aβ in cerebrospinal fluid (CSF) (Ju et al. 2013, Sprecher et al. 2017), and there is a correlation between impaired sleep quality, including sleep duration, and cortical amyloid plaque load (Spira et al. 2013).

How are sleep disturbances linked mechanistically to AD? Studies reported that the levels of soluble Aβ in CSF or interstitial fluid fluctuate during the sleep-wake cycle in mice or humans (Huang et al. 2012, Kang et al. 2009). These diurnal fluctuations are prominent before plaque formation and disappear after Aβ plaques are formed (Huang et al. 2012, Roh et al. 2012). Increasing evidence indicates that sleep disruption itself can determine the levels of Aβ in the CSF. Thus, short-time sleep deprivation can disrupt the diurnal fluctuation cycle of Aβ in the brain, and sleep deprivation for even just one night can increase the level of Aβ in CSF in healthy subjects (Ooms et al. 2014, Wei et al. 2017). Similarly, in patients with MCI, there is a correlation between impaired slow-wave sleep and increased levels of Aβ in blood plasma (Sanchez-Espinosa et al. 2014). The diurnal fluctuations in levels of Aβ may depend on many factors, including Aβ production by active neurons and the clearance of Aβ from the brain. In patients with late-onset AD, Aβ clearance was reported to be impaired, whereas the production rate, at least in the awake state, was normal (Mawuenyega et al. 2010). Potentially groundbreaking insights came from the recent identification of a glymphatic system (Xie et al. 2013). According to this model, during the sleep phase, glia cells shrink and the extracellular space widens correspondingly. This opens pathways that facilitate the transport of extracellular waste products, such as soluble Aβ, from the interstitial space.

At the circuit level, increasing evidence supports the notion that neuronal processing, particularly during non-REM (rapid eye movement) sleep, is important for memory consolidation. During this slow-wave sleep, recently acquired memories are thought to be transferred from short-term storage sites in the hippocampus to long-term memory storage sites in the neocortex (see Diekelmann & Born 2010). Experimental evidence obtained from rodents indicates that during slow-wave sleep there is repeated replay of hippocampal signaling patterns that were learned in the awake state (Wilson & McNaughton 1994). A similar form of replay takes place in humans during slow-wave sleep, as evidenced by studies of hippocampal activities in subjects tested during virtual reality maze trips and the following stages of sleep (Peigneux et al. 2004). Various studies underscored the importance of undisturbed slow-wave sleep for effective memory consolidation in healthy adults (Mander et al. 2014, Mednick et al. 2003, Takashima et al. 2006). The electrophysiological correlate of memory consolidation in non-REM sleep is cortical slow oscillations (Steriade et al. 1993), which are inherently linked to higher-frequency EEG rhythms, such as sleep spindles and hippocampal sharp-wave ripples (Staresina et al. 2015, Steriade 2006). There is a strong bidirectional link between those oscillations, their coordination, and memory consolidation (Clemens et al. 2005, Helfrich et al. 2018). On the basis of experiments using transcranial current stimulation (Marshall et al. 2006), auditory loop stimulation (Ngo et al. 2013), or pharmacological approaches (Mednick et al. 2013) in healthy adults, evidence suggests that enhancing slow-wave activity, associated sleep spindles, or both during sleep can boost memory performance. A recent study has even suggested a beneficial effect of enhancing sleep slow oscillations by transcranial direct current stimulation on memory in patients with early AD (Ladenbauer et al. 2017). Conversely, selective disruption of slow waves during sleep without changing overall sleep time can impair memory consolidation in healthy subjects (van der Werf et al. 2009).

In AD patients, disruption of slow-wave sleep can occur at early stages of the disease. Thus, APOE ε4 carriers at risk for developing AD (Hita-Yanez et al. 2012) as well as patients suffering only from mildly impaired memory performance (Westerberg et al. 2012) showed impaired slow oscillations during sleep. Particularly relevant is a recent study in which Mander et al. (2015) combined PET, fMRI, EEG, and memory tests to study the status of slow oscillations in AD. They found that the medial prefrontal cortex, a cortical region with a high susceptibility for slow wave generation (Murphy et al. 2009), is particularly prone to massive cortical Aβ plaque deposition (**Figure 2**). Their findings suggest that the Aβ plaque load in the medial prefrontal

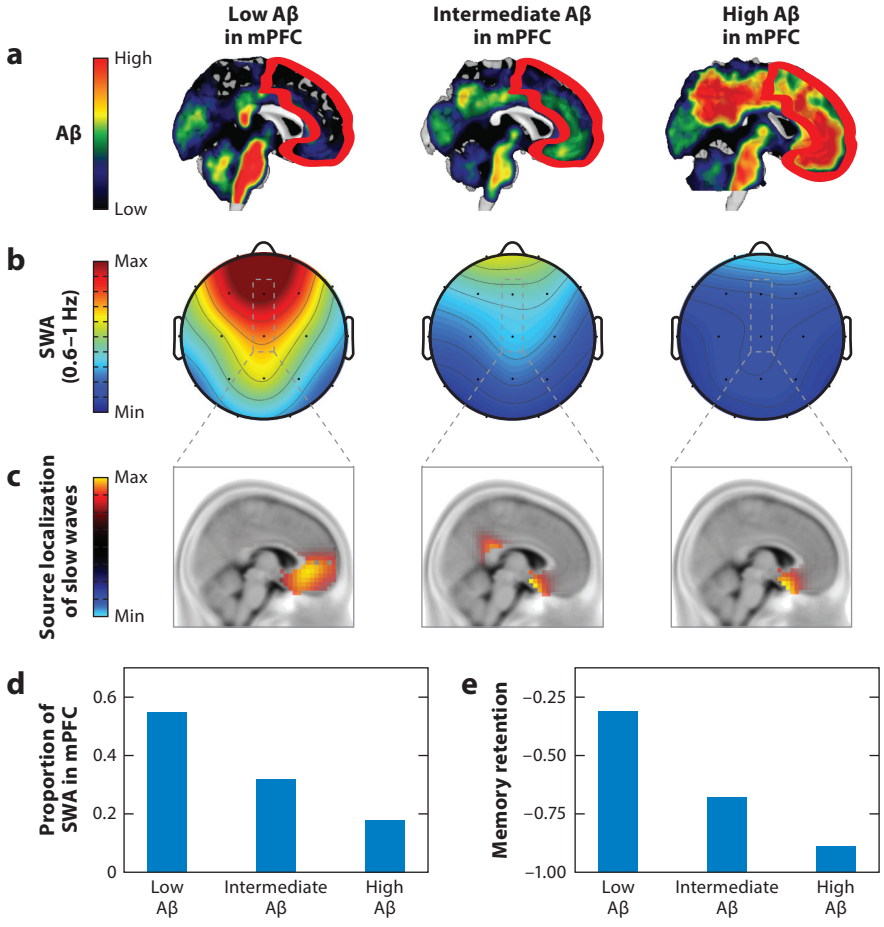


Figure 2

Aβ plaque load, slow oscillations during sleep, and memory performance in subjects without cognitive impairments. (*a*) Aβ plaque load measured with PiB-PET from subjects with low (*left*), intermediate (*middle*), and high (*right*) plaque load, respectively. The red outline indicates the location of the mPFC. (*b*) EEG-based maps of the power of sleep SWA (0.6–1 Hz) for the three subjects in panel *a*. (*c*) Corresponding source localization of mPFC slow waves for the three subjects in panel *a*. (*d*) Proportions of sleep SWA for the three subjects in panel *a*. (*e*) Memory retention for the three subjects in panel *a*. Panels *a–e* adapted from Mander et al. (2015) with permission from Macmillan Publishers Ltd. Abbreviations: Aβ, amyloid beta; mPFC, medial prefrontal cortex; PET, positron emission tomography; PiB, Pittsburgh compound B; SWA, slow-wave activity.

cortex can predict the level of impairments of slow oscillations during sleep and the worsening of memory performance.

Independent evidence for the disruption of slow-wave activity in AD also comes from studies that were performed in mouse models of β-amyloidosis. Experiments combining electrophysiology and calcium imaging, representing a direct and accurate way to probe for neuronal activity, demonstrated that the coherence of slow waves between different cortical regions, the hippocampus, and the thalamus is completely disrupted in an APP23 × PS45 mouse model compared with wild-type controls (**Figure 3*a–c***) (Busche et al. 2015b). Consistent with this observation, the acute

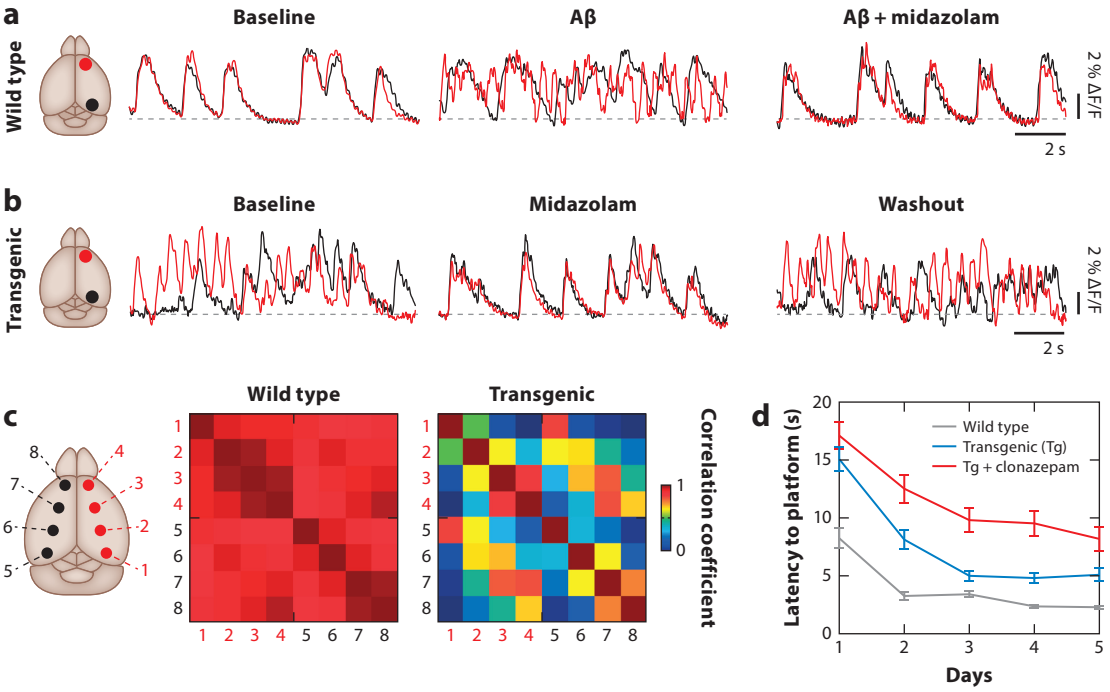


Figure 3

Disrupted cortical slow-wave oscillations in a transgenic mouse model of AD in vivo. (*a*) Overlay of SWA traces in the frontal (*red*) and occipital (*black*) cortices monitored with wide-field calcium imaging in a wild-type mouse (*left*). The application of soluble Aβ disrupts the synchrony of SWA (*middle*). Rescue of SWA by midazolam (*right*). (*b*) Disrupted SWA in the transgenic APP23 × PS45 mouse model of AD (*left*). The correlation can be transiently restored by application of midazolam (*middle* and *right*). The sites of recording are indicated in the corresponding schematics (*leftmost images*). (*c*) Disrupted SWA in transgenic AD mice. Cross-correlation matrices for eight cortical recording sites (as indicated) in wild-type (*left*) and transgenic AD mice (*right*). (*d*) Improvement of memory performance in a water maze test performed over five consecutive days in wild-type (*gray*), transgenic untreated (*red*), and clonazepam-treated transgenic (*blue*) mice. Panels *a–d* adapted from Busche et al. (2015b) with permission from Springer Nature. Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; PS, presenilin-1; SWA, slow-wave activity.

application of synthetic Aβ alone could also elicit such a breakdown of slow-wave coherence in wild-type mice. Conversely, slow oscillations in both AD mouse models and wild-type mice treated with Aβ were restored by increasing synaptic inhibition with GABA receptor agonists such as benzodiazepines (**Figure 3*a*,*b***). Remarkably, restoring slow oscillations also rescued normal memory function in those mice (**Figure 3*d***). In line with these findings, the pharmacological suppression of Aβ production with a BACE (β-secretase) (Neumann et al. 2015) inhibitor effectively restored neuronal and circuit dysfunction as well as memory deficits (Keskin et al. 2017). These results provide encouraging evidence that neuronal impairments can be restored even during late-stage AD.

ANALYSIS OF SYNAPTIC AND CELLULAR IMPAIRMENTS

Neuroanatomical and in vitro physiological studies suggest that synaptic impairment is a key pathomechanism underlying AD. In fact, synapse loss correlates more strongly with cognitive decline than do the numbers of plaques, tangles, or lost neurons (DeKosky et al. 1996, Masliah et al. 1994, Terry et al. 1991). Experimental studies even showed that synaptic dysfunction and

loss (i.e., synaptic failure) (Selkoe 2002) begin to occur at the earliest stages of pathology, prior to plaque formation and independent of neurodegeneration (D'Amelio et al. 2011, Hong et al. 2016, Hsia et al. 1999, Lanz et al. 2003, Roy et al. 2016). In line with these synaptic impairments and in view of the loss of memory in demented patients, it is of major interest to know how the cellular correlates of learning and memory, long-term potentiation (LTP) and long-term depression (LTD), are affected. For such an analysis, water-soluble extracts from patients with AD were applied to rodent hippocampal slices and shown to inhibit LTP or enhance LTD (Barry et al. 2011, Klyubin et al. 2008, Li et al. 2009, Shankar et al. 2008). Removal of Aβ from the extracts prevented these effects. Moreover, the acute exposure to synthetic or naturally secreted Aβ oligomers produced similar impairments in plasticity (Freir et al. 2001, Lambert et al. 1998, Walsh et al. 2002). Accumulating evidence indicates that a small pool of low-molecular-weight (LMW) oligomers, including dimers, trimers, and Aβ*56, are more potent in producing such synaptic and cognitive impairments than are high-molecular-weight oligomers (Lesne et al. 2006, Yang et al. 2017), which are much more prevalent in the AD brain (Yang et al. 2017). Intriguingly, picomolar concentrations of Aβ increased LTP in hippocampal slices, pointing toward a potential physiological role of extremely low amounts of Aβ in learning and memory processes (Puzzo et al. 2008).

Spine loss can occur independently of the formation of Aβ plaques (Hsieh et al. 2006, Jacobsen et al. 2006, Shankar et al. 2007, Spires et al. 2005, Wei et al. 2010). In fact, in the human AD brain, the levels of soluble Aβ, rather than plaques, are strongly correlated with the extent of synaptic loss (Lue et al. 1999). Hong et al. (2016) showed, for example, that injections of LMW dimers into the ventricles of wild-type mice were sufficient to induce substantial synapse loss within 3 days. The results indicated that synapses were eliminated by phagocytic microglia cells, which were activated by the deposition of the complement factor C1q at synapses. Such a mechanism is intriguing, as recent genome-wide association studies implicate microglia and complement pathways in AD (Mhatre et al. 2015). Furthermore, in vivo ratiometric calcium imaging in wild-type mice exposed to Aβ oligomers revealed that abnormal increases in intracellular calcium levels immediately precede the loss of synapses (Arbel-Ornath et al. 2017). In later stages of AD, synapse loss appears to be maximal at locations near amyloid plaques (Spires et al. 2005). Intriguingly, Aβ oligomers are also most abundant in the vicinity of plaques and accumulate at pre- and postsynaptic sites (Koffie et al. 2009), strongly suggesting their direct role in synaptic modifications. Their actions are not restricted to neuronal cell bodies but have a pathological effect on neurites (Kuchibhotla et al. 2008), astrocytes (Kuchibhotla et al. 2009, Pekny et al. 2016), and microglia (Prinz et al. 2011).

Because synaptic failure and plasticity defects were expected to result in the silencing of neurons, it was surprising that many neurons were hyperactive under in vivo conditions in mouse models (Busche et al. 2008, 2012, 2015a,b; Grienberger et al. 2012; Keskin et al. 2017; Liebscher et al. 2016; Maier et al. 2014; Rudinskiy et al. 2012; Scala et al. 2015; Siskova et al. 2014; Xu et al. 2015) (**Figure 4*a*,*b***). This hyperactivity is responsible for alterations of the sensory integration in the cortex and the corresponding behavioral defects. Thus, in the visual cortex of APP23 × PS45 mice, hyperactive neurons lose their ability to respond selectively to the orientation and direction of visual stimuli (Grienberger et al. 2012). This neuronal defect was associated with deficits in a visual pattern discrimination task. In line with these observations, electrophysiological studies of the hippocampus of aged rats revealed that hyperactivity impairs the ability of neurons to encode spatial locations (Koh et al. 2010, Wilson et al. 2005). Furthermore, hyperactivity can exacerbate and cause, in transgenic AD mouse models, epileptiform discharges as well as spontaneous, recurrent seizures (**Figure 4*c*,*d***) (Born 2015, Palop et al. 2007, Verret et al. 2012). A similar susceptibility to epilepsy is often observed in patients with AD (Scarmeas et al. 2009, Vossel et al. 2016).

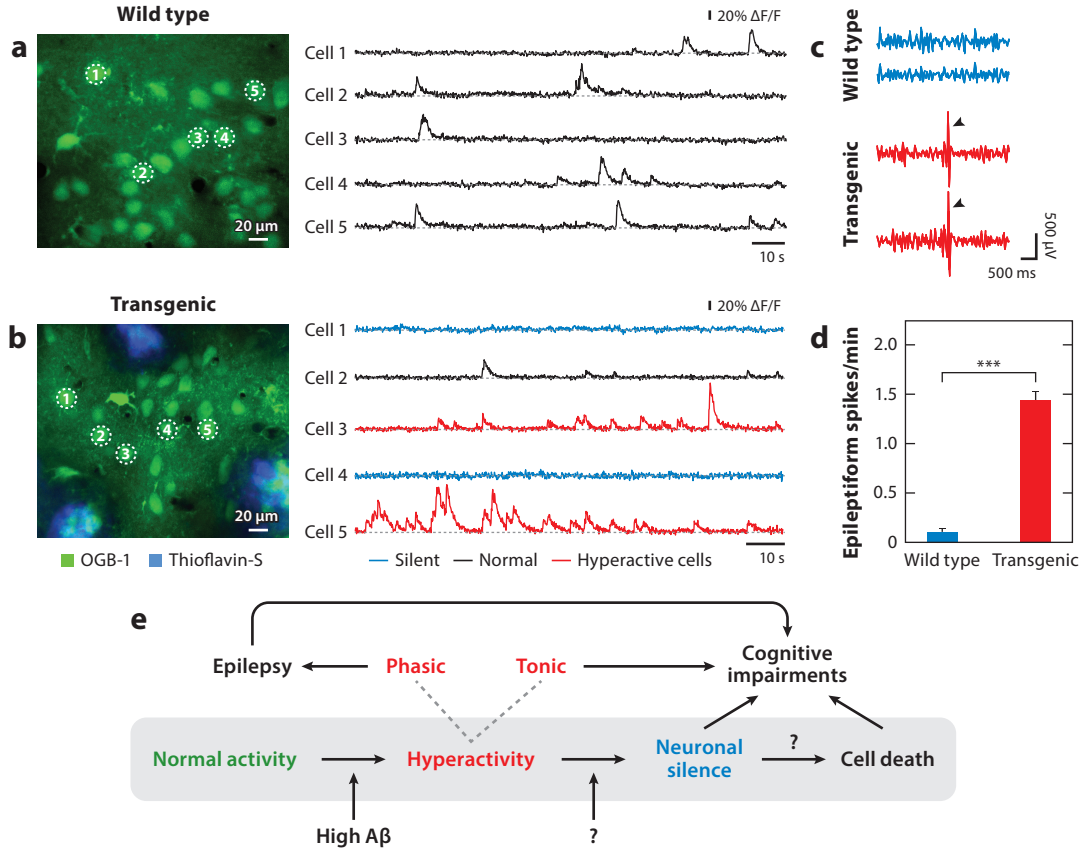


Figure 4

Impaired neuronal activity in mouse models of AD in vivo. (*a*) Two-photon calcium imaging recordings of spontaneous activity from layer-2/3 neurons (indicated as cells 1 through 5) in the frontal cortex of a wild-type mouse in vivo. The position of the neurons is indicated in the image on the left. (*b*) Recordings in an APP23 × PS45 transgenic mouse from a neuron with normal activity (*black*, cell 2), hyperactive neurons (*red*, cell 3 and cell 5), and silent neurons (*blue*, cell 1 and cell 4). In panels *a* and *b* the cortex was stained with the calcium indicator OGB-1 (*green*) and plaques were labeled with thioflavin-S (*blue*). Panels *a* and *b* adapted from Busche et al. (2008) with permission from AAAS. (*c*) Cortical EEG recordings from a wild-type mouse and a hAPPJ20 transgenic mouse. Arrowheads depict epileptiform spikes. (*d*) Epileptiform spike frequency in wild-type and transgenic mice; summary plot from panel *c* (***, $P < 0.001$). Panels *c* and *d* reprinted from Verret et al. (2012) with permission from Elsevier. (*e*) Schematic model indicating the sequence of events that may underlie the progression of neuronal dysfunction in AD. Reproduced from Busche & Konnerth (2015) with permission from Wiley. Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; OGB-1, Oregon green-BAPTA-1; PS, presenilin-1.

There is now substantial evidence that neuronal hyperactivity, both in the hippocampus and in the cortex, is directly mediated by Aβ, most likely in the form of soluble LMW oligomers. First, brain levels of Aβ correlate strongly with the amount of hyperactive cells in the cortex (Keskin et al. 2017). Second, suppression of Aβ production by γ-secretase (acute) or β-secretase (chronic) can rescue the hyperactivity phenotype in the hippocampus and cortex (Busche et al. 2012, Keskin et al. 2017). Third, reintroduction of soluble Aβ oligomers to mice that were successfully treated with a BACE inhibitor resulted in the recurrence of cortical hyperactivity (Keskin et al. 2017). Finally, local application of Aβ dimers to hippocampal neurons induced hyperactivity (Busche et al. 2012). That hyperactive neurons cluster around plaques at later stages of AD is not surprising because

plaques are surrounded by a halo of Aβ oligomers (Keskin et al. 2017, Koffie et al. 2009). Calcium overload in neuronal processes also seems to be due to the action of Aβ oligomers around plaques (Arbel-Ornath et al. 2017). Experimental evidence obtained in mouse models of AD indicates that soluble Aβ produces neuron-specific alterations of the excitation/inhibition (E/I) balance (Busche & Konnerth 2016, Busche et al. 2008). The E/I balance can be restored to normal levels, as indicated by experiments in which the pharmacological enhancement of GABAergic inhibition through the administration of benzodiazepines prevented cellular hyperactivity. Moreover, this treatment restored slow-wave oscillations and ameliorated memory deficits (**Figure 3*b*,*d***) (Busche et al. 2008, 2015b). A recent remarkable observation is that the interaction between oscillations and Aβ is bidirectional. There is evidence that the restoration of oscillatory activity can prevent plaque formation (Iaccarino et al. 2016, Kastanenka et al. 2017). Aβ-dependent impairments of synaptic inhibition can account for many of the known defects in the AD brain, including impairments of gamma and slow oscillations, epileptic activity and seizures, and hippocampal BOLD hyperactivation, as well as cognitive impairments (Bakker et al. 2012, Busche et al. 2015b, Palop & Mucke 2016, Verret et al. 2012). Even though Aβ can interact with multiple receptors and proteins at the synapse, other mechanisms, such as impaired glutamate homeostasis (Fogel et al. 2014, Kamenetz et al. 2003, Li et al. 2009), may shift the E/I balance toward excitation.

In addition to the presence of hyperactive neurons, a considerable fraction of neurons are hypoactive and even functionally completely silent in mouse models of AD (**Figure 4*a*,*b***) (Busche et al. 2008, 2012). Actually, such hypoactivity was more in line with the original synaptic failure hypothesis (Selkoe 2002). The hypoactivity was caused partly by an increase in synaptic inhibition (Busche et al. 2008). During the progression of the disease, hypoactive neurons occurred later than hyperactive neurons and were found only after plaque formation (Busche et al. 2012). Sensory responses to external stimuli are absent in these cells, even after spontaneous activity is restored by application of a $GABA_A$ antagonist (Grienberger et al. 2012). Although the presence of amyloid plaques seems to be required for hypoactivity, Aβ does not directly promote silencing of neurons in vivo. Hypoactivity may be a consequence of excessive hyperactivity, which may result in increased but maladaptive compensatory inhibition to prevent excessive firing (Busche & Konnerth 2015). However, the molecular mechanisms underlying hypoactivity may be more complex, as recent evidence points to the presence of a previously unknown but prevalent fragment of APP, Aη-alpha, that can directly promote silencing of neurons in vivo and inhibit LTP in vitro (Willem et al. 2015). In summary, there is now ample evidence from both in vitro and in vivo studies that Aβ impairs the functions of synapses, neurons, and larger circuits. Aβ exists in multiple forms in the brain—from monomers to plaques—but the small pool of LMW oligomers appears to be responsible for most of the known neuronal deficits. Aβ oligomers attack synapses, resulting in widespread plasticity defects as well as synapse dysfunction and loss. As a consequence, there is the expected silencing of circuits but, remarkably, also neuronal hyperactivity and epileptic activity. Together these effects may lead to cognitive impairments over time (**Figure 4*e***).

CONCLUSIONS

Neuronal circuits are functionally impaired even at early stages of AD, often before the onset of overt symptoms of dementia. The constant improvement of imaging technologies is increasingly used to develop better biomarkers for AD in PET studies and to improve fMRI analyses of those brain regions strongly affected by the disease. New variants of multimodal imaging provide better insights into the changes that occur in different cortical areas, including the DMN, and in the hippocampus. There is growing evidence that circuit disruption occurs early during the progression of the disease and that some dysfunctions are triggered by excessive levels of neuronal activity,

particularly in the hippocampus. How helpful are mouse studies? Mouse models of β-amyloidosis have many limitations, related mostly to the short lifetime of mice, the lack of brain atrophy, and the uncontrolled expression of Aβ in many transgenic models. Therefore, it is surprising that some of the neuronal impairments, primarily the sustained hyperactivity and the susceptibility to epilepsy as well as the impairment of the circuits underlying brain oscillations and memory consolidation, are remarkably well conserved in mice. Thus, mouse models seem to be particularly useful for the analysis of early dysfunctions of neurons and circuits. We anticipate that concerted studies of humans and appropriately tailored mouse models will have a strong potential to clarify those pathophysiological mechanisms needed for the design of effective treatments.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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