Review

Unsupervised excitation: GABAergic dysfunctions in Alzheimer's disease

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Highlights:

- **Review of the literature on GABAergic dysfunction in mouse models of AD**
- **GABAergic dysfunction from the human perspective**
- **Special focus on the relation to neuronal network dysfunction**

Abstract

Alzheimer's disease (AD) is characterized by the classical hallmarks of Aβ-deposition and tau-pathology that are thought to ultimately lead to synapse and neuron loss. Although long known, neuroinflammation has recently attracted a substantial amount of attention by researchers due to genome wide association studies (GWAS) that identified microglia associated genes to be correlated with sporadic AD. Besides that, cholinergic degeneration and gamma-aminobutyric acid (GABA) abnormalities have been identified in the brains of AD patients already decades ago, but have not received much attention over the last ten years. Recently, the neuronal network dysfunction hypothesis has revived interest in how impairments of neuronal communication at the network level lead to epileptiform activity and disrupted oscillations observed in the brains of AD patients and mouse models. Thereby, deficits in neuronal networks involved in learning and memory might ultimately cause memory impairments. In this context, an imbalance between excitation and inhibition has been hypothesized to contribute to neuronal network dysfunction. Here, disturbances of cholinergic and GABAergic transmission might play a crucial role. In this review, we will focus on GABAergic dysfunction in AD and mouse models of AD and how those might relate to neuronal network aberration and memory impairment.

Keywords:

Alzheimer's disease, GABAergic neurons, inhibition excitation balance, neuronal network dysfunction hypothesis, mouse model of AD, human AD

Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's disease
ApoE ε4	Apolipoprotein E ε4
APP	Amyloid precursor protein
BAC	Bacterial artificial chromosome
CA1	Cornu ammonis 1
Ca^{2+}	Calcium
ChAT	Choline acetyltransferase
Cl^-	Cloride
CR	Calretinin
DG	Dentate gyrus
EEG	Electroencephalography
eGFP	Enhanced green fluorescent protein
FAD	Familial Alzheimer's disease
FTD	Fronto temporal dementia
FYN	Proto-oncogene tyrosine-protein kinase Fyn
GABA	Gammy-aminobutyric acid
GAD1	Glutamate decarboxylase 1
GWAS	Genome wide association studies
K^+	Potassium
KCC2	K^+ – Cl^- co-transporter 2
KI	Knock in
MGE	medial ganglionic eminence neurons
MRI	Magnet resonance imaging
mRNA	Messenger ribonucleic acid
MRS	Magnet resonance spectroscopy
Nav1.1	Voltage-gated sodium channel type1
NMDAR	N-methyl-D-aspartate receptor
NPY	Neuropeptide Y
PET	Positron emission tomography
PMI	Post mortem interval
PV	Parvalbumin
PS	Presenilin
PS1	Presenilin 1
qPCR	quantitative polymerase chain reaction
SOM	Somatostatin
SPECT	Single-photon emission computed tomography
TREM2	Triggering receptor expressed on myeloid cells 2)
3xTgAD	Tripple transgenic mouse model of AD

1. Introduction

For almost a century, Alzheimer's disease (AD) has been in the spotlight of researchers and clinicians that have both described the pathology and tried to understand its etiology. AD is the most prevalent cause and form of dementia worldwide (Scheltens et al., 2016). Therefore, it does not come as a surprise that distinct individuals affected by the pathology present a plethora of symptoms that may be more or less aggravated by a complex interplay of environmental and genetic factors. Moreover, these confounding factors are paralleled by the lack of knowledge about the molecular and cellular mechanisms behind the pathology,

Consequently, the multiple efforts made to combat and cure the deleterious symptoms of AD patients have yielded dramatically poor results. Neurodegenerative diseases encompass multiple pathological processes that only at later, irreversible stages culminate with neuronal loss (Palop et al., 2006). In the context of AD and other neurodegenerative disorders like Parkinson's disease, newly identified pathophysiological processes have opened promising perspectives towards the development of more effective and specific treatments for the disease. These are aimed at reinstating the equilibrium in the pathologically disturbed system at an early stage, rather than at reverting the system to its healthy state once the pathology is full-blown. In particular, emerging evidence supports the view of an imbalance between excitation and inhibition in the central nervous system to be an exacerbating factor, if not one of the causes of AD (Frere and Slutsky, 2018; Palop et al., 2006; Palop and Mucke, 2016). Consequently, increasing interest has been directed towards the role of gamma amino butyric acid (GABA)-secreting inhibitory neurons, and their dysfunction under AD conditions.

Information processing within the brain requires precise temporal and spatial control of action potential transmission within and between neural populations that fire in a concerted way (Panzeri et al., 2015). Both the recruitment and modulation of distinct neuronal populations are brought about by a wide variety of inhibitory neurons, whose morphological and physiological diversity reflects their capability to exert effective and specific regulatory control on all compartments of the targeted cells (Roux and Buzsaki, 2015). By gating and modulating all aspects of signal transmission (i.e. from integration of an input to production of an output), inhibitory neurons orchestrate computations at the synaptic, cellular and network scales (Klausberger and Somogyi, 2008; Roux and Buzsaki, 2015). Malfunctions in one of these processes will trigger a cascade of events that can ultimately cause severe behavioral and cognitive defects (Palop et al., 2006; Palop and Mucke, 2010). Indeed, inhibitory neuron dysfunction and its consequences have been appointed as pathological processes underlying not only neurodegenerative disorders such as AD, but also neuropsychiatric disorders like schizophrenia (Uhlhaas and Singer, 2012).

The diversity of inhibitory neurons is most evident in the hippocampus and neighboring brain regions. Here, more than 20 types of inhibitory neurons, defined by molecular markers such as neuropeptide content (Baraban and Tallent, 2004), control and shape the firing of the relatively uniform population of excitatory pyramidal cells (Freund and Buzsaki, 1996; Klausberger et al., 2003; Klausberger and Somogyi, 2008; Kullmann, 2011; Roux and Buzsaki, 2015). Inhibitory neuron control is engaged in response to sensory stimuli (for review, see (Roux and Buzsaki, 2015)), during specific behavioral states (Arriaga and Han, 2017; Katona et al., 2016; Katona et al., 2017; Lapray et al., 2012) or during higher order computations such as memory encoding or recall (Allen et al., 2011; Fuchs et al., 2007; Korotkova et al., 2010; Lovett-Barron et al., 2014; Murray et al., 2011; Ognjanovski et al., 2017). Besides, ever since the discovery of place cells, grid cells, and other spatially tuned cells in the hippocampal system (Hafting et al., 2005; O'Keefe, 1976), researchers have tried to disentangle whether and how each class of inhibitory neurons contributes to the emergence of these unique firing patterns in excitatory neurons (Buetfering et al., 2014; Miao et al., 2017; Royer et al., 2012). Being readily accessible for *in vivo* imaging and electrophysiological measurements, and being among the first regions to be affected in AD (Braak and Braak, 1991), the hippocampal system has been the primary focus of multiple studies carried out in animal models of AD (Booth et al., 2016; Busche, 2018; Cayzac et al., 2015; Gu et al., 2014; Schmid et al., 2016; Siskova et al., 2014). Hence, a number of articles have already elucidated how disrupted hippocampal place-cell (Cacucci et al., 2008; Cheng and Ji, 2013; Mably et al., 2017; Zhao et al., 2014) and entorhinal grid-cell firing (Fu et al., 2017) are pathological signatures of mouse models of beta amyloidosis and tau pathology., providing a potential explanation for the typical disorientation and loss of spatial memory observed in AD patients and transgenic mice. However, whether andhow inhibitory neuron dysfunction may worsen or provoke aberrant functionality of spatially modulated cells is still to be elucidated.

In conclusion, inhibitory neurons are key for the proper timing and coordination of neural populations within and between brain regions, and hence for the maintenance of the physiological state of the central nervous system. This places them in a position of particular interest in the context of diseases such as Alzheimer’s, as one of the first symptoms observed is the presence of epileptiform activity in the electroencephalogram (EEG) of patients that will develop dementia. This argues for an early alteration of the physiological inhibition/excitation balance, which may be the first event of a cascade ultimately culminating in neurodegeneration.

In the next paragraphs, we will summarize relevant studies that have investigated how impaired inhibitory neuron number and function is related to various AD mouse models and human patients.

2. GABAergic dysfunction in mouse models of AD

The multi-faceted nature of AD is reflected by the numerous animal models that have been generated to study many aspects of the familial form of the disease (for review see (Hall and Roberson, 2012)). These mouse models are genetically unique, as they carry specific sets of mutations that are found in the human conditions. Further, within each mouse model, the time of investigation introduces substantial phenotypical variations, as the pathology follows a progressive time course the same way the human does, but at a shorter scale. Most mouse models of AD that have been generated are based on three genes and their genetic mutations with the aim to mimic the main pathological hallmarks of AD – Aβ- and tau-pathology. There are 160 mouse models of AD available today (https://www.alzforum.org/research-models/alzheimers-disease). To mimic Aβ-pathology, mutations in the human gene for the amyloid precursor protein (APP) that accelerate Aβ-generation have been reintroduced into the mouse. These mutations in the *APP* gene lead to an accumulation of Aβ due to the preferred cleavage of APP at the γ-secretase cleavage site favoring the amyloidogenic pathway. Human mutations in the presenilin (PS) genes have been combined with *APP* mutations to accelerate Aβ-generation even more (Radde et al., 2008). Surprisingly, *PS* mutations alone did not lead to full AD-like pathology in mice (Elder et al., 2010). They always had to be combined with *APP* mutations. Moreover, most mouse models based on *APP* or *APP/PS* mutations usually were generated on an intact mouse *App* and *Ps* background, which was rarely controlled for. However, the overexpression of *APP* or *APP/PS* mutations under different promoters directed the expression either intracellularly for example in the case of *thy1.2* promoter (Willuweit et al., 2009) or extracellularly in the case of the prion protein (*Prp*) promoter (Jankowsky et al., 2004; Kalback et al., 2002). In these mouse models the classical hallmark "Aβ-plaques" arises dependent on the level of overproduced Aβ. In addition, several of these mouse models display synapse loss and neuron loss to various degrees (Bittner et al., 2012; Schmid et al., 2016; Spires et al., 2005; Tsai et al., 2004). In contrast to the amyloid cascade hypothesis that postulated Aβ-generation as the primary molecular cause initiating all other pathological events like tau-pathology (Hardy and Higgins, 1992), these mice did not develop a prominent tau-pathology (Radde et al., 2008). To achieve tau-pathology further genetic mutations in the *TAU* gene had to be introduced. These TAU mutations were not associated with AD, but rather were found in fronto temporal dementia (FTD). Thus, mouse models bearing *APP/PS* and *TAU* mutations are not representing AD, but rather are a mixture model of AD and FTD. However, mouse models with *APP*, *PS* and *TAU* mutations develop a combined Aβ- and tau-pathology, which is characteristic of human AD brains (Oddo et al., 2003). Recently, new mouse knock-

in mouse models have been generated that may not suffer from interfering expression of endogenous mouse APP (Saito et al., 2014). However, whether they are better suited to model AD remains to be clarified. All these mouse models have the main problem that they are based on human mutations that lead to familial AD. Yet only about 1-5% of all AD cases are familial, whereas the remaining are termed sporadic AD – i.e. not having a clear genetic background. While breaking down the disease into single pathogenic processes may help in identifying aspects of cell and network vulnerability to a specific factor, it certainly does not ease the combination of knowledge derived from different models and experimental approaches. In spite of this seemingly insurmountable variability, there are common lines of evidence as to how AD-like pathology impacts the central nervous system of rodent models of the disease.

2.1 Amyloid, hyperphosphorylated Tau and GABAergic neurons

Toxic protein species like extracellular amyloid beta (Aβ) and hyperphosphorylated Tau have profound effects on synaptic transmission and intracellular signaling cascades of excitatory neurons. Short-term incubation with Aβ causes excessive Ca^{2+} influx into neurons (Kelly and Ferreira, 2006), which subsequently increases the chance of glutamate release causing generalized excitotoxicity. Chronic exposure to Aβ has the diametrically opposite effect, as it stimulates endocytosis of N-methyl-D-aspartate receptors (NMDARs) (Snyder et al., 2005). Less is known about the cell-autonomous effects exerted by Aβ, or its physiological precursor (APP), on GABAergic transmission at the pre- and post-synaptic compartment. It has been shown that in neuronal cultures derived from the anterior cingulate cortex, Aβ had a dampening effect on presynaptic GABA-release from fast-spiking interneurons onto pyramidal cells. This mechanism was mediated by dopamine D1 receptor activation on the inhibitory cells (Ren et al., 2018). At the post-synapse, the most toxic species of Aβ (Aβ-42) induces the downregulation of $GABA_A$ receptors in cortical neuron preparations (Ulrich, 2015). Furthermore, two contradicting studies identified the non-mutated form of APP as a stabilizing (Chen et al., 2017) and a destabilizing (Doshina et al., 2017) agent of the KCC2 transporter on hippocampal slices and cortical neuron cultures from embryonic APP knockout mice, respectively. KCC2 is essential for neuronal Cl^- homeostasis and GABAergic transmission, as it mediates the developmental shift of GABA from being depolarizing to hyperpolarizing (Rivera et al., 1999). The opposing results of these two studies are likely due to the age differences of the mice from which the preparations were made, as stated by Doshina et al.; the authors also claim that a similar lack of KCC2 is observed when culturing neurons from adult mice (data not shown). Finally, concerning Tau phosphorylation, it was shown that $GABA_A$ receptor activation can lead to abnormal phosphorylation of Tau, giving

an insight onto how the use of anesthetics relying on GABA receptors, or excess of alcohol, worsen the progression of dementia (Nykanen et al., 2012).

Evidence on the direct effect of amyloid and hyperphosphorylated Tau on GABAergic transmission is still sparse and contradictory. More investigation is required to determine how these toxic species affect GABAergic neurons specifically, as this is the first step to understand their selective vulnerability – together with the cholinergic neurons – in the context of Alzheimer's disease (see chapter 2).

2.2 Neuropathology of GABAergc neurons in mouse models of AD

Neurodegeneration is a key aspect of AD. In subjects that display signs of AD dementia, post-mortem or *in vivo* MRI investigations reveal a massive loss of gray matter (see chapter 3). Usually, brain atrophy can be found in the temporal lobe, particularly in the hippocampal system. Loss of hippocampal pyramidal cells has been reported in the 5xFAD model (Eimer and Vassar, 2013; Jawhar et al., 2012; Oakley et al., 2006) and in the 3xTgAD model (Fuhrmann et al., 2010; Wirths and Bayer, 2010). The fate of inhibitory neurons is less clearly described. Three studies reporting reductions of inhibitory neurons in the hippocampal system were conducted in the laboratory of Antonia Gutierrez. Through stereological examinations and quantitative mRNA expression analyses, the authors showed a loss of somatostatin/neuropeptide Y (SOM/NPY$^+$) positive interneurons in the CA1 area and in the dentate gyrus (DG) of an APP/presenilin1(PS1) double transgenic $PS1_{M146L}$::APP_{751SL} mouse model (Ramos et al., 2006). In a following study, loss of SOM/NPY$^+$ and pyramidal neurons was reported in the entorhinal cortex of young animals (6 months of age); this reduction was linked to accumulation of Aβ-plaques in the extracellular matrix and to microglial induced excitotoxicity (Moreno-Gonzalez et al., 2009). Loss of calretinin (CR$^+$) interneurons and mRNA, but not CR$^+$ Cajal-Retzius cells, was shown in the same model, starting at 4 months of age and progressively aggravating with age. Parvalbumin (PV$^+$) positive interneurons were spared in an APPxPS1 double transgenic mouse model at the time of investigation (Ramos et al., 2006). SOM- and NPY-immunoreactive cells, alongside PV+ interneurons were also reduced in the hippocampus of a pre-plaque TgCRND8 mouse model in a study conducted by Albuquerque et al. (Albuquerque et al., 2015; Mahar et al., 2016). Hamm et al. reported a reduction in PV but not SOM immunoreactivity in the hippocampus of these mice, at the same stage of pathology (Hamm et al., 2017). Alterations in PV$^+$ and CR$^+$ interneuron numbers were also investigated by Takahashi et al. in two mouse models and human tissue of AD patients (Takahashi et al., 2010). In the APP^{SL}/PS1ho KI mouse model, but not in the PS1ho KI alone, CR-immunoreactivity was slightly reduced in the DG of 10 months old animals. Vice versa, PV-immunoreactivity was reduced in the CA3 area of PS1ho KI, but not in APP^{SL}/PS1ho KI mice. These variations were hand-in-hand with the human condition, in

spite of the potential absence of a PS1 or APP mutation in the individuals. By two-photon imaging through a hippocampal window, we showed that in the Gad1-EGFP reporter line crossed with the APPswe/PS1dE9 model the number of putative O-LM interneurons (SOM^+) in CA1 was not altered in diseased mice when compared to age-matched wild types. However, these cells abruptly lost entire axons in transgenic animals, and their dendritic spines underwent a higher turnover compared to wild type controls (Schmid et al., 2016). These results are unbiased for variability in immunohistochemical stainings, and they confirm that changes at the synaptic and axonal level reveal disruption of network connectivity even in absence of clear loss of cell somata.

Loss, impairment or dysfunction of SOM^+ inhibitory neurons seems to be a recurrent pattern in AD mouse models with amyloid beta plaque deposition. Interestingly, SOM^+ interneurons are also particularly affected in human AD patients' brains, and the dysfunction of SOM/NPY^+ hilar interneurons has been linked to epileptogenesis, which shows comorbidity with AD (Chapter3 and (Palop and Mucke, 2009)). Noteworthy, these are among the few spiny inhibitory neuron subtypes; whether the presence of dendritic spines increases the susceptibility of these cells to amyloid pathology remains to be determined. Finally, it is worth stressing that stereology studies should be taken with caution, as the absence of molecular markers does not necessarily imply the loss of the cell bodies (Takahashi et al., 2010), although protein expression in a cell is a proxy for alterations in the cell's functionality.

2.3 Impact of GABAergic dysfunctions on DG inhibition excitation balance and neurogenesis

The dentate gyrus (DG) occupies a position of particular interest, both anatomically and functionally. Noteworthy, this compartment of the hippocampus is particularly vulnerable to amyloidosis (Chin et al., 2005; Palop et al., 2003; Palop et al., 2005). In a comprehensive investigation of four mouse models of AD (hAPP-I5, hAPP-J20, hAPPARC48 and hAPPJ9/FYN aged 4 to 7 months), Palop et al. showed how amyloidosis-induced aberrant excitation triggered a compensatory mechanism that lead to sprouting of not only hilar SOM^+/NPY^+ GABAergic axons within the granule cell layer of the DG (Diez et al., 2000; Diez et al., 2003; Palop et al., 2007), but also of granular layer mossy fibers onto inhibitory basket cells. This profound excitatory and inhibitory microcircuit remodeling had nonetheless a net excitatory effect, as these mice displayed epileptic episodes in their EEG in absence of obvious convulsions (see paragraph 3.1). Improper short-term synaptic plasticity in the DG was also reported by voltage sensitive dye imaging in tissue from aged APPswe/PS1dE9 (Hazra et al., 2013). In the same preparation, inhibitory interneurons failed to reliably

generate action potentials, confirming how hyperexcitability at the micro-circuit level is a feature shared by different mouse models.

Within the DG,adult neurogenesis steadily takes place in rodents and humans (for review, see (Ming and Song, 2011)), although ther is evidence arguing both for and against the existence of adult neurogenesis in humans (Boldrini et al., 2018; Sorrells et al., 2018). Adult neurogenesis has been implied in various physiological (e.g. memory and pattern separation) and pathological processes, including AD (Mu and Gage, 2011). For example, in a study conducted by Verret et al., proliferation and short-term survival of neural progenitors in the hippocampus was unaffected by APP/Abeta overproduction (Verret et al., 2007); however, survival of newborn cells 4 weeks later was dramatically diminished in transgenic mice with amyloid pathology. GABAergic and glutamatergic inputs and synaptic transmission tightly regulate adult neurogenesis in the DG (Ming and Song, 2011; Toni et al., 2008) in a temporally staggered way throughout post-natal development. Sun et al. found that adult born granule cells were increased in number and additionally displayed an accelerated development in the first 28 days after birth in mice, but were delayed in their maturation after this time point (Sun B., 2009). This was then linked to excessive levels of ambient GABA, possibly derived from the Aβ-induced SOM/NPY^{+} interneuron sprouting in the granule cell layer. While Sun et al. pinpoint excessive GABAergic transmission as a factor preventing proper maturation of adult-born granule cells, Gang Li et al. showed that knock-in and expression of the *APOE ε4* gene, which is the most accurate predictor of sporadic late onset AD (Nalbantoglu et al., 1994),caused a reduction of GABAergic interneurons and synapses in the dentate gyrus, and a concomitant lack of mature adult-born granule cells (Li et al., 2009). In line with the previous findings, increased proliferation of neural progenitor cells and lack of maturation of the newborn granule cells also occurred in APP knockout mice, where GABAergic synaptic transmission was strongly reduced as well (Wang et al., 2014).

These studies confirm that two potentially independent but not mutually exclusive hallmarks observed in familial- and sporadic- AD patients (i.e.: presence of mutated APP and the ApoE ε4 isoform, respectively) are both possibly mediated and counteracted by impairment in GABAergic transmission.

2.4 GABAergic disturbances underlying network dysfunctions

Pathological alterations of the finely tuned GABAergic and glutamatergic signaling at the molecular and cellular level may be echoed in larger scale abnormalities of network activity. Indeed, epileptiform activity is recurrent in the EEG of AD patients and mouse models (Busche and Konnerth, 2016; Palop et al., 2006; Palop and Mucke, 2016). Hyperexcitability was also manifested as shown by *in vivo* calcium imaging of cortical neurons in

APP23xPS45 mice (Busche and Konnerth, 2015). In fact, network dysfunctions in AD go beyond epileptic-like activity in the EEG, as AD-related dysrhythmias can be observed throughout the spectrum of brain oscillations (Cayzac et al., 2015; Cramer et al., 2012; Goutagny et al., 2013; Gurevicius et al., 2013; Scott et al., 2012; Siwek et al., 2015; Verret et al., 2012; Zhang et al., 2016). The presence of neurons that function as "rhythm generators" is necessary – although not sufficient – for the generation of intrinsic, stimulus-independent oscillations in the brain (Buzsaki, 2002). Inhibitory neurons that discharge rhythmically are therefore particularly suited to impose periodicity on their target cells. This GABAergic "waves" impose periods of increased and decreased excitability on neuronal ensembles that oscillate at the same frequency. On a simplistic note, synchrony of smaller subsets of neurons results in faster and smaller-amplitude oscillations correlated with execution of cognitive processes (Mizuseki and Buzsaki, 2014). Dysrhythmias, in turn, correlate with cognition defects (Uhlhaas and Singer, 2012). Therefore, lack of proper inhibitory control may underlie the appearance of abnormal network activity patterns and, ultimately, be the cause of the observed behavioral and cognitive impairment.

Villette et al. were among the first to link Aβ-pathology in the hippocampus to inhibitory neuron dysfunction, behavioral and *in vivo* network aberrations, in rats seeded with Aβ deposits (Villette et al., 2010). Interestingly, misfolded Aβ not only reduced the frequency of the learning-associated theta oscillations in the hippocampal local field potentials (4-10 Hz band), but it also caused reductions in firing rate of rhythmic septal PV^+ long-range projecting neurons, which highly contribute to the generation of theta waves. Verret et al. expanded these investigations as they showed that in transgenic hAPP/J20 mice PV^+ interneurons have lower levels of the Nav1.1 channel (Verret et al., 2012). This deficiency was directly linked to decreased action potential amplitude of PV^+ interneurons (*in vitro*), aberrant network hypersynchrony (epileptiform discharges in the EEG) and reduced gamma power (20-80 Hz range) *in vivo.* Both these findings were subsequently reproduced by Hamm et al. (Hamm et al., 2017), where a deficiency of Nav1.1 and 1.6 expression was also correlated to diminished gamma oscillation power. Further, in the study of Verret et al. increasing levels of Nav1.1 via BAC transgene insertion was sufficient to promote gamma activity and consequently reducte epileptiform activity in the cortical EEGs of relatively young 4-7 month old transgenic mice (Verret et al., 2012). In a follow up study, Martinez-Losa et al. transplanted Nav1.1 overexpressing medial ganglionic eminence neurons (MGE) into the cortex and hippocampi of 7-8 month old hAPP/J20 mice showing a consistent deposition of Aβ-plaques; this was sufficient to restore gamma oscillations and behavioral impairments in a battery of tests (Martinez-Losa et al., 2018). MGE neuron transplant had already resulted effective in increasing inhibitory tone and cognitive deficits in a mouse model of epilepsy (Hunt et al., 2013) and an ApoE ε4 overexpressing mouse lacking amyloid pathology (Tong

et al., 2014). These studies show that transplantation of inhibitory neurons to restore the balance in GABAergic transmission holds great translational potential for the cure or prevention of both sporadic and familiar cases of AD.

Further proof that inhibitory neurons are a key node for adequate network functionality, and that their dysfunction is directly linked to the phenotypic alterations observed in AD mouse models, was provided by (Schmid et al., 2016). The authors showed thatdecreased responses of O-LM inhibitory interneurons during associative learning, andabsence of newly emerging synapses on their dendrites upon learning were associated with neurodegeneration of cholinergic afferents from the medial septum in an APP/PS1 mouse model of AD. Further, they showed that boththe GABAergic neuron dysfunction and the impaired neuronal network rewiring on the synaptic level were partly responsible for the cognitive defects displayed by the transgenic mice in a contextual fear conditioning paradigm, as rescuing the activity of O-LM interneurons was beneficial to the transgenic mice.In conclusion, restoring GABAergic functionality was shown to be necessary – and sufficient – to reduce and ameliorate network and behavioral defects observed in various mouse models of AD, at diverse stages of the disease.

2.5 GABAergic impairments and glial dysfunction

Glial cells response in the brain can quickly evolve from being a blessing to being a curse. In fact, dysregulated glial responses and functionality have been implicated in the pathogenesis of neuropsychiatric and neurodegenerative disorders. In this context, chronically activated microglia are paralleled to constant exposition of neurons to pro-inflammatory agents, eventually leading to their cell death (Heneka et al., 2014; Labzin et al., 2018). Reactive astrocytosis and increased gliotransmission are well-established hallmarks of AD. Besides, whole-genome sequencing revealed that variants of TREM2 receptor (triggering receptor expressed on myeloid cells 2), a microglial receptor, are a genetic risk factor for AD (Miyashita et al., 2014). Astrocytes, in turn, are the primary source of ApoE ε4 in the brain (Elliott et al., 2010). Presence of the ε4 isoform increases plaque seeding at early stages of the disease (Liu et al., 2017), possibly by interfering with microglia-mediated clearance of Aβ among other pathological consequences. In the context of AD, in addition to potential mutations directly affecting glial functionality, a secondary mechanism arises, where hyper- or hypoactivity of neurons trigger pathological glial responses aimed at compensating the perturbed balance of excitation and inhibition.

In the DG of both APPswe/PS1dE9 mice and *APOE ε4* knock-in mice, astrocytes were shown to release excessive GABA, causing abnormal levels of tonic inhibition and lack of proper long-term potentiation upon electric stimulation of the perforant path (Jo et al., 2014; Wu et al., 2014). Working memory (Wu et al., 2014) and spatial reference memory (Jo et al., 2014) were both rescued by reducing GABA synthesis or tonic inhibition, respectively. Increased GABA synthesis and release by astrocytes could be triggered as a compensatory response to excessive excitation, which is in line with the previously mentioned findings (see paragraph 2.2). Finally, a first direct link between neuronal activity and microglial response has been suggested by Iaccarino et al., who showed that gamma entrainment in CA1 by optogenetic PV^+ neuron stimulation promoted microglial gene expression changes and microglial-mediated Aβ-clearance in 5xFAD mice (Iaccarino et al., 2016). The authors expanded these results by utilizing a 40 Hz light flicker independent of optogenetic tools, which resulted in reduced Aβ-40 and Aβ-42 protein load in the visual cortex of 8-month-old transgenic and wild-type mice. However, the authors did not investigate whether amyloid clearance had beneficial effects on the behavior of transgenic mice, which would be expected when entraining physiological gamma oscillations.

To conclude, the interaction between GABAergic and glial cells has not been extensively investigated, although this is of particular relevance for AD, as excessive glial activation in response to dysregulated neural activity is a major factor exacerbating the neurodegenerative processes of the disease. Enhancing GABAergic activity could be a potent mean to directly and indirectly counteract reactive micro- and astrogliosis.

3. GABAergic dysfunction in human AD

The classic hallmarks of AD are the deposition of amyloid beta (Aβ) and the aggregation of hyperphosphorylated tau into neurofibrillary tangles (Beyreuther and Masters, 1991; Brion et al., 1985; Goedert et al., 1988; Grundke-Iqbal et al., 1986; Hardy and Allsop, 1991; Selkoe, 1991). Both Aβ- and tau-pathology are thought to ultimately contribute to synapse and neuron loss in AD brains giving rise to cognitive deficits, especially memory impairment (Selkoe, 2002; Terry et al., 1991). The amyloid cascade hypothesis has an Aβ-centered view on the disease, holding this hallmark responsible for later occurring deficits, like tau-pathology, neuron- and synapse loss (Hardy and Higgins, 1992). However, the role of inflammation carried by microglia has long been known and experienced a revival over the past 5-10 years. Mainly, because of epidemiologic genome wide association studies (GWAS) identifying new loci associated with risk of developing sporadic AD (Harold et al., 2009). These genomic loci are close to genes that are related to inflammatory functions and served as a starting point for the identification of new targets for the treatment of AD (Hollingworth et al., 2011; Jones et al., 2010; Sims et al., 2017). However, besides these relatively new hypothesis and findings, there exist further knowledge about AD that has already been initially discovered in the 70s and 80s of the 20th century (Davies and Maloney, 1976; Davies et al., 1980). This concerns the cholinergic deficit as well as the vulnerability of GABAergic neurons in AD brains. Of note, one of the first drugs used for the treatment of AD is based on the finding of cholinergic neuron's degeneration. Donepezil, an acetylcholine-esterase inhibitor, prolongs the presence of Acetylcholine within the synaptic cleft, thereby initially improving synaptic transmission in AD patients (Birks, 2006). However, since the drug turned out to be inefficient in curing or halting the disease, research for better drug targets continued. Surprisingly though the loss of cholinergic neurons is a widely reproduced and accepted deficit in the AD field (Lane et al., 2004), but drug development in this direction received only few interest lately. Similarly, impairments of inhibitory neurons have been known since the 80s of the 20th century (Chan-Palay, 1987; Davies et al., 1980). Nevertheless, GABAergic dysfunctions in AD have been widely neglected.

3.1 EEG alterations – link to impaired excitation/inhibition balance

EEG abnormalities have been described for AD-patients early on (Brenner et al., 1988; Coben et al., 1985; Coben et al., 1990; Hauser et al., 1993; Penttila et al., 1985) and might be associated with periods of episodic amnestic wandering (Rabinowicz et al., 2000).

Patients with sporadic AD have an up to 10 times higher risk developing clinical seizures (Beagle et al., 2017; Hauser et al., 1986; Hesdorffer et al., 1996; Pandis and Scarmeas, 2012), which promoted their consideration as a diagnostic marker (Besthorn et al., 1997). But since the measured EEG changes were often mild, difficult to detect and interpret compared with alterations found in epilepsy patients, they have been widely neglected (Vossel et al., 2017). Using EEG power mapping indicated that the measured parameters correlated with the cognitive state, the APOE ε4 allele status and the amyloid burden (Michels et al., 2017). Thus improved and prolonged measurements and methods to accurately measure electric changes non-invasively deep within human brains are highly demanded. A recent study using long-term EEG recordings in AD patients detected more subclinical epileptiform activity compared with age-matched controls (Vossel et al., 2016). In addition, APOE ε4 carriers that are at risk to develop AD also show EEG abnormalities (Ponomareva et al., 2008). In addition to EEG, magnetic resonance imaging (MRI) and functional MRI (fMRI) might be an option for diagnosis, although data has to be interpreted carefully with respect to how fMRI signals relate to neuronal activity (Dickerson et al., 2005; Putcha et al., 2011; Sperling et al., 2009). A recent study reproduced earlier findings of resting state fMRI differences between AD and healthy controls, however MRI measurements of hippocampal volume showed a higher diagnostic accuracy (Teipel et al., 2018). Furthermore, grid-cell like representations in the entorhinal cortex of APOE ε4 carriers were found to be disturbed in a virtual arena spatial memory test (Kunz et al., 2015). Summarizing, there is no doubt about neuronal network aberrations in AD, but the reasons remain elusive.

That GABAergic dysfunction is important for network dysfunction in AD had been postulated and investigated (Kurudenkandy et al., 2014; Marczynski, 1998). However, Palop and Mucke expanded the neuronal network dysfunction hypothesis and postulated an integrated view, for the first time taking into account that molecular, synaptic and neuronal changes ultimately pile up and disturb neuronal networks (Palop and Mucke, 2010). These neuronal network disturbances might indeed represent the basis for unexpected fluctuations in episodic memory of patients. Already in 2007 Palop hypothesized an imbalance of excitation and inhibition as the cause for epileptiform activity in AD and showed that inhibitory interneuron remodeling was apparent in the hAPPJ20 mouse model of AD (paragraph 1.3, (Palop et al., 2007)). Since then, several pre-clinical experiments have been conducted, aimed at relating GABAergic neuron dysfunction with cognitive deficits in different mouse models (see chapter 2 and (Palop and Mucke, 2016)). Furthermore, since existing anti-epileptic drugs are frequently targeting GABAergic transmission to increase inhibition, some of these already available medications might be used to treat AD patients as well (Vossel et al., 2017). Indeed, first clinical trials with the anti-epileptic drug Levetiracetam showed positive effects

(Bakker et al., 2012; Sanchez et al., 2012). These data are promising and further trials have to be carried out to strengthen these findings. Besides these successful initial trials, the underlying mechanisms remain widely unknown – especially in humans. A disturbance of GABAergic neurons is an obvious possible mechanism, but the existing data in support is often inconsistent and difficult to interpret. In the next chapters we will therefore review the existing literature on GABAergic dysfunction in human AD.

3.2 Neuropathology of GABAergic neurons in AD

The neurochemical analysis of human AD brains already in the 70s and 80s of the last century lead to the finding of changes in several neurochemical markers. Besides Aβ and tau, these were several neurotransmitters and the enzymes involved in their synthesis like choline acetyltransferase (ChAT), noradrenalin, serotonin, dopamine, GABA, GAD and somatostatin (Rossor, 1982). The reduction of ChAT was a consistent and reproduced finding (Davies and Maloney, 1976; Davies, 1979; Spillane et al., 1977). In addition, somatostatin and GABA were investigated in the early eighties and found to be reduced in human AD brains (Davies et al., 1980; Rossor et al., 1980; Rossor et al., 1982). The expression of somatostatin receptors was found to be similarly reduced (Beal et al., 1985) and decreased levels of somatostatin in cerebrospinal fluid of AD patients correlated with EEG disturbances and cognitive measures (Soininen et al., 1988). This study for the first time investigated the correlation of the neurotransmitter somatostatin, which is a marker of some inhibitory neurons, with EEG measurements and neuropsychological tests. It can be seen as the first study trying to establish the relationship of impaired inhibitory neurotransmission, neuronal network dysfunction and memory impairment. The use of antisera raised against the neuropeptide somatostatin lead to the first immunohistochemical analysis of human AD brains revealing loss of somatostatin positive neurons in brain regions affected by classical neuropathological hallmarks like neurofibrillary tangles (Chan-Palay, 1987; Gabriel et al., 1993). Somatostatin positive neurons exhibited shorter dendrites and axons and were found in thioflavin positive neuritic plaques. Impaired GABA-uptake by synaptosomal preparations from AD brains supported the view that not only neuronal cell bodies, but mainly synapses might be affected (Hardy et al., 1987). Similar decreased GABA uptake was found in human AD brains using a radioactive labeling technique, which lead to the conclusion of GABAergic synapse loss (Simpson et al., 1988). Besides the neurotransmitter GABA and the neuropeptide somatostatin, several other markers exist for the identification of inhibitory neurons in the brain and hippocampus (Klausberger and Somogyi, 2008), which have been investigated in human AD. The three calcium-binding proteins Calretinin (CR), calbindin D28k (CB) and paravalbumin (PV) are markers of

GABAergic neurons that are mainly expressed in non-overlapping neuronal populations in the cortex (Klausberger and Somogyi, 2008; Tremblay et al., 2016). CR-positive neurons have been initially described unaltered between control and AD cases investigating prefrontal temporal cortex (Fonseca and Soriano, 1995; Hof et al., 1993) and later also the visual cortex (Leuba et al., 1998). However, studies investigating brain regions that are mainly affected by Aβ- and tau-pathology like the hippocampus and entorhinal cortex consistently display reduced CR neuron numbers and dystrophic neurites (Brion and Resibois, 1994; Kaufmann et al., 1998; Mikkonen et al., 1999). Similar brain region specific alterations have been described for calbindin. In the visual cortex calbindin-positive neuron numbers were found to be preserved (Leuba et al., 1998), whereas they were reduced in the entorhinal, frontal cortex and hippocampus (Ferrer et al., 1993b; Mikkonen et al., 1999; Palop et al., 2003). PV is a marker for fast-spiking inhibitory neurons that has been found either to be reduced or preserved comparing AD patient and healthy control brains. Early studies found unaffected PV-positive neuron numbers in the temporal, visual and prefrontal cortex (Ferrer et al., 1991; Ferrer et al., 1993a; Hof et al., 1991; Leuba et al., 1998). Again, brain regions that are mainly affected by Aβ- and tau-pathology like the entorhinal cortex and hippocampus consistently showed decreased PV-positive neuron numbers (Arai et al., 1987; Brady and Mufson, 1997; Fonseca et al., 1993; Inaguma et al., 1992; Mikkonen et al., 1999; Satoh et al., 1991; Solodkin et al., 1996; Takahashi et al., 2010). Interestingly, impairments in neuronal network function like altered hippocampal oscillations have been shown to be associated with deficits in PV-positive inhibitory neuron function in AD and mouse models of AD (Verret et al., 2012); Chaper2).

Summarizing, the currently available data supports the view that GABAergic neurons are affected in specific brain regions of human AD patients. This mainly concerns brain regions that are already influenced by Aβ- and tau-pathololgy and most presumably also by neuroinflammation. Thus targeting GABAergic neurons to identify novel therapeutic targets might be very promising.

3.3 GABA and $GABA_A$-R expression levels

The neurotransmitter γ-aminobutyric-acid (GABA) is generated by α-decarboxylation from L-glutamate in neurons. The enzyme catalyzing this irreversible reaction is the glutamic acid decarboxylase (GAD). The two isoforms of GAD, 65 and 67 kDa sized, are both expressed in the brain, the former in presynaptic terminals and the latter distributed in the cytosol. After release from synaptic vesicles, GABA binds to GABA receptors located on the postsynaptic membrane. GABA spill-over from synapses is taken up by astrocytes that catalyze it to

glutamine with the help of the citric acid cycle. Glutamine is back transported into neurons, where it is converted to glutamate and the recycling circle is complete. GABA binds to GABA receptors, which are either ionotropic $GABA_{A/C}$ or metabotropic $GABA_B$. $GABA_A$Rs are the most frequent ones that consist of five heteromeric subunits that form a central chloride channel. Chloride influx through the membrane hyperpolarizes the postsynaptic neuron decreasing the probability of action potential firing. Eight different subunits have been described and can be found in different combinations in different brain regions. However, the most frequent pentamers found in $GABA_A$Rs are $2\alpha:2\beta:1\gamma$. Other combinations can also be found but are present in different brain regions (Wisden and Seeburg, 1992). Metabotropic $GABA_B$Rs ($GABA_{B1}$ and $GABA_{B2}$) are G-protein coupled receptors that connect to the classical signal transduction machineries. Changes in GABA and GABA receptor levels in AD have been recently reviewed (Calvo-Flores Guzman et al., 2018; Govindpani et al., 2017; Kwakowsky et al., 2018). We will therefore give a summary of the current status on the one hand on GABA levels and on the other hand on GABA receptor changes in human AD. The measurement of GABA levels in postmortem AD brains is depending on several factors. The most crucial factor is post mortem interval (PMI) time. PMI times are usually not easily controllable and are therefore introducing large variability into measurements and differ widely between different studies. Furthermore, AD patients and healthy controls may have received medications that interfere with the GABAergic system. These medications are even harder to be controlled for. Thus, the data on GABA levels has to be interpreted carefully. Generally speaking there exist several studies that found decreased GABA concentrations in brains of AD patients or patients with AD-like pathology in temporal, parietal, occipital and frontal cortex (Arai et al., 1984; Ellison et al., 1986; Gueli and Taibi, 2013; Lowe et al., 1988; Mohanakrishnan et al., 1995; Perry et al., 1987; Rossor et al., 1982; Rossor et al., 1984; Sasaki et al., 1986; Seidl et al., 2001). In contrast other post-mortem studies investigating human AD brains found no alterations in GABA levels (Lowe et al., 1988; Perry et al., 1987; Rossor et al., 1984; Sasaki et al., 1986; Yew et al., 1999). However, the majority of studies identified decreased GABA brain levels in patients with AD. Whether those are due to loss of synapses, altered GABA metabolism, neuron loss or other factors remains to be mechanistically determined. Standardization of PMI times and recording of other diagnosis and treatments have to be improved in future human trials to obtain higher data quality.

On the receptor side, mainly expression levels of $GABA_A$Rs have been analyzed by different methods, like mRNA expression analysis, in situ hybridization and immunohistochemistry (for review see (Govindpani et al., 2017; Kwakowsky et al., 2018)). Studies using mRNA expression-based qPCR methods to analyze the expression of different $GABA_A$R subunits in temporal, prefrontal and entorhinal cortex often detected decreased levels and sometimes unchanged expression levels (Howell et al., 2000; Limon et al., 2012; Luchetti et al., 2011).

Studies using antibody-based methods measuring protein levels found decreased α1 and α5 subunit levels in CA regions of the hippocampus (Limon et al., 2012; Mizukami et al., 1998; Rissman et al., 2003; Rissman et al., 2004), whereas β_1, β_2, β_3 and γ_2 subunits remained unaffected in AD (Iwakiri et al., 2009; Mizukami et al., 1997; Rissman et al., 2003). In addition α3 units were found to be preserved (Kwakowsky et al., 2018). Although α1 subunits were decreased in several regions of the hippocampus they were upregulated in the CA3-region, granule cell layer and hilus of the dentate gyrus. Similarly, α5 units seemed to be region specifically regulated: unchanged in hippocampus, subiculum, entorhinal cortex and granule cell layer, but increased in stratum pyramidale, oriens, and subiculum of CA1. Again, investigating region specific differences also revealed decreased β3 subunit expression in stratum oriens, radiatum of CA2 and stratum radiatum of CA3. Further β2 subunits were decreased in stratum moleculare and a trend for stratum granulare (Kwakowski et al. 2018). Surprisingly, the $\gamma_{1/3}$ subunits were found to be upregulated in the hippocampus of AD patients compared with healthy controls (Iwakiri et al., 2009). In addition, γ3 subunits were increased (Kwakowski et al. 2018). In summary, several changes become visible when subregions are analyzed. In addition, same as for GABA levels, $GABA_A$Rs expression level may depend on PMI times that will introduce unwanted variability. To circumvent this problem GABA levels have also been measured in the CSF and were reduced in confirmed AD cases (Enna et al., 1977; Manyam et al., 1980; Mohr et al., 1986; Zimmer et al., 1984). However, GABA levels in the CSF may neither reflect GABA levels in neurons nor GABAergic presynaptic terminals. This is also true for non-invasive measurements analyzing $GABA_A$ receptor levels in brains of living AD patients using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). For PET imaging an analog of the $GABA_A$R binding molecule benzodiazepine ^{11}C-flumazenil has been used. No significant changes were detected comparing control and AD cases (Meyer et al., 1995; Ohyama et al., 1999). For SPECT, ^{123}I-iomazenil was used and a small reduction was detected in the frontal and parietal cortex, whereas other brain regions were unchanged (Fukuchi et al., 1997). In the future direct measurements of GABA levels using magnet resonance spectroscopy (MRS) may be used to more reliably measure neurotransmitter levels in the intact brain non-invasively. Indeed GABA and glutamate levels were reduced in individuals displaying mild cognitive impairment. However, they were unrelated to amyloid beta deposition or APOE ε4 allele status (Riese et al., 2015).

Summarizing, measuring GABA and $GABA_A$Rs levels in human AD brains might be useful for diagnosis, but needs to be significantly improved to represent valuable tools in this direction. Furthermore we have to realize that the relevant aspects of GABAergic dysfunction might not solely be the deregulation of GABA synthesis, GABA binding to the receptor or changes in

$GABA_AR$ expression. More likely, these changes impinge on the function of inhibitory neurons and on their ability to orchestrate and balance excitatory neurons and maintaining neuronal network function plays a crucial role for memory and cognition. We ought to widen our perspective from solely molecular to neuronal network changes.

4. Conclusion

Integrating the previous and newly acquired knowledge on inhibitory dysfunction in the intricate picture of AD is not easy. Contrasting evidence argues towards the existence of compensatory and remodeling processes occurring as the disease evolves. Therefore, not only the object of investigation should be taken into account (i.e. mouse strains vs. human studies), but most importantly the time of the investigation. Nevertheless, the "GABAergic hypothesis" has gained its place among the classical AD hypotheses, as confirmed by the increasing amount of original and review articles on this issue. GABAergic disturbances may indeed be a critical node linking the diverse pathological synaptic, cellular and network processes underlying the development and the progression of AD. Furthermore, mechanistic research aiming at unraveling how dysfunction of GABAergic neurons on the molecular level impinge on their crucial function within neuronal networks will most likely lead to the identification of new drug targets and causal therapies to treat not only AD, but all forms of neurologic disorders related to GABAergic malfunction. In this direction, the development, improvement and usage of novel imaging and *omics* approaches on the transcriptome, proteome and metabolome level will lead to a better understanding of the role of GABAergic neurons within neuronal networks.

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Figure

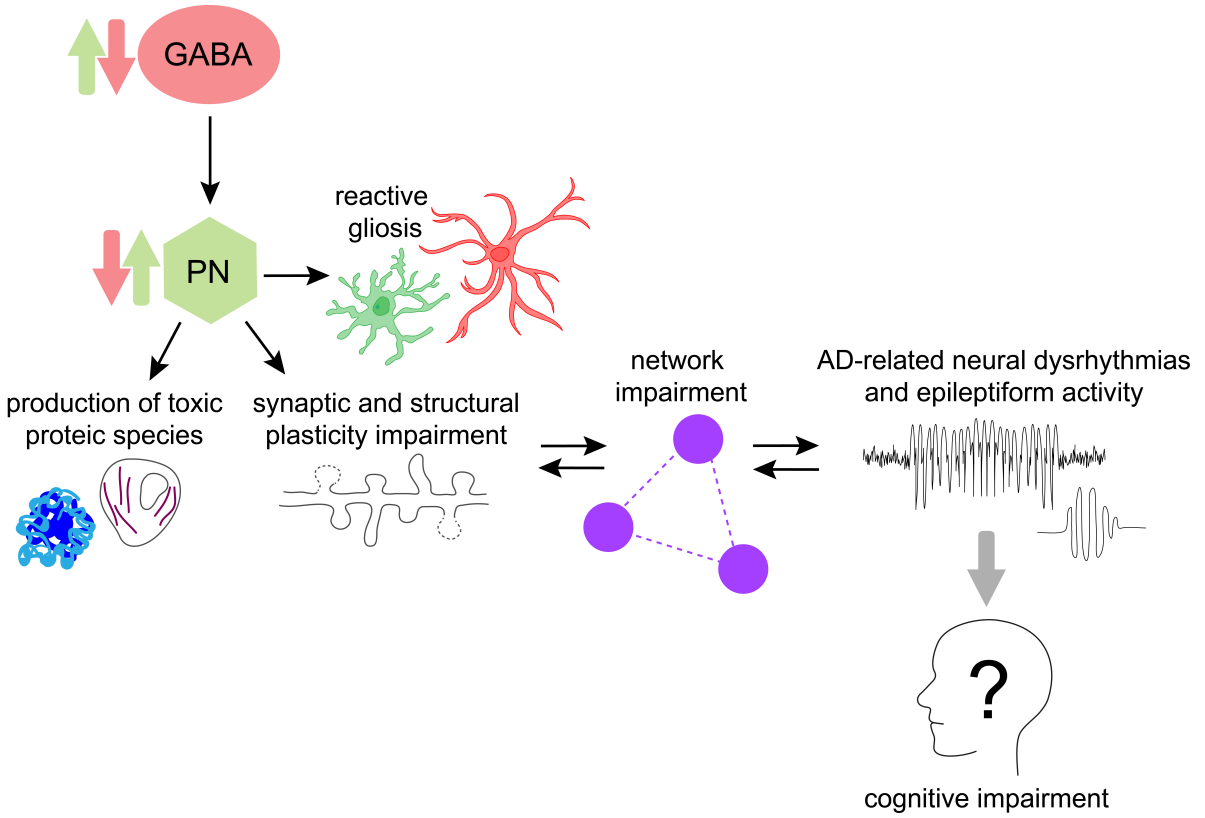

Figure 1. Simplified schematic of the GABAergic hypothesis of Alzheimer's disease
With this review, we want to highlight how GABAergic dysfunction might lie at the core of Alzheimer's disease (AD) pathology and how, ultimately, changes in inhibitory function might lead to network failure and subsequent cognitive defects. GABAergic transmission alterations in either direction are echoed in uncontrolled principal neuron (PN) responses. These, in turn, provoke disruptive microglial and astroglial responses, which may lead to the production of toxic protein species like amyloid deposits and hyperphosphorylated Tau. These will cause defects in synaptic and structural plasticity such as long-term depression and synaptic loss. All these factors lead to improper network functionality and impaired neural communication within and between brain areas that are responsible for learning and memory processes. These alterations are reflected in the epileptiform discharges and other AD related dysrhythmias observed in the electroencephalograms of individuals who will develop AD dementia, but at earlier stages of the pathology, prior to neurodegeneration. Proper neural oscillatory function is thought to be crucial for learning and memory processes; hence, its aberrance might underlie the cognitive defects such as loss of spatial orientation and short-term memory that are characteristic of early stage AD patients. Intervening on restoring or promoting GABAergic transmission could be of potent therapeutic value, as it might help preventing the deleterious cascade of events that ultimately leads to irreversible neural loss in AD patients.