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Review

BACE1-dependent metabolism of neuregulin 1: Bridging the gap in explaining the occurrence of schizophrenia-like symptoms in Alzheimer's disease with psychosis?

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ABSTRACT

Alzheimer's disease is a neurodegenerative disease mainly characterized by cortico-neuronal atrophy, impaired memory and other cognitive declines. On the other hand, schizophrenia is a neuro-developmental disorder with an overtly active central nervous system pruning system resulting into abrupt connections with common symptoms including disorganised thoughts, hallucination and delusion. Nevertheless, the fronto-temporal anomaly presents itself as a common denominator for the two pathologies. There is even a strong presumption of increased risk of developing co-morbid dementia for schizophrenic individuals and psychosis for Alzheimer's disease patients, overall leading to a further deteriorated quality of life. However, convincing proofs of how these two disorders, although very distant from each other when considering their aetiology, develop coexisting symptoms is yet to be resolved. At the molecular level, the two primarily neuronal proteins β -amyloid precursor protein and neuregulin 1 have been considered in this relevant context, although the conclusions are for the moment only hypotheses. In order to propose a model for explaining the psychotic schizophrenia-like symptoms that sometimes accompany AD-associated dementia, this review projects out on the similar sensitivity shared by these two proteins regarding their metabolism by the β -site APP cleaving enzyme 1.

1. Introduction

Neurodegenerative diseases and mental disorders attack rates are growing sharply all over the world and the estimated risk of health hazards and the subsequent economical burden are going to be huge in no time. Thus, sufficient preventives and proper therapeutics are strong demands of the running century. Dementia is one of the very common symptoms among different neural and neuropsychiatric disorders. Alzheimer's disease (AD) is a leading neurodegenerative disease associated with severe dementia, memory loss and neurobehavioral problems (Zhao et al., 2016). However, schizophrenia, is too a frequently diagnosed neuro-psychiatric disorder and these two disorders often coexist. Dementia-like symptoms at late phase of schizophrenia have been reported since long (Prohovnik et al., 1993) and this coincidence was evident even in absence of organic factors aiding in dementia directly (de Vries et al., 2001). In 1999, schizophrenia was claimed to be a "dementia praecox" to include all aspects of cognition impairment in

this brain disorder (Adityanjee et al., 1999).

In the first decade of the twentieth century, while AD was being modelled by the German psychiatrist and neuropathologist Alois Alzheimer in 1906 on the basis of the presenting symptoms and silver stained brain tissue of his first patient (Alzheimer, 1906; Shakir and Dugger, 2022), memory decrement in schizophrenia individuals was reported in 1908 by the Swiss psychiatrist Eugen Bleuler (Bleuler, 1908; Hany et al., 2022). He explained this symptom of dementia as "Organic psychosyndrome" (Bondi et al., 2017). Later on, in the mid-20th century, the Diagnostic and Statistical Manual of Mental Disorders, Second Edition (DSM-2) combined the features and categorized it as "Organic brain syndrome" (Bondi et al., 2017). However, the apparent simplistic grouping was further criticized (Fox, 1983) and, in fact, the classification of the disorders is still in the process of reformation (Laughren, 2011; Simpson, 2014). With the advent of DSM-5, the specifications were stringently made, yet an underlying gap remains to be (Lacasse, 2014; Nemeroff et al., 2013).

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According to DSM-5, AD falls under the umbrella of Major Neurocognitive Disorder while schizophrenia belongs to the Schizophrenia Spectrum Disorder group (American Psychiatric Association 2013; Sachdev et al., 2015). However, it is a fact that chances of developing AD pathology in elderly schizophrenia and the chances of psychosis during the course of AD are not exceptional, rather very obvious. Different approaches have been adopted to resolve this paradox. Evidences for common genetic mediators of variable penetrance, heritability and familiarity between them have been frequently suggested (Creese et al., 2019; DeMichele-Sweet et al., 2018). Here, we propose, in spite of appreciating the substantial contributions of genes, to focus on the symptomatic manifestation of the disorders and then adopted a top down view on what may be considered significant in term of pathophysiology at the molecular level, rather than looking into the genetic makeover of these diseases.

2. The occurrence of schizophrenic-like symptoms in AD and AD-related alteration in schizophrenia

Based on the diagnostic criteria outlined by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and DSM-5, schizophrenia and AD are completely different neurobiological disorders residing at opposite poles. Schizophrenic patients suffer from disorganized thoughts, psychosis, social withdrawal and most of them present the symptoms in adolescence or young adulthood. The psychosis in schizophrenia refers to auditory hallucination and delusion of one's insecurity or vulnerability of getting harmed by others. AD starts penetrating much later in life (after 65 if sporadic). The initial symptoms of AD starts with declarative memory loss, working memory inefficiencies and gradually lead to wider range of memory loss and several domain of cognitive impairment (Jahn, 2013).

Nevertheless, as originally reported as early as 1998 (Gormley and Rizwan, 1998), a subgroup of AD patients do exhibit behavioural abnormalities, also known as behavioural and psychological symptoms of dementia (BPSD) (Lanctôt et al., 2017) that are very similar to schizophrenia symptoms (Gaser et al., 2004; Plaze et al., 2011). However, the psychotic symptoms are mostly observed as apathy, visual hallucination and specific forms of delusions, (delusion of persecution or abandonment) (Koppel et al., 2014; Ropacki and Jeste, 2005; Zhao et al., 2016). Often, the severity is so high that it was proposed to consider the psychotic symptoms of AD as a separate endophenotype (Jeste and Finkel, 2000). In spite of different magnitude of frequency and severity of BPSD, psychosis and apathy were found to be common in AD (Lanctôt et al., 2017), more especially in late onset form of the disease (Ferreira et al., 2018). In a three-year longitudinal study, it has been shown that the severities of hallucination and or delusion increase along with sharp fall in cognitive functions necessitating institutionalization (Connors et al., 2018) and that these symptoms are strongly correlated to the level of cognitive impairment (Fuller et al., 2020). This psychotic problem of AD is also as heritable as the disease itself (DeMichele-Sweet and Sweet, 2010). An in-depth review work involving fifty five studies from 1990 to 2003 also affirmed the presence of psychotic symptoms like delusion (36%) and hallucination (18%) among AD patients (Ropacki and Jeste, 2005). However, it was also reflected from the same study that the incidence of psychosis was gradually increased within the first three years of observation, after which it seemed to be consistent without any further increase. The psychotic symptoms on an average lasted for several months, but the severity was less following one year.

Importantly, psychotic AD patients (AD+P) showed reduced accuracy in rapid visual performance and lack of adequate identification skill as compared to non-psychotic AD (Reeves et al., 2015). In a comparative analysis on the severity in neuro-psychiatric symptoms among AD+P, Lewy body dementia and late onset schizophrenia, the AD+P group was found to be placed at the middle and was affected by higher delusions, reduced learning and consolidation (Van Assche et al., 2019).

Similarly, with a close resemblance to AD, schizophrenic patients do

show cognitive decline and executive dysfunction (Seidman and Mirsky, 2017). An exhaustive study from South Korea found that prevalence of dementia was higher in schizophrenic individuals than in control patients (Ku et al., 2016). In this national study carried out between 2010 and 2013 and involving a large cohort of more than 275,000 individuals, out of which 26591 were diagnosed with schizophrenia, they projected that the chance of getting dementia among schizophrenic to non-schizophrenic was 4.7 odds. In addition, an eighteen-year follow up study on 20683 individuals from six nationwide registers of Denmark reached to the similar conclusion (Ribe et al., 2015). They found almost three-time higher risk of developing dementia among the schizophrenic patients than their non-schizophrenic controls. Another three years down the line, a meta-analytic report (5,063,316 participants and 206,694 schizophrenic cases) suggested the same notion of increased risk of dementia in the schizophrenic patients (Cai and Huang, 2018).

At the molecular level, it has been shown 25 years ago, at a time when it was thought that schizophrenic patients were less prone to develop AD, that haloperidol, a classical antipsychotic given as a first line medicine for schizophrenia, could reduce A β in cultured cells (Higaki et al., 1997). In addition, A β level was found to be associated with more severe psychotic symptoms (Goukasian et al., 2019). It was also proposed that neuro-stimulation could be an effective intervention to reduce the risk of developing AD in schizophrenic individuals (Sfera, 2013). Moreover, high anti-cholinergic burden was suggested to be a risk factor for developing AD-like dementia in advanced stage of schizophrenia (Tsoutsoulas et al., 2017). Finally, while impaired adult neurogenesis appears as an early event in transgenic mouse models of AD (Unger et al., 2016), an aberrant neurogenesis during critical post-natal developmental periods leads to the manifestation of schizophrenia-like symptoms (Sheu et al., 2019). Therefore, the developmental consequences during childhood and the geriatric changes taking place at the old age may be the possible manifestations of similar deficits at different time points. On the backdrop of these facts and figures, it is necessary to consider AD and schizophrenia common neuropathological roots. In this context, BACE1-dependent A β pathology is central to AD and the BACE1-neuregulin-ErbB axis is involved in schizophrenia. In order to model a concept linking both diseases, we thus focussed on the BACE1-dependent processing of both the β -amyloid precursor protein (β APP) and neuregulin 1 (Nrg1) in a way to understand their possible substantial and complementary implications in the concomitant manifestation of "classical" memory impairment and the more intriguing schizophrenia-like psychosis during the time course of AD.

3. The β -amyloid precursor protein and neuregulin 1 share a common sensitivity to secretases

3.1. The β -amyloid precursor protein (β APP)

ADAM10, BACE1 and the heterotetrameric γ -secretase complex are the three main proteases involved in β APP processing (Fig. 1). However, in addition to β APP, there exists a large and constantly growing number of membrane proteins identified as ADAM10 (>50) (Vincent and Chelcer, 2012), BACE1 (>20) (Barão et al., 2016) and γ -secretase (>150) (Güner and Lichtenhaler, 2020) substrates.

The β APP type-I transmembrane glycoprotein is involved in many important processes during neuronal development (Cho et al., 2022). However, in the context of AD, it is crystal clear that the β -site amyloidogenic processing of β APP by BACE1 is the rate-limiting step for A β generation that ultimately leads to the formation of one main hallmark of AD, the senile plaque (Luo et al., 2001). Nevertheless, there exists an alternate, concomitant, competitive and major non amyloidogenic processing of β APP carried out by the α -secretase ADAM10 cleavage, which, beyond its ability to prevent the production of A β , provides a neuroprotective environment thanks to the secreted metabolite sAPP α (Mockett et al., 2017). Back to the amyloidogenic processing of β APP,

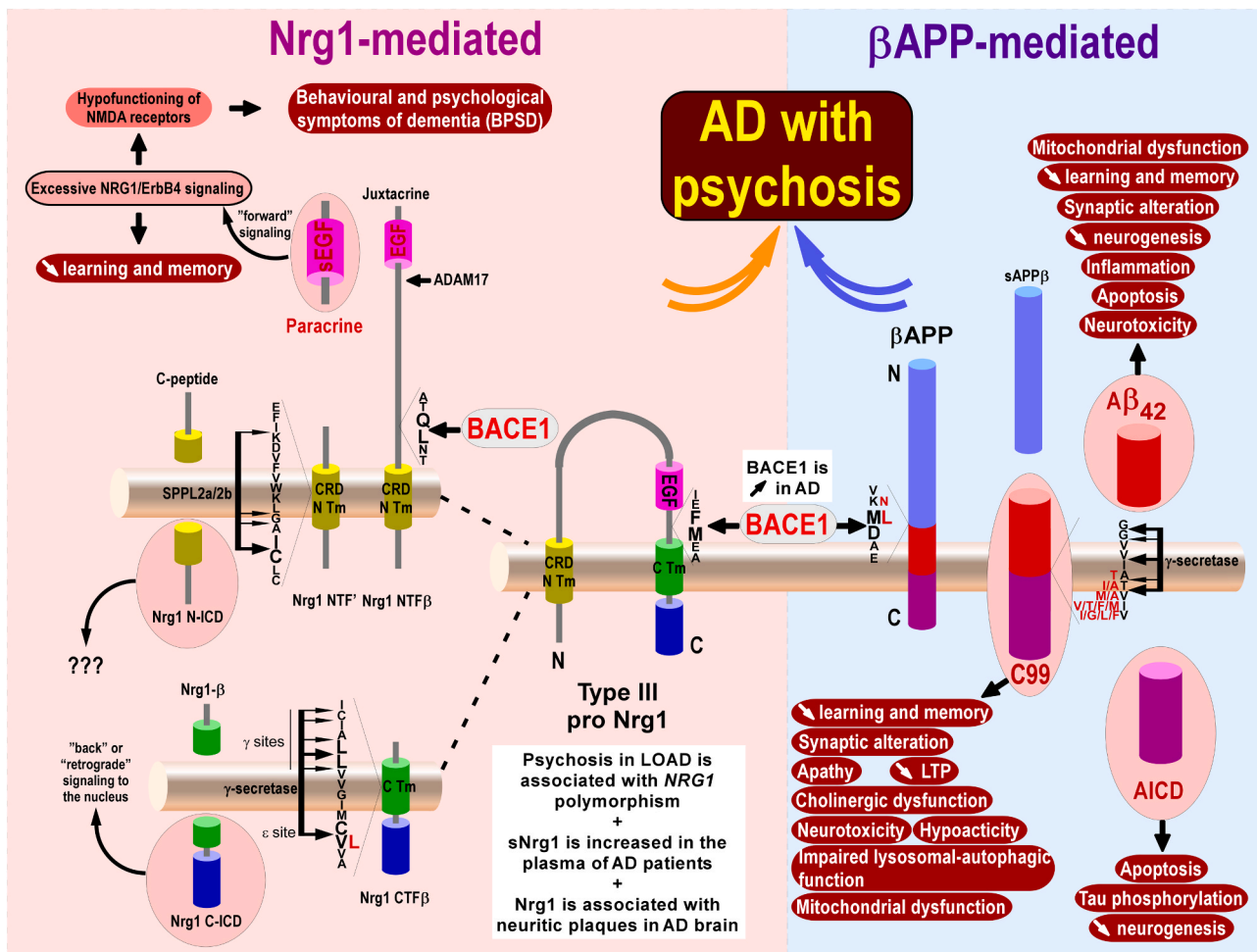


Fig. 1. Schematic representation of the possible dual implication of BACE1 in AD through the processing of both β APP and Nrg1. On the one hand, BACE1 is the first of a series of cleavages of the type 1 transmembrane β APP ultimately leading to $A\beta$ generation (light blue background, right side of the figure). Indeed, BACE1 is directly producing C99 that conveys a certain number of harmful events and is thereby initiating the two-step process (which then requires the cleavage of C99 by γ -secretase) engendering the AICD and $A\beta$ metabolites, both fragments also promoting the occurrence of deleterious effects. On the other hand, BACE1 is a major player in the metabolism of Type III Nrg1 (light orange background, left side of the figure). Thus, it first cleaves the polytopic pro Nrg1 type III transmembrane protein to release the EGF-like domain, therefore able to transduce ErbB4-mediated signals in a juxtacrine manner. In a second time, BACE1 will increase the field of action of the EGF domain by dissociating it from the NTF β fragment and thus allowing it to act remotely in a paracrine fashion. Ultimately, BACE1 is therefore regulating Nrg1-ErbB4 signaling to monitor the activity of NMDA receptors. In parallel and as is also the case vis-à-vis β APP, BACE1 initiates a cascade of proteolytic events leading to the intracellular production of Nrg1 C-ICD capable of transcriptional regulation of certain genes. Because BACE1 activity is obviously increased in AD, β APP and Nrg1 metabolism will be amplified, thereby exacerbating C99-, $A\beta$ -, AICD- and EGF-like domain of Nrg1-mediated effects. Particularly concerning Nrg1, the overproduction of sEGF and the subsequent hyper activation of the Nrg1/ErbB4 signaling are supposed to both trigger an excessive hypo functioning of NMDARs putatively responsible for BPSD and to theoretically alter learning and memory. In summary, high BACE1-dependent processing of Nrg1 (orange arrow) may account for the psychotic schizophrenic-like symptoms sometimes accompanying the classical β APP-driven cognitive decay (blue arrow) observed during the time course of AD.

the BACE1 cleavage gives rise to the production of the secreted sAPP β product with properties not yet clearly established, as well as the C99 C-terminal fragment (CTF) that triggers a series of deleterious processes more and more suspected to be at the origin of the early (even before $A\beta$ is overproduced) pathological events of AD (Lauritzen et al., 2019; Vaillant-Beuchot et al., 2021). Finally and interestingly, although both α -derived (C83) and β -generated (C99) β APP CTF are subjected to proteolysis by γ -secretase to produce a similar AICD product, the fate of which is different depending on the pathway considered. Thus, since it is suggested to be rapidly degraded by the proteasome and insulin-degrading enzyme (IDE) in the non amyloidogenic pathway (Flammang et al., 2012; Goodger et al., 2009), AICD is stabilized by adaptors in the amyloidogenic route of production and can therefore migrate to the nucleus to transcriptionally regulate some genes with a globally deleterious effect (Bukhari et al., 2017).

In summary, any increase in the activity of BACE1 is expected to be

triply deleterious with regard to β APP processing since it directly (C99) or indirectly ($A\beta_{42}$ and AICD) increases the production of three harmful β APP-derived metabolites (Fig. 1, right panel).

3.2. Neuregulin 1 (Nrg1)

Neuregulins (Nrgs) belong to the epidermal growth factor (EGF) family of extracellular ligands and have gained much attention for their role in myelination, synapse formation, plasticity, migration and neuronal growth via their binding to the ErbB class of receptor tyrosine kinases (Mei and Nave, 2014). In mammals, the neuregulin family members are the products of 4 distinct genes NRG1, NRG2, NRG3 and NRG4 with NRG1–3 being expressed in the central nervous system (CNS). Nrg1 is by far the most studied neuregulin due to its numerous pivotal roles in the CNS and its implication in neurodevelopmental and neurodegenerative disorders (Mei and Nave, 2014; Ou et al., 2021; Shi

and Bergson, 2020). Thus, under physiological conditions, Nrg1 plays important roles in the CNS first by controlling several key processes occurring during development such as the promotion of synapse maturation and function (Li et al., 2007; Ting et al., 2011), the assembly of neural circuitry (Fazzari et al., 2010; Ozaki et al., 1997) and myelination (Willem et al., 2006). Later on in the adult brain, Nrg1 is implicated in the control of several neurotransmitters including dopamine (Kwon et al., 2008) and GABA (Woo et al., 2007) as well as in myelin repair (Stassart et al., 2013) and synaptic plasticity (Jiang et al., 2013).

Nrg1 exists as six different isoforms (type I to type VI) deriving from alternative splicing of the NRG1 gene. On a structural point of view, all Nrg1 isoforms are single pass transmembrane proteins except type III that has a cysteine-rich hydrophobic domain in place of an Ig-like domain and therefore possesses an additional transmembrane region.

Because type III is the predominant Nrg1 isoform in the human brain (Liu et al., 2011), given its important contribution in the control of hippocampal glutamatergic transmission (Zhong et al., 2017) and synaptic plasticity (Agarwal et al., 2014) and considering its particular topology requiring twice the intervention of BACE1 to fully release the EGF domain, we have decided to focus exclusively on this isoform in the context of this review.

Initially anchored to the plasma membrane through two transmembrane segments as a pro-protein, type III Nrg1 will undergo several proteolytic attacks allowing the EGF-like ectodomain to bind to the ErbB family of receptors and to initiate signaling cascades involved in several important brain functions. The first cleavage occurs between the EGF-like domain and the C-terminal transmembrane segment and is mainly carried out by BACE1 (Fleck et al., 2013; Hu et al., 2006; Luo et al., 2011; Willem et al., 2006) to give rise to the production of Nrg1-NTF β and Nrg1-CTF β (Fig. 1, left panel), in opposition to the NTF α and CTF α fragments derived from the processing of Nrg1 by some members of the ADAM family of protease (ADAM10, ADAM17 and ADAM19) at slightly different sites (Horiuchi et al., 2005; Luo et al., 2011; Willem et al., 2006) (not shown). Of note, the involvement of ADAM10 in this process has been questioned (Freese et al., 2009). At this stage, Nrg1-NTF β can only operate in a juxtacrine manner (requiring cell-cell contact) since the EGF-like domain is retained at the plasma membrane by the cysteine-rich transmembrane domain. In order to release soluble EGF-like domain (sEGF) able to fulfill paracrine functions, additional cuts are made by ADAM17 and BACE1 in two distinct places (Fig. 1, left panel) (Fleck et al., 2013). sEGF will then transduce some intracellular signals via its binding to the ErbB4 receptor resulting in the regulation of inhibitory local neural circuit processes (Shi and Bergson, 2020).

Importantly, the two sequential here above described extracellular proteolytic events both stimulate the intramembranous processing of the membrane-bound stubs that they themselves engendered (Nrg1 CTF β and Nrg1 NTF' respectively) by intramembrane cleaving proteases (I-CLiPs). The identity of the proteases involved (γ -secretase for Nrg1 CTF β and SPPL2a/2b for Nrg1 NTF' (Fleck et al., 2016)) as well as the demonstration of functional roles of the γ -secretase-derived C-ICD product in the transcriptional regulation of some genes expression (Bao et al., 2004; Bao et al., 2003), undoubtedly consisted of a step forward in our comprehension of the fine mechanisms regulating the physiology of this protein.

4. Neuregulin 1 is functionally linked with both schizophrenia and Alzheimer's disease

4.1. Nrg1 in schizophrenia

4.1.1. Genetic

The Nrg1 gene (*NRG1*) located on human chromosome 8 was identified as the first gene to be linked with schizophrenia and has been considered a candidate gene for the disease for now more than 20 years (Mostaid et al., 2016, for review). Thus, following genome wide genetic linkage analyses that have identified chromosomes 8p as a susceptibility

loci for schizophrenia (Gurling et al., 2001; Kendler et al., 1996; Pulver et al., 1995), extensive fine-mapping of this locus in an Icelandic population and haplotype-association analysis, supplemented by a transmission/disequilibrium test, identified *NRG1* as a candidate gene for this brain disorder, with the single nucleotide polymorphism (SNP) SNP8NRG221533 giving the best association score (Stefansson et al., 2002). Subsequently, several studies carried out on various populations have confirmed this fact (Stefansson et al., 2003; Williams et al., 2003; Yang et al., 2003a, 2003b). To date, a significant number of SNPs (>80) located in either the coding or the non coding regions of *NRG1* have been associated with schizophrenia (Mostaid et al., 2016). Among them, a valine to leucine substitution at position 322 of exon 11 of *NRG1* (rs74942016) is located at the C-terminal end of the Nrg1 type III trans-membrane domain (Walss-Bass et al., 2006), close to the γ -secretase-dependent ϵ cleavage site (Fleck et al., 2016).

4.1.2. Expression

Despite the high genetic polymorphism associated with schizophrenia, how genetic variation in *NRG1* impacts the disease susceptibility long remained elusive mostly because the SNPs associated with schizophrenia are in their vast majority noncoding elements. In this context of uncertainty, a slight increase in the mRNA levels of type-1 Nrg1 isoform (23%) has been observed in the post mortem dorsolateral prefrontal cortex (PFC) of schizophrenic patients (Hashimoto et al., 2004). Subsequently, this initial tendency has been supported by the demonstration that the SNPs that localized to the 5' region of *NRG1* up regulate Nrg1 expression, as shown by a 34% increase in Nrg1 mRNA levels in the hippocampus of schizophrenic individuals (Law et al., 2006). In addition, an investigation of the effect of the disease on Nrg1 at the protein level has reported an increase in the amounts of Nrg1-ICD by 20% in the cytoplasmic fraction of the PFC of schizophrenic subjects (Chong et al., 2008). At that time, whether these observations were truly a reflection of an increase in the expression of Nrg1 or simply reflected an increase in the cleavage of the protein by γ -secretase remained unclear. The development of transgenic mice overexpressing Nrg1 made it possible to decide on this question and to establish that schizophrenia and an increase in the protein levels of Nrg1 were intimately associated. Thus, inducible over-expression of Type I Nrg1 (Yin et al., 2013), neuronal-specific overexpression of Type IV Nrg1 (Papaleo et al., 2016) and forebrain-driven overexpression of Type III Nrg1 (Olaya et al., 2018) all display schizophrenia-like behaviors.

4.1.3. Mechanisms

The molecular mechanisms through which Nrg1 is promoting schizophrenia most likely rely on an excessive Nrg1-EGF-like domain/ErbB4 interaction and signalling at the post-synaptic level (for review see (Banerjee et al., 2010)). This is primarily supported by the fact that, in addition to the observed increase in Nrg1 expression in schizophrenic subjects (Chong et al., 2008; Hashimoto et al., 2004; Law et al., 2006) theoretically leading to an enhanced production of sEGF, ErbB4 protein levels is also boosted (~30%) in the PFC of schizophrenic patients (Chong et al., 2008). Furthermore, a marked augmentation of Nrg1-induced activation of ErbB4, together with a significant increase in ErbB4/PSD-95 interactions in the PFC of schizophrenic patients has been reported, thus suggesting that an aberrant NRG1 signaling may contribute to N-methyl-D-aspartate (NMDA) hypo function in schizophrenia (Hahn et al., 2006). Concomitantly, Nrg1/ErbB4 interaction has been shown to heighten the susceptibility to schizophrenia (Norton et al., 2006). The additional observation that the Nrg1/ErbB4 pathway lessens the Src-dependent up-regulation of the NMDA receptors (NMDARs) interestingly further goes in favor of a deleterious and schizophrenia-promoting Nrg1/ErbB4-dependent hyper hypo activation of the glutamatergic transmission (Pitcher et al., 2011). Moreover, inhibition of the Nrg1/ErbB4-mediated PI3K/Akt signaling pathways has been identified as a possible therapeutic target for the treatment of schizophrenia (Law et al., 2012).

4.1.4. BACE1-dependent Nrg1 processing and schizophrenia

The probable implication of the BACE1-dependent processing of Nrg1 on the development of schizophrenia comes from several independent observations. At first glance and in a very factual way, BACE1 is involved twice in the metabolism of type III Nrg1, a first time to produce the NTF β and CTF β fragments and a second time to release the EGF-like domain in the extracellular medium and allow it to act in a paracrine manner (Fig. 1). Therefore, BACE1 is preponderantly responsible for the production of sEGF, which binding to its ErbB4 receptor is tightly associated with schizophrenia.

It also appeared that a drastic modification of BACE1 levels in any direction (invalidation or overexpression) initiates the symptoms of schizophrenia. Thus, while BACE1 knockout and the consequent suppression of Nrg1 signalling was shown to impart schizophrenia-like phenotypes in mice by affecting the BACE1/Nrg1/ErbB4/PSD-95 signalling cascade (Hu et al., 2016 for review, Savonenko et al., 2008), abnormally high Nrg1 signalling also raised schizophrenia-like symptoms in transgenic mice overexpressing either full length Nrg1 (Olaya et al., 2018) or the BACE1-derived NTF β fragment (Luo et al., 2014). In line with this, enhanced BACE1 catalytic activity was found in the plasma of schizophrenic patients when compared to control subjects and was correlated with the disease severity and duration (Zhang et al., 2019). Also going in the same direction, a preliminary study carried out on a relatively low number of post mortem samples (6) has detected a higher production of Nrg1-NTF β in the PFC but not in the hippocampus of schizophrenic individuals (Marballi et al., 2012). Finally, a case-control study performed with 50 patients with schizophrenia and 50 healthy controls has reported an up-regulation of BACE1 gene expression in the blood of schizophrenic subjects, this increment being more pronounced in male (Nafisi-Far et al., 2018). Taken together, these data, although requiring confirmation on a larger number of cases, make it possible to reasonably postulate that an increase in the activity of BACE1, the cause of which remains unknown to date, could contribute to the development of schizophrenia.

4.2. Nrg1 in AD

4.2.1. Genetic

Besides the ample number of evidences suggesting a plausible role of the Nrg1-ErbB4 axis in schizophrenia, there are also countable reports on its effect on AD pathology. Nevertheless, the genetic link between Nrg1 and AD is much less than that established with respect to schizophrenia. Indeed, a study reported the existence of one SNP within *NRG1* showing a significant association with late onset AD+P (LOAD) (rs392499, arginine to glutamine substitution in exon 2 at position 38 of the Ig-like domain of Nrg1) (Go et al., 2005), while a later work did not find any association between this SNP and psychotic symptoms of AD in a different LOAD cohort (Middle et al., 2010). It should be noted, in addition to this, that more recently, two SNPs (rs17685233 and rs17101017) within the neuregulin 3 gene (*NRG3*) were significantly associated with AD, regardless of the occurrence of psychoses (Wang et al., 2014).

4.2.2. Expression

Several studies have documented some changes in the expression/level of either Nrg1 or its receptor ErbB4. Taking advances in the field in chronological order, it has been shown twenty years ago that ErbB4 and Nrg1 are strongly associated with neuritic plaques in the hippocampus of both AD patients and APP/PS1 transgenic mice (Chaudhury et al., 2003). It took another 8 years before substantial progress was made on the question with the demonstration of an increase in hippocampal levels of erbB4 and phospho-erbB4 both in the brains of Alzheimer's patients and in that of APP/ transgenic mice PS1 (Woo et al., 2011). Additional more recent works in the field have respectively evidenced that Nrg1 expression was increased in the frontal cortex of AD patients (Jiang et al., 2016) and that the levels of soluble Nrg1 were significantly

higher in the plasma of AD subjects than in age-matched controls (Chang et al., 2016; Mouton-Liger et al., 2020). However, an important decrease (~70%) in Nrg1 protein levels in the hippocampus of AD patients was evidenced (Kim et al., 2018). Finally, Nrg1 has been very recently proposed as a synaptic marker of AD (Vrillon et al., 2022).

4.2.3. Mechanisms

It is currently difficult to locate the cause as well as the true impact (beneficial or harmful) of the observed variations in Nrg1 levels in AD. Indeed, the significant number of studies having shown the same ability for Nrg1 to protect against the toxic events associated with AD suggests that these increases in Nrg1 levels could reflect a phenomenon of compensation.

First regarding the effect of Nrg1 on β APP, contrary results have been reported. Thus, while recombinant Nrg1 decreases β APP protein and mRNA levels in mouse skeletal muscle cells (Rosen et al., 2003), it increases the amount of β APP at the cell surface in SH-SY5Y cells and in rat primary cortical neurons (Kim et al., 2018). Whether this discrepancy is due to different mechanism of action of Nrg1 depending on the cell types remains to be clarified.

Turning now to the impact of this protein in conditions mimicking Alzheimer's disease, Nrg1 was found to protect against apoptosis in β APP_{swE}-overexpressing and A β ₄₂-treated human neuroblastoma cells by increasing Bcl2 expression and decreasing caspase3 activation and mitochondrial ROS generation in an ErbB4-dependent manner (Woo et al., 2012). Another study reported a protective effect of Nrg1 against A β ₂₅₋₃₅-induced cell death through a PI3K-dependent signalling pathway in ErbB4-overexpressing PC12 cells (Di Segni et al., 2005). The involvement of an ErbB4-dependent and PI3K-mediated pathway in the anti-apoptotic effect of Nrg1 was later confirmed in vivo in APP/PS1 Tg mice and in vitro in A β ₄₂- and A β ₂₅₋₃₅-treated primary hippocampal neurons (Cui et al., 2013). In agreement with these results, PI3K inhibition suppresses the Nrg1-dependent rescue of neurotoxicity induced by A β ₄₂ treatment in primary rat cortical neurons (Baik et al., 2016).

Moreover, Nrg1 prevents A β ₄₂-induced impairment of long-term potentiation (LTP) in mice hippocampal slices in an ErbB4-dependent manner (Min et al., 2011). Interestingly, ErbB4 is also mandatory for Nrg1 to protect against APP-CTF (C59 and C100)-induced neurotoxicity (Ryu et al., 2012) and APP-CT31-induced apoptosis (Yoo et al., 2021) in the human SH-SY5Y neuroblastoma cell line.

In addition, the intracerebroventricular delivery of Nrg1 attenuates cognitive impairment in Tg2576 transgenic mice, while treatment with recombinant Nrg1 reduces the loss of dendritic spine density in A β ₄₂ oligomers-treated rat primary hippocampal neurons and alleviates the decrease in neural differentiation in A β ₄₂ oligomers-treated mouse foetal neural stem cells (Ryu et al., 2016). Recently it has been shown that the intracerebroventricular injection of recombinant Nrg1 can improve spatial and associative learning and memory in A β ₄₂-injected rats (Jalilzad et al., 2019).

Finally, Nrg1 also increases the protein level of the A β -degrading enzyme neprilysin both in vivo after the injection of lentiviruses expressing Nrg1 in the hippocampus of APP Tg mice and in vitro following treatment of mouse primary hippocampal neurons with recombinant Nrg1 (Xu et al., 2016).

The opposite variations in Nrg1 levels observed depending on whether one considers the prefrontal cortex (increase in a region of the brain mainly involved in schizophrenia (Jiang et al., 2016)) or the hippocampus (decrease in an area particularly affected in Alzheimer's disease (Mouton-Liger et al., 2020)) further support the probable compensatory nature of these phenomena, especially considering that repression of the Nrg1/ErbB4 signaling pathway is critical for learning and memory (Tian et al., 2016).

5. BACE1 levels and activity are increased in AD

As is the case for β APP, Nrg1-type III is processed by ADAMS, BACE1

and I-CliPs and can therefore produce a variety of distinct fragments (Fleck et al., 2013; Fleck et al., 2016) (Fig. 1), the balanced production of which is expected to be disturbed by any modification of these catalytic activities. Specifically referring to BACE1 that stands as the rate-limiting initiator of A β generation from β APP and represents the major enzyme responsible for the release of the EGF-like domain from Nrg1, despite the lack of genetic association of the protease with AD (Cruts et al., 2001; Li et al., 2004; Zhou et al., 2010), it has been largely evidenced that BACE1 levels and catalytic activity are increased in many ways in the pathology. Thus, several studies have evidenced an augmentation of both BACE1 protein levels and BACE1 catalytic activity in several regions of the brain of sporadic AD patients including the temporal cortex, the frontal cortex and the hippocampus (Ahmed et al., 2010; Cheng et al., 2014; Fukumoto et al., 2002; Li et al., 2004; Tyler et al., 2002; Yang et al., 2003a, 2003b) and that the elevation of BACE1 activity correlates with A β plaques number (Li et al., 2004). Other studies have reported an elevation of BACE1 protein amounts alone in the brain of sporadic AD cases (Holsinger et al., 2002; Sun et al., 2002). The fact that BACE1 mRNA levels were also shown to be increased in the frontal cortex (Li et al., 2004) and the superior parietal gyrus (Coulson et al., 2010) of sporadic AD subjects suggests that the observed rises in BACE1 protein loads may result from the transcriptional up-regulation of the protease.

The interesting additional observation that BACE1 catalytic activity is also higher in the cerebrospinal fluid (CSF) of AD subjects when compared to age-matched controls (Holsinger et al., 2004; Holsinger et al., 2006) identified BACE1 as a possible diagnostic biomarker candidate of AD. Such an eventuality, requiring that the rise in BACE1 is an early event of the pathology, has received support from two works having reported an augmentation of BACE1 protein levels and catalytic activity in mild cognitive impairment (MCI) brains (Cheng et al., 2014) as well as an increased BACE1 activity in the CSF of MCI patients (Alexopoulos et al., 2018).

Finally, in another attempt to determine the potential use of BACE1 as an AD biomarker, it has been evidenced that BACE1 mRNA levels are augmented and that the BACE1 promoter region is more accessible and more prone to histone H3 acetylation in peripheral blood mononuclear cells (PBMC) from AD subjects when compared to controls (Marques et al., 2012), this later observation denoting some epigenetic regulation of BACE1. However, measurement of BACE1 protein levels at the periphery in leucocytes and platelets did not reveal any difference between AD patients and control individuals (Bram et al., 2019).

6. A synergy between the excessive BACE1-dependent cleavages of β APP and Nrg1 in AD?

The well established up regulation of BACE1 in AD combined to the importance of this protease in the metabolism of β APP and Nrg1 and to the obvious association of both substrates with the pathology, make it reasonable to think that a deleterious synergy can be set up, causing the appearance, via β APP, of the stigmata classically associated with Alzheimer's disease (cognitive deficits) and, via Nrg1, associated symptoms more related to psychosis (BPSD). Indeed, a close look at the BACE1-dependent processing of β APP and Nrg1 indicates that any elevation of BACE1 activity is likely to produce abnormally high quantities of metabolites causing a whole series of deleterious events. In the case of β APP, BACE1 over activation leads to overproduction of the C99 fragment and subsequently to an excessive release of A β and AICD, all of these three metabolites conveying adverse effects through neurotoxicity and the loss of function of several vital physiological processes, as extensively described in recent reviews (Bukhari et al., 2017; Checler et al., 2021; Findeis, 2007) (Fig. 1). Two distinct and fully independent origins for the increased BACE1-mediated processing of β APP have to be considered: a double mutation (Swedish) at the β site of β APP (familial AD, representing less than 1% of all AD cases) conferring higher susceptibility of β APP to be cut by BACE1 and a higher expression/activity

of BACE1 (sporadic AD) discussed above and the cause of which is at present still unknown. This later phenomenon, beside its consequences on β APP metabolism leading to an increased A β production, is also promoting the two-step processing of Nrg1-type III, first by cleaving between the EGF-like domain and to produce the membrane-tethered NTF β and CTF β metabolites, and then by releasing sEGF from NTF β (Fig. 1).

As a result, excessive production of sEGF will trigger ErbB4 receptors dimerization and activation via the so-called "forward" signaling pathway of Nrg1 to promote ErbB4/PSD-95 interaction and consequently ErbB4/NMDARs association (Hahn et al., 2006). This will then cause a reduction in NMDA currents due to an induced internalization of the NR1 subunit of NMDA receptors (Gu et al., 2005). In the end, the increase in the activity of BACE1 would therefore lead to an excessive hypo regulation of NMDA transmission, which could underlie the symptoms of psychosis observed in certain Alzheimer's subjects. This hypothetical AD-associated and BACE1/Nrg1-mediated cascade of events (Fig. 2) is strongly reinforced by the fact that the schizophrenia-like phenotypes observed in mice overexpressing the BACE1-cleaved Nrg1 NTF β fragment are reversible (Luo et al., 2014). In summary, the increased levels and activity of BACE1 associated with Alzheimer's disease induces a triad of adverse events through the metabolism of two distinct substrates. Two of these proteolytic cascades lead to an alteration of cognitive functions associated with memory and learning, one via the production of C99 from β APP and the subsequent production of A β and AICD by γ -secretase (Fig. 1, right panel), the other via the release of sEGF from Nrg1 and the sole over activation of the Nrg1/ErbB4 pathway. (Fig. 1 left panel and Fig. 2 right panel). The third deleterious event stems from the same over activation of the Nrg1/ErbB4 pathway but acts downstream of it by disrupting NMDARs activity both through a lessening of the Src-dependent up-regulation of NMDARs (Pitcher et al., 2011) and an increase of their internalization rate (Gu et al., 2005) (Fig. 2). As a consequence, the deficits in NMDARs activity will induce psychotic schizophrenia-like behaviour as demonstrated long ago (Belforte et al., 2010; Mohn et al., 1999).

Another important perspective linked to BACE1 hyper activation is the influence of Nrg1 on the dopaminergic system, which is a vital mediator of learning, memory and other cognitive functions. Thus, Nrg1 induces LTP-depotentiation by increasing extracellular dopamine (DA) levels via type-4 dopamine receptors (D4Rs) in the hippocampus (Andersson et al., 2012; Kwon et al., 2008), although it has been shown that Nrg1 and D4Rs can also operate independently (Izumi and Zorumski, 2017). Therefore, dysfunctions of the dopaminergic transmission reported in AD, schizophrenia and BPSD is also connected to the BACE1-Nrg1 axis.

On a therapeutic point of view, it seems obvious that BACE1 inhibition as an anti-AD therapy has its own pitfall, because of which most of the clinical trials using this strategy probably failed. In this context, it has been suggested to specifically deliver BACE1 inhibitor within the endosomal compartment to select β APP processing without affecting the metabolism of its other substrates (Ben Halima et al., 2016). However, at the light of what is discussed in the present review, the recommendation to be extremely careful when considering therapeutic strategies aimed at developing BACE1-targeting drugs by focusing on the preferential inhibition of the amyloidogenic processing of β APP versus the cleavages of other BACE1 substrates, including Nrg1, has to be tempered, all the more so if we consider that BACE1 physiological roles evolve drastically during lifespan. Thus, while BACE1 inhibition during the neuronal development of mice is undoubtedly deleterious due to severe hypomyelination (Hu et al., 2006; Willem et al., 2006), it has been evidenced that long term BACE1 inhibition leads to a loss of synaptic proteins at different developmental stages but is not affecting the already developed synapses (Kamikubo et al., 2017). This altogether means that diminishing BACE1 activity at adulthood, at advanced ages and even more so in AD subjects, could be triply beneficial via the decrease in both β APP and Nrg1 processing, this hypothesis of course having to be confirmed

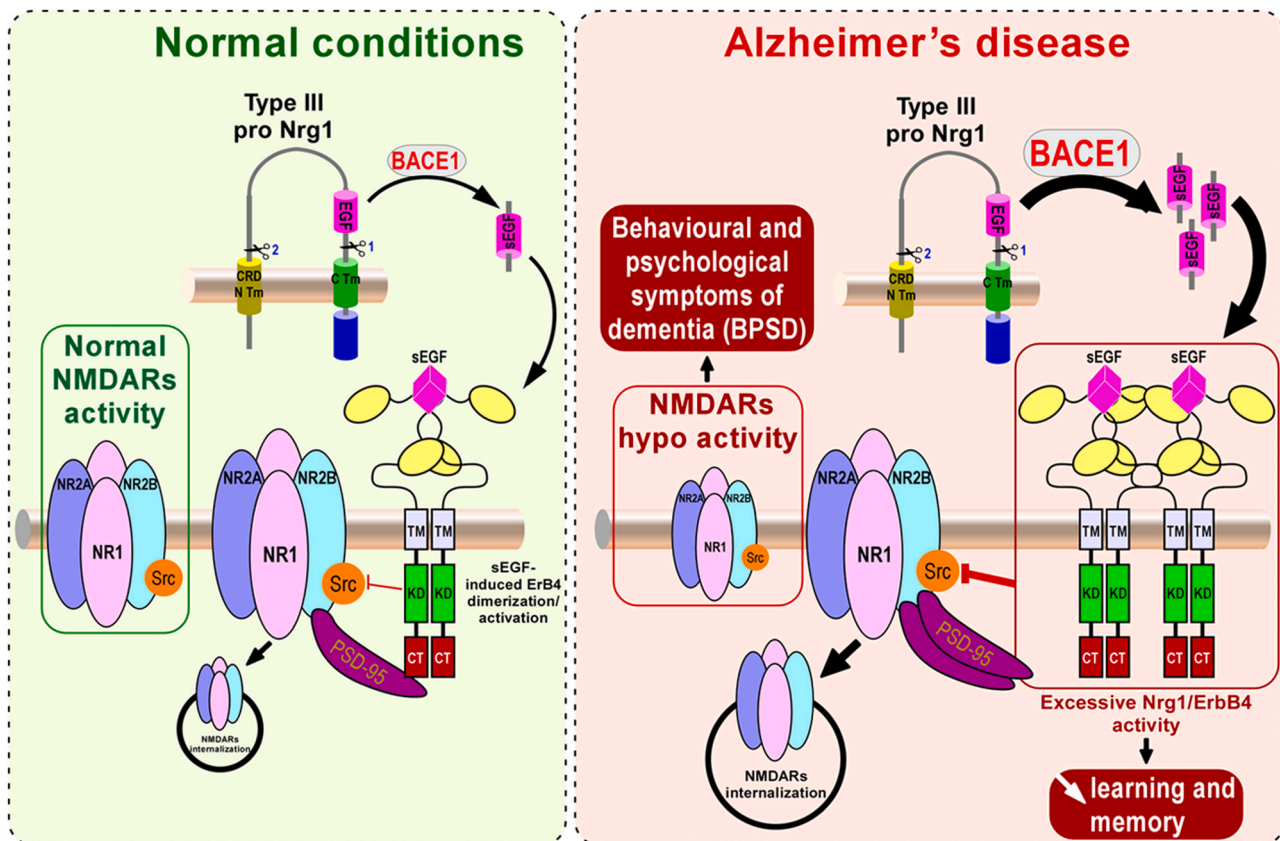


Fig. 2. Illustration of BACE1-dependent Nrg1-mediated signalling pathways under normal and AD conditions. Under normal conditions (green background, left side of the figure), basal BACE1 activity will engender physiological levels of sEGF that will trigger the dimerization and activation of ErbB4 receptors. This will lead to a double inhibition of NMDARs, one via the association with the PSD-95 protein which promotes its internalization, the other via the inhibition of Src, an activating kinase of NMDARs. Under AD pathological conditions where BACE1 activity is increased (orange background, right side of the figure), the dimerization/activation of ErbB4 receptors is exacerbated following an higher production of sEGF. This consequently provides an increased inhibition of Src as well as more NMDARs internalization via PSD-95, thereby causing an abnormally strong drop in the activity of these receptors, resulting in the manifestation of AD-associated psychotic syndromes (BPSD).

by additional studies.

7. Concluding remarks

The occurrence of psychotic symptoms resembling those observed in schizophrenia during the time course of AD has been well documented over the past three decades. Thus, approximately 50% of AD subjects develop such signs among which 35% experiencing delusions and 15% hallucinations (Gormley et al., 1998; Jeste and Finkel, 2000; Ropacki et al., 2005). The reason why not all Alzheimer's patients develop these symptoms remains unknown, although it may be based on genetic and/or environmental factors. Anyhow, the ability of BACE1 to simultaneously convey psychosis and cognitive deficits via the processing of two distinct substrates, combined with the fact that its activity is increasing with age (Fukumoto et al., 2004) and is higher in AD than in healthy individuals (Ahmed et al., 2010; Cheng et al., 2014; Coulson et al., 2010; Fukumoto et al., 2002; Holsinger et al., 2002; Holsinger et al., 2004; Holsinger et al., 2006; Li et al., 2004; Sun et al., 2002; Tyler et al., 2002; Yang et al., 2003a, 2003b), make this protease a credible initiator of the onset of schizophrenia-like psychotic disorders in about half of Alzheimer's patients.

In summary, this review brings, in the light of the work carried out in the field, an additional stone to the concept according to which most brain disorders share common pathogenic processes involving in some cases the same molecular entities.

Thus, this overlap of AD with schizophrenia described here via BACE1 adds to the already established existence of shared mechanisms

and molecular common denominators between AD and other brain disorders including PD (Checler and Alves da Costa, 2022; Tan et al., 2019; Xie et al., 2014), Huntington disease (HD) (Ehrnhoefer et al., 2011; Spiess and Hannan, 2007), amyotrophic lateral sclerosis (ALS) (Bryson et al., 2012; Mhatre et al., 2004) and prion diseases (Checler and Vincent, 2002; Purro et al., 2018). These multiple overlaps could allow the implementation of therapeutic strategies aimed at targeting pathways shared by distinct neurodegenerative pathologies.

CRedit authorship contribution statement

Bruno Vincent: Conceptualization, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Subhamita Maitra:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

References

- Adityanjee, Aderibigbe, Y.A., Theodoridis, D., Vieweg, V.R., 1999. Dementia praecox to schizophrenia: the first 100 years. In: *Psychiatry Clin. Neurosci.* 53, pp. 437–448. <https://doi.org/10.1046/j.1440-1819.1999.00584.x>
- Agarwal, A., Zhang, M., Trembak-Duff, I., Unterbarnscheidt, T., Radyushkin, K., Dibaj, P., Martins de Souza, D., Boretius, S., Brzózka, M.M., Sreffiens, H., Berning, S., Teng, Z., Gummert, M.N., Tantra, M., Guest, P.C., Willig, K.I., Frahm, J., Hell, S.W., Bahn, S., Rossner, M.J., Nave, K.A., Ehrenreich, H., Zhang, W., Schwab, M.H., 2014.

- Dysregulated expression of neuregulin-1 by cortical pyramidal neurons disrupts synaptic plasticity. *Cell Rep.* 8 (4), 1130–1145. <https://doi.org/10.1016/j.celrep.2014.07.026>.
- Ahmed, R.R., Holler, C.J., Webb, R.L., Li, F., Beckett, T.L., Murphy, M.P., 2010. BACE1 and BACE2 enzymatic activities in Alzheimer's disease. *J. Neurochem.* 112 (4), 1045–1053. <https://doi.org/10.1111/j.1471-4159.2009.06528.x>.
- Alexopoulos, P., Thierjung, N., Grimmer, T., Ortner, M., Economou, P., Assimakopoulos, K., Gourzis, P., Politis, A., Pernecky, R., 2018. The Alzheimer's Disease Neuroimaging Initiative, Cerebrospinal fluid BACE1 activity and sAPP β as biomarker candidates of Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* 45 (3–4), 152–161. <https://doi.org/10.1159/000488481>.
- Alzheimer, A., 1906. Über einen eigenartigen schweren Erkrankungsprozeß der Hirnrinde. *Neurol. Cent.* 23, 1129–1136.
- Andersson, R.H., Johnston, A., Herman, P.A., Winzer-Serhan, U.H., Karavanova, I., Vullhorst, D., Fisahn, A., Buonanno, A., 2012. Neuregulin and dopamine modulation of hippocampal gamma oscillations is dependent on dopamine D4 receptors. *Proc. Natl. Acad. Sci. USA* 109 (32), 13118–13123. <https://doi.org/10.1073/pnas.1201011109>.
- Baik, T.K., Kim, Y.J., Kang, S.M., Song, D.Y., Min, S.S., Woo, R.S., 2016. Blocking the phosphatidylinositol 3-kinase pathway inhibits neuregulin-1-mediated rescue of neurotoxicity induced by A β ₁₋₄₂. *J. Pharm. Pharm.* 68 (8), 1021–1029. <https://doi.org/10.1111/jphp.12563>.
- Banerjee, A., Macdonald, M.L., Borgmann-Winter, K.E., Hahn, C.G., 2010. Neuregulin 1-erbB4 pathway in schizophrenia: from genes to an interactome. *Brain Res. Bull.* 83 (3–4), 132–139. <https://doi.org/10.1016/j.brainresbull.2010.04.011>.
- Bao, J., Wolpowitz, D., Role, L.W., Talmage, D.A., 2003. Back signalling by the Nrg-1 intracellular domain. *J. Cell Biol.* 161 (6), 1133–1141. <https://doi.org/10.1083/jcb.200212085>.
- Bao, J., Lin, H., Ouyang, Y., Lei, D., Osman, A., Kim, T.W., Mei, L., Dai, P., Ohlemiller, K. K., Ambron, R.T., 2004. Activity-dependent transcription regulation of PSD-95 by neuregulin-1 and Eos. *Nat. Neurosci.* 7 (11), 1250–1258. <https://doi.org/10.1038/nrn1342>.
- Barão, S., Moechars, D., Lichtenthaler, S.F., De Strooper, B., 2016. BACE1 physiological functions may limit its use as therapeutic target for Alzheimer's disease. *Trends Neurosci.* 39 (3), 158–169. <https://doi.org/10.1016/j.tins.2016.01.003>.
- Belforte, J.E., Zsiros, V., Sklar, E.R., Jiang, Z., Yu, G., Li, Y., Quinlan, E.M., Nakazawa, K., 2010. Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat. Neurosci.* 13 (1), 76–83. <https://doi.org/10.1038/nn.2447>.
- Ben Halima, S., Mishra, S., Raja, K.M.P., Willem, M., Baici, A., Simons, K., Brüstle, O., Koch, P., Haass, C., Cafilisch, A., Rajendran, L., 2016. Specific inhibition of β -secretase processing of the Alzheimer disease amyloid precursor protein. *Cell Rep.* 14 (9), 2127–2141. <https://doi.org/10.1016/j.celrep.2016.01.076>.
- Bleuler, E., 1908. Die prognose der dementia praecox (Schizophreniegruppe). *Allg. Z. Psychiatr. Psych. Med.* 65, 436–464.
- Bondi, M.W., Edmonds, E.C., Salmon, D.P., 2017. Alzheimer's disease: past, present, and future. *J. Int. Neuropsychol. Soc.* 23 (9–10), 818–831. <https://doi.org/10.1017/S15565171700100x>.
- Bram, J.M.F., Talib, L.L., Joaquim, H.P.G., Sarno, T.A., Gattaz, W.F., Forlenza, O.V., 2019. Protein levels of ADAM10, BACE1, and PSEN1 in platelets and leukocytes of Alzheimer's disease. *Eur. Arch. Psychiatry Clin. Neurosci.* 269 (8), 963–972. <https://doi.org/10.1007/s00406-018-0905-3>.
- Bryson, J.B., Hobbs, C., Parsons, M.J., Bosch, K.D., Pandraud, A., Walsh, F.S., Doherty, P., Greensmith, L., 2012. Amyloid precursor protein (APP) contributes to pathology in the SOD(G93A) mouse model of amyotrophic lateral sclerosis. *Hum. Mol. Genet.* 21 (17), 3871–3882. <https://doi.org/10.1093/hmg/das215>.
- Bukhari, H., Glotzbach, A., Kolbe, K., Leonhardt, G., Loosche, C., Müller, T., 2017. Small things matter: Implications of APP intracellular domain AICD nuclear signalling in the progression and pathogenesis of Alzheimer's disease. *Prog. Neurobiol.* 156, 189–213. <https://doi.org/10.1016/j.pneurobio.2017.05.005>.
- Cai, J., Huang, L., 2018. Schizophrenia and risk of dementia: a meta-analysis study. *Neuropsychiatr. Dis. Treat.* 14, 2047–2055. <https://doi.org/10.2147/ndt.s172933>.
- Chang, K.A., Shin, K.Y., Nam, E., Lee, Y.B., Moon, C., Suh, Y.H., Lee, S.H., 2016. Plasma soluble neuregulin-1 as a diagnostic biomarker for Alzheimer's disease. *Neurochem. Int.* 97, 1–7. <https://doi.org/10.1016/j.neuint.2016.04.012>.
- Chaudhury, A.R., Gerecke, K.M., Wyss, J.M., Morgan, D.G., Gordon, M.N., Carroll, S.L., 2003. Neuregulin-1 and erbB4 immunoreactivity is associated with neuritic plaques in Alzheimer disease brain and in a transgenic model of Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 62 (1), 42–54. <https://doi.org/10.1093/jnen/62.1.42>.
- Checler, F., Alves da Costa, C., 2022. Parkin as a molecular bridge linking Alzheimer's and Parkinson's diseases? *Biomolecules* 12 (4), 559. <https://doi.org/10.3390/biom12040559>.
- Checler, F., Vincent, B., 2002. Alzheimer's and prion diseases: distinct pathologies, common proteolytic denominators. *Trends Neurosci.* 25 (12), 616–620. [https://doi.org/10.1016/S0166-2236\(02\)02263-4](https://doi.org/10.1016/S0166-2236(02)02263-4).
- Checler, F., Afram, E., Pardossi-Piquard, R., Lauritzen, I., 2021. Is γ -secretase a beneficial inactivating enzyme of the toxic APP C-terminal fragment C99? *J. Biol. Chem.* 296, 100489. <https://doi.org/10.1016/j.jbc.2021.100489>.
- Cheng, X., He, P., Lee, T., Yao, H., Li, R., Shen, Y., 2014. High activities of BACE1 in brains with mild cognitive impairment. *Am. J. Pathol.* 184 (1), 141–147. <https://doi.org/10.1016/j.ajpath.2013.10.002>.
- Cho, Y., Bae, H.G., Okun, E., Arumugam, T.V., Jo, D.G., 2022. Physiology and pharmacology of amyloid precursor protein. *Pharmacol. Ther.* 235, 108122. <https://doi.org/10.1016/j.pharmthera.2022.108122>.
- Chong, V.Z., Thompson, M., Beltaifa, S., Webster, M.J., Law, A.J., Weickert, C.S., 2008. Elevated neuregulin-1 and ErbB4 protein in the prefrontal cortex of schizophrenic patients. *Schizophr. Res.* 100 (1–3), 270–280. <https://doi.org/10.1016/j.schres.2007.12.474>.
- Connors, M.H., Ames, D., Woodward, M., Brodaty, H., 2018. Psychosis and clinical outcomes in Alzheimer disease: a longitudinal study. *Am. J. Geriatr. Psychiatry* 26 (3), 304–313. <https://doi.org/10.1016/j.jagp.2017.10.011>.
- Coulson, D.T.R., Beyer, N., Quinn, J.G., Brockbank, S., Hellemans, J., Irvine, G.B., Ravid, R., Johnston, J.A., 2010. BACE1 mRNA expression in Alzheimer's disease postmortem brain tissue. *J. Alzheimers Dis.* 22 (4), 1111–1122. <https://doi.org/10.3233/jad-2010-101254>.
- Creese, B., Vassos, E., Bergh, S., Athanasiu, L., Johar, I., Rongve, A., Tøndel Medbøen, I., Vasconcelos Da Silva, M., Aakhus, E., Andersen, F., Bettella, F., Braekhus, A., Djurovic, S., Paroni, G., Proitsi, P., Saltvedt, I., Seripa, D., Stordal, E., Fladby, T., Aarsland, D., Andreassen, O.A., Ballard, C., Selbaek, G., 2019. Examining the association between genetic liability for schizophrenia and psychotic symptoms in Alzheimer's disease. *Transl. Psychiatry* 9 (1), 273. <https://doi.org/10.1038/s41398-019-0592-5>.
- Cruts, M., Dermaut, B., Rademakers, R., Roks, G., Van den Broeck, M., Munteanu, G., van Duijn, C.M., Van Broeckhoven, C., 2001. Amyloid beta secretase gene (BACE) is neither mutated in nor associated with early-onset Alzheimer's disease. *Neurosci. Lett.* 131 (1–2), 105–107. [https://doi.org/10.1016/S0304-3940\(01\)02234-0](https://doi.org/10.1016/S0304-3940(01)02234-0).
- Cui, W., Tao, J., Wang, Z., Ren, M., Zhang, Y., Sun, Y., Peng, Y., Li, R., 2013. Neuregulin1beta1 antagonizes apoptosis via ErbB4-dependent activation of PI3-Kinase/Akt in APP/PS1 transgenic mice. *Neurochem. Res.* 38 (11), 2237–2246. <https://doi.org/10.1007/s11064-013-1131-z>.
- DeMichele-Sweet, M.A., Sweet, R.A., 2010. Genetics of psychosis in Alzheimer's disease: a review. *J. Alzheimers Dis.* 19 (3), 761–780. <https://doi.org/10.3233/jad-2010-1274>.
- DeMichele-Sweet, M.A., Weamer, E.A., Klei, L., Vranag, D.T., Hollingshead, D.J., Seltman, H.J., Sims, R., Foroud, T., Hernandez, I., Moreno-Grau, S., Tárrega, L., Boada, M., Ruiz, A., Williams, J., Mayeux, R., Lopez, O.L., Sibille, E.L., Kamboh, M.I., Devlin, B., R.A., 2018. Sweet, Genetic risk for schizophrenia and psychosis in Alzheimer disease. *Mol. Psychiatry* 23 (4), 963–972. <https://doi.org/10.1038/mp.2017.81>.
- Di Segni, A., Shaharabani, E., Stein, R., Pinkas-Kramarski, R., 2005. Neuregulins rescue PC12-ErbB-4 cells from cell death induced by beta-amyloid peptide: involvement of PI3K and PKC. *J. Mol. Neurosci.* 26 (1), 57–69. <https://doi.org/10.1385/jmn:26:1:057>.
- Ehrnhoefer, D.E., Wong, B.K.Y., Hayden, M.R., 2011. Convergent pathogenic pathways in Alzheimer's and Huntington's diseases: shared targets for drug development. *Nat. Rev. Drug Discov.* 10 (11), 853–867. <https://doi.org/10.1038/nrd3556>.
- Fazzari, P., Paternani, A.V., Valiente, M., Pla, R., Lujan, R., Lloyd, K., Lerma, J., Marin, O., Rico, B., 2010. Control of cortical GABA circuitry development by Nrg1 and ErbB4 signalling. *Nature* 464 (7293), 1376–1380. <https://doi.org/10.1038/nature08928>.
- Ferreira, M.D.C., Abreu, J.A., Machado, C., Santos, B., Machado, A., Costa, A.S., 2018. Neuropsychiatric profile in early versus late onset Alzheimer's disease. *Am. J. Alzheimers Dis. Other Demen.* 33 (2), 93–99. <https://doi.org/10.1177/1533317517744061>.
- Findeis, M.A., 2007. The role of amyloid beta peptide 42 in Alzheimer's disease. *Pharmacol. Ther.* 116 (2), 266–288. <https://doi.org/10.1016/j.pharmthera.2007.06.006>.
- Flammang, B., Pardossi-Piquard, R., Sevalle, J., Debayle, D., Dabert-Gay, A.S., Thévenet, A., Lauritzen, I., Checler, F., 2012. Evidence that the amyloid- β protein precursor intracellular domain, AICD, derives from β -secretase-generated C-terminal fragment. *J. Alzheimers Dis.* 30 (1), 145–153. <https://doi.org/10.3233/jad-2012-112186>.
- Fleck, D., van Bèber, F., Colombo, A., Galante, C., Schwenk, B.M., Rabe, L., Hampel, H., Novak, B., Kremmer, E., Tahirovic, S., Edbauer, D., Lichtenthaler, S.F., Scmid, B., Willem, M., Haass, C., 2013. Dual cleavage of neuregulin 1 type III by BACE1 and ADAM17 liberates its EGF-like domain and allows paracrine signalling. *J. Neurosci.* 33 (18), 7856–7869. <https://doi.org/10.1523/jneurosci.3372-12.2013>.
- Fleck, D., Voss, M., Brankatschk, B., Giudici, C., Hampel, H., Schwenk, B., Edbauer, D., Fukumori, A., Steiner, H., Kremmer, E., Haug-Kröper, M., Rossner, M.J., Fluhner, R., Willem, M., Haass, C., 2016. Proteolytic processing of neuregulin 1 type III by three intramembrane-cleaving proteases. *J. Biol. Chem.* 291 (1), 318–333. <https://doi.org/10.1074/jbc.m115.697995>.
- Fox, H.A., 1983. The DSM-III concept of organic brain syndrome. *Br. J. Psychiatry* 142, 419–421. <https://doi.org/10.1192/bjp.142.4.419>.
- Freese, C., Garratt, A.N., Fahrenholz, F., Endres, K., 2009. The effects of alpha-secretase ADAM10 on the proteolysis of neuregulin-1. *FEBS J.* 276 (6), 1568–1580. <https://doi.org/10.1111/j.1742-4658.2009.06889.x>.
- Fukumoto, H., Cheung, B.S., Hyman, B.T., Irizarry, M.C., 2002. Beta-secretase protein and activity are increased in the neocortex in Alzheimer's disease. *Arch. Neurol.* 59 (9), 1381–1389. <https://doi.org/10.1001/archneur.59.9.1381>.
- Fukumoto, H., Rosene, D.L., Moss, M.B., Raju, S., Hyman, B.T., Irizarry, M.C., 2004. Beta-secretase activity increases with aging in human, monkey, and mouse brain. *Am. J. Pathol.* 164 (2), 719–725. [https://doi.org/10.1016/S0002-9440\(10\)63159-8](https://doi.org/10.1016/S0002-9440(10)63159-8).
- Fuller, J.T., Choudhury, T.K., Lowe, D.A., Balsis, S., 2020. Hallucinations and delusions signal Alzheimer's associated cognitive dysfunction more strongly compared to other neuropsychiatric symptoms. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 75 (9), 1894–1904. <https://doi.org/10.1093/geronb/gbz032>.
- Gaser, C., Nenadic, I., Volz, H.P., Büchel, C., Sauer, H., 2004. Neuroanatomy of 'hearing voices': a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cereb. Cortex* 14 (1), 91–96. <https://doi.org/10.1093/cercor/bhg107>.

- Go, R.C.P., Perry, R.T., Wiener, H., Bassett, S.S., Blacker, D., Devlin, B., Sweet, R.A., 2005. Neuregulin-1 polymorphism in late onset Alzheimer's disease families with psychoses. *Am. J. Genet. B Neuropsychiatr. Genet.* 139B (1), 28–32. <https://doi.org/10.1002/ajmg.b.30219>.
- Goodger, Z.V., Rajendran, L., Trutzel, A., Kholi, B.M., Nitsch, R.M., Konietzko, U., 2009. Nuclear signaling by the APP intracellular domain occurs predominantly through the amyloidogenic processing pathway. *J. Cell Sci.* 122 (20), 3703–3714. <https://doi.org/10.1242/jcs.048090>.
- Gormley, N., Rizwan, M.R., 1998. Prevalence and clinical correlates of psychotic symptoms in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 13 (6), 410–414. [https://doi.org/10.1002/\(sici\)1099-1166\(199806\)13:6%3C410::aid_gps787%3E3.0.co;2-s](https://doi.org/10.1002/(sici)1099-1166(199806)13:6%3C410::aid_gps787%3E3.0.co;2-s).
- Goukasian, N., Hwang, K.S., Romero, T., Grotts, J., Do, T.M., Groh, J.R., Bateman, D.R., Apostolova, L.G., 2019. Association of brain amyloidosis with the incidence and frequency of neuropsychiatric symptoms in ADNI: a multisite observational cohort study. *BMJ Open* 9, e031947. <https://doi.org/10.1136/bmjopen-2019-031947>.
- Gu, Z., Jiang, Q., Fu, A.K.Y., Ip, N.Y., Yan, S., 2005. Regulation of NMDA receptors by neuregulin signalling in prefrontal cortex. *J. Neurosci.* 25 (20), 4974–4984. <https://doi.org/10.1523/jneurosci.1086-05.2005>.
- Güner, G., Lichtenthaler, S., 2020. The substrate repertoire of γ -secretase/presenilin. *Semin. Cell Dev. Biol.* 105, 27–42. <https://doi.org/10.1016/j.semcdb.2020.05.019>.
- Gurling, H.M., Kalsi, G., Brynjolfson, J., Sigmundsson, T., Sherrington, R., Mankoo, B.S., Read, T., Murphy, P., Blaveri, E., McQuillin, A., Petursson, H., Curtis, D., 2001. Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosome 11q23.3-24 and 20q12.1-11.23. *Am. J. Hum. Genet.* 68 (3), 661–673. <https://doi.org/10.1086/318788>.
- Hahn, C.G., Wang, H.Y., Cho, D.S., Talbot, K., Gur, R.E., Berrettini, W.H., Bakshi, K., Kamins, J., Borgmann-Winter, K.E., Siegel, S.J., Gallop, R.J., Arnold, S.E., 2006. Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. *Nat. Med.* 12 (7), 824–828. <https://doi.org/10.1038/nm1418>.
- Hany, M., Rehman, B., Azhar, Y., Chapman, J., 2022. Schizophrenia. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
- Hashimoto, R., Straub, R.E., Weickert, C.S., Hyde, T.M., Kleinman, J.E., Weinberger, D.R., 2004. Expression analysis of neuregulin-1 in the dorsolateral prefrontal cortex in schizophrenia. *Mol. Psychiatry* 9 (3), 299–307. <https://doi.org/10.1038/sj.mp.4001434>.
- Higaki, J., Murphy Jr, G.M., Cordell, B., 1997. Inhibition of β -amyloid formation by haloperidol: a possible mechanism for reduced frequency of Alzheimer's disease pathology in schizophrenia. *J. Neurochem.* (68) (1), 333–336. <https://doi.org/10.1046/j.1471-4159.1997.68010333.x>.
- Holsinger, R.M.D., McLean, C.A., Beyreuther, K., Masters, C.L., Evin, G., 2002. Increased expression of the amyloid precursor beta-secretase in Alzheimer's disease. *Ann. Neurol.* 51 (6), 783–786. <https://doi.org/10.1002/ana.10208>.
- Holsinger, R.M.D., McLean, C.A., Collins, S.J., Masters, C.L., Evin, G., 2004. Increased beta-secretase activity in cerebrospinal fluid of Alzheimer's disease subjects. *Ann. Neurol.* 55 (6), 898–899. <https://doi.org/10.1002/ana.20144>.
- Holsinger, R.M.D., Lee, J.S., Boyd, A., Masters, C.L., Collins, S.J., 2006. CSF BACE1 activity is increased in CJD and Alzheimer disease versus other dementias. *Neurology* 67 (4), 710–712. <https://doi.org/10.1212/01.wnl.0000229925.52203.4c>.
- Horiuchi, K., Zhou, H.M., Kelly, K., Manova, K., Blobel, C.P., 2005. Evaluation of the contributions of ADAM9,12,15,17, and 19 to heart development and ectodomain shedding of neuregulins beta1 and beta2. *Dev. Biol.* 283 (2), 459–471. <https://doi.org/10.1016/j.ydbio.2005.05.004>.
- Hu, X., Hicks, C.W., He, W., Wong, P., Macklin, W.B., Trapp, B.D., Yan, R., 2006. Bace1 modulates myelination in the central and peripheral nervous system. *Nat. Neurosci.* 9 (12), 1520–1525. <https://doi.org/10.1038/nn1797>.
- Hu, X., Fan, Q., Hou, H., Yan, R., 2016. Neurological dysfunctions associated with altered BACE1-dependent neuregulin-1 signaling. *J. Neurochem.* 136 (2), 234–249. <https://doi.org/10.1111/jnc.13395>.
- Izumi, Y., Zorumski, C.F., 2017. Neuregulin and dopamine D4 receptors contribute independently to depotentiation of Schaffer collateral LTP by temperoammonic path stimulation. *ENEURO* 0176–17, 2017. <https://doi.org/10.1523/eneuro.0176-17.2017>.
- Jahn, H., 2013. Memory loss in Alzheimer's disease. *Dialog.- Clin. Neurosci.* 15 (4), 445–454. <https://doi.org/10.31887/dcms.2013.15.4/hjahn>.
- Jalilzad, M., Jafari, A., Babaei, P., 2019. Neuregulin β improves both spatial and associative learning and memory in Alzheimer model of rats possibly through signaling pathways other than Erk1/2. *Neuropeptides* 78, 101963. <https://doi.org/10.1016/j.npep.2019.101963>.
- Jeste, D.V., Finkel, S.I., 2000. Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. *Am. J. Geriatr. Psychiatry* 8 (1), 29–34. <https://doi.org/10.1097/00019442-200002000-00004>.
- Jiang, Q., Chen, S., Hu, C., Huang, P., Shen, H., Zhao, W., 2016. Neuregulin-1 (Nrg1) signaling has a preventive role and is altered in the frontal cortex under the pathological conditions of Alzheimer's disease. *Mol. Med. Rep.* 14 (3), 2614–2624. <https://doi.org/10.3892/mmr.2016.5542>.
- Jiang, L., Emmetsberger, J., Talmage, D.A., Role, L.W., 2013. Type III neuregulin 1 is required for multiple forms of excitatory synaptic plasticity of mouse cortico-amygdala circuits. *J. Neurosci.* 33 (23), 9655–9666.
- Kamikubo, Y., Takasugi, N., Niisato, K., Hashimoto, Y., Sakurai, T., 2017. Consecutive analysis of BACE1 function on developing and developed neuronal cells. *J. Alzheimers Dis.* 56 (2), 641–653. <https://doi.org/10.3233/jad-160806>.
- Kendler, K.S., MacLean, C.J., O'Neill, F.A., Burke, J., Murphy, B., Duke, F., Shinkwin, R., Easter, S.M., Webb, B.T., Zhang, J., Walsh, D., Straub, R.E., 1996. Evidence for a schizophrenia vulnerability locus on chromosome 8p in the Irish study of high-density schizophrenia families. *Am. J. Psychiatry* 153 (12), 1534–1540. <https://doi.org/10.1176/ajp.153.12.1534>.
- Kim, Y.J., Yoo, J.Y., Kim, O.S., Kim, H.B., Ryu, J., Kim, H.S., Lee, J.H., Yoo, H.I., Song, D.Y., Baik, T.K., Woo, R.S., 2018. Neuregulin 1 regulates amyloid precursor protein cell surface expression and non-amyloidogenic processing. *J. Pharmacol. Sci.* 137 (2), 146–153. <https://doi.org/10.1016/j.jphs.2018.05.004>.
- Koppel, J., Sunday, S., Goldberg, T.E., Davies, P., Christen, E., Greenwald, B.S., 2014. Alzheimer's Disease Neuroimaging Initiative, Psychosis in Alzheimer's disease is associated with frontal metabolic impairment and accelerated decline in working memory: findings from the Alzheimer's Disease Neuroimaging Initiative. *Am. J. Geriatr. Psychiatry* 22 (7), 698–707. <https://doi.org/10.1016/j.jagp.2012.10.028>.
- Ku, H., Lee, E.K., Lee, K.U., Lee, M.Y., Kwon, J.W., 2016. Higher prevalence of dementia in patients with schizophrenia: A nationwide population-based study. *Asia Pac. Psychiatry* 8 (2), 145–153. <https://doi.org/10.1111/appy.12239>.
- Kwon, O.B., Paredes, D., Gonzalez, C.M., Neddens, J., Hernandez, L., Vullhorst, D., Buonanno, A., 2008. Neuregulin-1 regulates LTP at CA1 hippocampal synapses through activation of dopamine D4 receptors. *Proc. Natl. Acad. Sci. USA* 105 (40), 15587–15592. <https://doi.org/10.1073/pnas.0805722105>.
- Lacasse, J.R., 2014. After DSM-5: a critical mental health research agenda for the 21st century. *Res. Soc. Work Pract.* 24 (1), 5–10. <https://doi.org/10.1177/1049731513510048>.
- Lancôt, K.L., Amatniek, J., Ancoli-Israel, S., Arnold, S.E., Ballard, C., Cohen-Ransfield, J., Ismail, Z., Lyketsos, C., Miller, D.S., Musiek, E., Osorio, R.S., Rosenberg, P.B., Satlin, A., Steffens, D., Tariot, P., Bain, L.J., Carrillo, M.C., Hendrix, J.A., Jurgens, H., Boot, B., 2017. Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms. *Alzheimers Dement.* 3 (3), 440–449. <https://doi.org/10.1016/j.trci.2017.07.001>.
- Laughren, T., 2011. FDA perspective on the DSM-5 approach to classification of "cognitive" disorders. *J. Neuropsychiatry Clin. Neurosci.* 23 (2), 126–131. <https://doi.org/10.1176/jnp.23.2.jnp126>.
- Lauritzen, I., Pardossi-Piquard, R., Bourgeois, A., Bécot, A., Checler, F., 2019. Does intraneuronal accumulation of carboxy-terminal fragments of the amyloid precursor protein trigger early neurotoxicity in Alzheimer's disease? *Curr. Alzheimer Res* 16 (5), 453–457. <https://doi.org/10.2174/1567205016666190325092841>.
- Law, A.J., Lipska, B.K., Weickert, C.S., Hyde, T.M., Straub, R.E., Hashimoto, R., Harrison, P.J., Kleinman, J.E., Weinberger, D.R., 2006. Neuregulin 1 transcripts are differentially expressed in schizophrenia and regulated by 5' SNPs associated with the disease. *Proc. Natl. Acad. Sci.* 103 (17), 6747–6752. <https://doi.org/10.1073/pnas.0602002103>.
- Law, A.J., Wang, Y., Sei, Y., O'Donnell, P., Piantadosi, P., Papaleo, F., Straub, R.E., Huang, W., Thomas, C.J., Vakkalanka, R., Besterman, A.D., Lipska, B.K., Hyde, T.M., Harrison, P.J., Kleinman, J.E., Weinberger, D.R., 2012. Neuregulin-1-ErbB4-PI3K signaling in schizophrenia and phosphoinositide 3-kinase-p110 γ inhibition as a potential therapeutic strategy. *Proc. Natl. Acad. Sci. USA* 109 (30), 12165–12170. <https://doi.org/10.1073/pnas.1206118109>.
- Li, B., Woo, R.S., Mei, L., Malinow, R., 2007. The neuregulin-1 receptor ErbB4 controls glutamatergic synapse maturation and plasticity. *Neuron* 54, 583–597. <https://doi.org/10.1016/j.neuron.2007.03.028>.
- Li, R., Lindholm, K., Yang, L.B., Yue, X., Citron, M., Yan, R., Beach, T., Sue, L., Sabbagh, M., Cai, H., Wong, P., Price, D., Shen, Y., 2004. Amyloid beta peptide load is correlated with increased beta-secretase activity in sporadic Alzheimer's disease patients. *Proc. Natl. Acad. Sci. USA* 101 (10), 3632–3637. <https://doi.org/10.1073/pnas.0205689101>.
- Liu, X., Bates, R., Yin, D.M., Shen, C., Wang, F., Su, N., Kirov, S.A., Luo, Y., Wang, J.Z., Xiong, W.C., Mei, L., 2011. Specific regulation of NRG1 isoform expression by neuronal activity. *J. Neurosci.* 31 (23), 8491–8501. <https://doi.org/10.1523/jneurosci.5317-10.2011>.
- Luo, X., Prior, M., He, W., Hu, X., Tang, X., Shen, W., Yadav, S., Kiryu-Seo, S., Miller, R., Trapp, B.D., Yan, R., 2011. Cleavage of neuregulin-1 by BACE1 or ADAM10 protein produces differential effects on myelination. *J. Biol. Chem.* 286 (27), 23967–23974. <https://doi.org/10.1074/jbc.m111.251538>.
- Luo, X., He, W., Hu, X., Yan, R., 2014. Reversible overexpression of Bace1-cleaved Neuregulin-1 N-terminal fragment induces schizophrenia-like phenotypes in mice. *Biol. Psychiatry* 76 (2), 120–127. <https://doi.org/10.1016/j.biopsych.2013.09.026>.
- Luo, Y., Colon, B., Kahn, S., Bennett, B.D., Babu-Khan, S., Denis, P., Fan, W., Kha, H., Zhang, J., Gong, Y., Martin, L., Louis, J.C., Yan, Q., Richards, W.G., Citron, M., Vassar, R., 2001. Mice deficient in BACE1, the Alzheimer's beta-secretase, have normal phenotype and abolished beta-amyloid generation. *Nat. Neurosci.* 4 (3), 231–232. <https://doi.org/10.1038/85059>.
- Marballi, K., Cruz, D., Thompson, P., Walss-Bass, C., 2012. Differential neuregulin 1 cleavage in the prefrontal cortex and hippocampus in schizophrenia and bipolar disorder: preliminary findings. *PLoS One* 7 (5), e36431. <https://doi.org/10.1371/journal.pone.0036431>.
- Marques, S.C.F., Lemos, R., Ferreiro, E., Martins, M., de Mendonça, A., Santana, I., Outeiro, T.F., Pereira, C.M.F., 2012. Epigenetic regulation of BACE1 in Alzheimer's disease patients and in transgenic mice. *Neuroscience* 220, 256–266. <https://doi.org/10.1016/j.neuroscience.2012.06.029>.
- Mei, L., Nave, K.A., 2014. Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron* 83 (1), 27–49. <https://doi.org/10.1016/j.neuron.2014.06.007>.
- Mhatre, M., Floyd, R.A., Hensley, K., 2004. Oxidative stress and neuroinflammation in Alzheimer's disease and amyotrophic lateral sclerosis: common links and potential therapeutic targets. *J. Alzheimers Dis.* 6 (2), 147–157. <https://doi.org/10.3233/jad-2004-6206>.
- Middle, F., Pritchard, A.L., Handoko, H., Haque, S., Holder, R., Bentham, P., Lendon, C.L., 2010. No association between neuregulin 1 and psychotic symptoms in

- Alzheimer's disease patients. *J. Alzheimers Dis.* 20 (2), 561–567. <https://doi.org/10.3233/jad-2010-1405>.
- Min, S.S., An, J., Lee, J.H., Seol, G.H., Im, J.H., Kim, H.S., Baik, T.K., Woo, R.S., 2011. Neuregulin-1 prevents amyloid β -induced impairment of long-term potentiation in hippocampal slices via ErbB4. *Neurosci. Lett.* 505 (1), 6–9. <https://doi.org/10.1016/j.neulet.2011.05.246>.
- Mockett, B.G., Richter, M., Abraham, W.C., Müller, U.C., 2017. Therapeutic potential of secreted amyloid precursor protein sAPP α . *Front. Mol. Neurosci.* 10, 30. <https://doi.org/10.3389/fnmol.2017.00030>.
- Mohn, A.R., Gainetdinov, R.R., Caron, M.G., Koller, B.H., 1999. Mice with reduced NMDA receptor expression display behaviours related to schizophrenia. *Cell* 98 (4), 427–436. [https://doi.org/10.1016/S0092-8674\(00\)81972-8](https://doi.org/10.1016/S0092-8674(00)81972-8).
- Mostaid, M.S., Lloyd, D., Liberg, B., Sundram, S., Pereira, A., Pantelis, C., Karl, T., Weickert, C.S., Everall, I.P., Bousman, C.A., 2016. Neuregulin-1 and schizophrenia in the genome-wide association study era. *Neurosci. Biobehav. Rev.* 68, 387–409. <https://doi.org/10.1016/j.neubiorev.2016.06.001>.
- Mouton-Liger, F., Dumurgier, J., Cognat, E., Hourregue, C., Zetterberg, H., Vanderstichele, H., Vanmechelen, E., Bouaziz-Amar, E., Blennow, K., Hugon, J., Paquet, C., 2020. CSF levels of the BACE1 substrate NRG1 correlate with cognition in Alzheimer's disease. *Alzheimers Res. Ther.* 12 (1), 88. <https://doi.org/10.1186/s13195-020-00655-w>.
- Nafisi-Far, N., Ghafouri-Fard, S., Panah, A.S.T., Sayad, A., Taheri, M., 2018. A gender dimorphism in up-regulation of BACE1 gene expression in schizophrenia. *Metab. Brain Dis.* 33 (3), 933–937. <https://doi.org/10.1007/s11011-018-0205-7>.
- Nemeroff, C.B., Weinberger, D., Rutter, M., MacMillan, H.L., Bryant, R.A., Wessely, S., Stein, D.J., Pariente, C.M., Seemüller, F., Berk, M., Malhi, G.S., Preisig, M., Brüne, M., Lysaker, P., 2013. DSM-5: a collection of psychiatrist views on the changes, controversies, and future directions. *BMC Med* 11, 202. <https://doi.org/10.1186/1741-7015-11-202>.
- Norton, N., Moskvina, V., Morris, D.W., Bray, S., Zammit, N.J., Williams, N.M., Williams, H.J., Preece, A.C., Dwyer, S., Wilkinson, J.C., Spurlock, G., Kirov, G., Buckland, P., Waddington, J.L., Gill, M., Corvin, A.P., Owen, M.J., O'Donovan, M.C., 2006. Evidence that interaction between neuregulin 1 and its receptor erbB4 increases susceptibility to schizophrenia. *Am. J. Genet. B Neurosci. Psychiatr. Genet.* 141B (1), 96–101. <https://doi.org/10.1002/ajmg.b.30236>.
- Olaya, J.C., Heusner, C.L., Matsumoto, M., Weikert, C.S., Karl, T., 2018. Schizophrenia-relevant behaviours of female mice overexpressing neuregulin 1 type III. *Behav. Brain Res.* 353, 227–235. <https://doi.org/10.1016/j.bbr.2018.03.026>.
- Ou, G.Y., Lin, W.W., Zhao, W.J., 2021. Neuregulins in neurodegenerative diseases. *Front. Aging Neurosci.* 13, 662474. <https://doi.org/10.3389/fnagi.2021.662474>.
- Ozaki, M., Sasner, M., Yano, R., Lu, H.S., Buonanno, A., 1997. Neuregulin-beta induces expression of an NMDA-receptor subunit. *Nature* 390 (6661), 691–694. <https://doi.org/10.1038/37795>.
- Papaleo, F., Yang, F., Paterson, C., Palumbo, S., Carr, G.V., Wang, Y., Floyd, K., Huang, W., Thomas, C.J., Chen, J., Weinberger, D.R., Law, A.J., 2016. Behavioral, neurophysiological, and synaptic impairment in a transgenic neuregulin1 (NRG1-IV) murine schizophrenia model. *J. Neurosci.* 36 (17), 4859–4875. <https://doi.org/10.1523/jneurosci.4632-15.2016>.
- Pitcher, G.M., Kalia, L.V., Ng, D., Goodfellow, N.M., Yee, K.T., Lambe, E.K., Salter, M.W., 2011. Schizophrenia susceptibility pathway neuregulin 1-ErbB4 suppresses Src upregulation of NMDA receptors. *Nat. Med.* 17 (4), 470–478. <https://doi.org/10.1038/nm.2315>.
- Plaze, M., Paillère-Martinot, M.L., Penttilä, J., Januel, D., de Beaupaire, R., Bellivier, F., Andoh, J., Galinowski, A., Gallarda, T., Artiges, E., Olié, J.P., Mangin, J.F., Martinot, J.L., Cachia, A., 2011. "Where do auditory hallucinations come from?"—a brain morphometry study of schizophrenia patients with inner or outer space hallucinations. *Schizophr. Bull.* 37 (1), 212–221. <https://doi.org/10.1093/schbul/sbp081>.
- Prohovnik, I., Dwork, A.J., Kaufman, M.A., Willson, N., 1993. Alzheimer-type neuropathology in elderly schizophrenia patients. *Schizophr. Bull.* 19 (4), 805–816. <https://doi.org/10.1093/schbul/19.4.805>.
- Pulver, A.E., Lasseter, V.K., Kasch, L., Wolyniec, P., Nestadt, G., Blouin, J.L., Kimberland, M., Babb, R., Vourlis, S., Chen, H., 1995. Schizophrenia: a genome scan targets chromosomes 3p and 8p as potential sites of susceptibility genes. *Am. J. Med. Genet.* 60 (3), 252–260. <https://doi.org/10.1002/ajmg.1320600316>.
- Purro, S.A., Nicoll, A.J., Collinge, J., 2018. Prion protein as a toxic acceptor of amyloid- β oligomers. *Biol. Psychiatry* 83 (4), 358–368. <https://doi.org/10.1016/j.biopsych.2017.11.020>.
- Reeves, S.J., Clark-Papasavas, C., Gould, R.L., Ffytche, D., Howard, R.J., 2015. Cognitive phenotype of psychotic symptoms in Alzheimer's disease: evidence for impaired visuo-perceptual function in the misdiagnosis subtype. *Int. J. Geriatr. Psychiatry* 30 (12), 1147–1155. <https://doi.org/10.1002/gps.4265>.
- Ribe, A.R., Laursen, T.M., Charles, M., Katon, W., Fenger-Grøn, M., Davydow, D., Chwastiak, L., Cerimele, J.M., Vestergaard, M., 2015. Long-term risk of dementia in persons with schizophrenia: a Danish population-based cohort study. *JAMA Psychiatry* 72 (11), 1095–1101. <https://doi.org/10.1001/jamapsychiatry.2015.1546>.
- Ropacki, S.A., Jeste, D.V., 2005. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am. J. Psychiatry* 162 (11), 2022–2030. <https://doi.org/10.1176/appi.ajp.162.11.2022>.
- Rosen, K.M., Ford, B.D., Querfurth, H.W., 2003. Downregulation and increased turnover of beta-amyloid precursor protein in skeletal muscle cultures by neuregulin-1. *Exp. Neurol.* 181 (2), 170–180. [https://doi.org/10.1016/S0014-4886\(03\)00031-1](https://doi.org/10.1016/S0014-4886(03)00031-1).
- Ryu, J., Yu, H.N., Cho, H., Kim, H.S., Baik, T.K., Lee, S.S., Woo, R.S., 2012. Neuregulin-1 exerts protective effects against neurotoxicities induced by C-terminal fragments of APP via ErbB4 receptor. *J. Pharmacol. Sci.* 119 (1), 73–81. <https://doi.org/10.1254/jphs.12057fp>.
- Ryu, J., Hong, B.H., Kim, Y.J., Yang, E.J., Choi, M., Kim, H., Ahn, S., Baik, T.K., Woo, R.S., Kim, H.S., 2016. Neuregulin-1 attenuates cognitive function impairments in a transgenic mouse model of Alzheimer's disease. *Cell Death Dis.* 7 (2), e2117. <https://doi.org/10.1038/cddis.2016.30>.
- Sachdev, P.S., Mohan, A., Taylor, L., Jeste, D.V., 2015. DSM-5 and mental disorders in older individuals: an overview. *Harv. Rev. Psychiatry* 23 (5), 320–328. <https://doi.org/10.1097/hrp.000000000000090>.
- Savonenko, V., Melnikova, T., Laird, F.M., Stewart, K.A., Price, D.L., Wong, P.C., 2008. Alteration of BACE1-dependent NRG1/ErbB4 signaling and schizophrenia-like phenotypes in BACE1-null mice. *Proc. Natl. Acad. Sci. USA* 105 (14), 5585–5590. <https://doi.org/10.1073/pnas.0710373105>.
- Seidman, L.J., Mirsky, A.F., 2017. Evolving notions of schizophrenia as a developmental neurocognitive disorder. *J. Int. Neuropsychol. Soc.* 23 (9–10), 881–892. <https://doi.org/10.1017/s135561771001114>.
- Sfera, A., 2013. Can neurostimulation prevent the risk of Alzheimer's disease in elderly individuals with schizophrenia. *Front. Psychiatry* 4, 111. <https://doi.org/10.3389/fpsy.2013.00111>.
- Shakir, M.N., Dugger, B.N., 2022. Advances in deep neuropathological phenotyping of Alzheimer disease: past, present, and future. *J. Neuropathol. Exp. Neurol.* 81 (1), 2–15. <https://doi.org/10.1093/jnen/nlab122>.
- Sheu, J.R., Hsieh, C.Y., Jayakumar, T., Tseng, M.F., Lee, H.N., Huang, S.W., Manubolu, M., Yang, C.H., 2019. A critical period for the development of schizophrenia-like pathology by aberrant postnatal neurogenesis. *Front. Neurosci.* 13, 635. <https://doi.org/10.3389/fnins.2019.00635>.
- Shi, L., Bergson, C.M., 2020. Neuregulin 1: an intriguing therapeutic target for neurodevelopmental disorders. *Transl. Psychiatry* 10 (1), 190. <https://doi.org/10.1038/s41398-020-00868-5>.
- Simpson, J.R., 2014. DSM-5 and neurocognitive disorders. *J. Am. Acad. Psychiatry Law* 42 (2), 159–164.
- Spire, T.L., Hannan, A.J., 2007. Molecular mechanisms mediating pathological plasticity in Huntington's disease and Alzheimer's disease. *J. Neurochem* 100 (4), 874–882. <https://doi.org/10.1111/j.1471-4159.2006.04275.x>.
- Stassart, R.M., Fledrich, R., Velanac, V., Brinkmann, B.G., Schwab, M.H., Meijer, D., Sereda, M.W., Nave, K.A., 2013. A role for Schwann cell-derived neuregulin-1 in remyelination. *Nat. Neurosci.* 16 (1), 48–54. <https://doi.org/10.1038/nn.3281>.
- Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T., Hjaltason, O., Birgisdottir, B., Jonsson, H., Gudnadottir, V.G., Gudmundsdottir, E., Bjornsson, A., Ingvarsson, B., Ingason, A., Sigfusson, S., Haradardottir, H., Harvey, R.P., Lai, D., Zhou, M., Brunner, D., Mutel, V., Gonzalo, A., Lemke, G., Sainz, J., Johannesson, G., Andresson, T., Gudbjartsson, D., Manolescu, A., Frigge, M.L., Gurney, M.E., Kong, A., Gulcher, J.R., Petursson, H., Stefansson, K., 2002. Neuregulin 1 and susceptibility to schizophrenia. *Am. J. Hum. Genet.* 71 (4), 877–892. <https://doi.org/10.1086/342734>.
- Stefansson, H., Sarginson, J., Kong, A., Yates, P., Steinthorsdottir, V., Gudfinnsson, E., Gunnarsdottir, S., Walker, N., Petursson, H., Crombie, C., Ingason, A., Gulcher, J.R., Stefansson, K., St Clair, D., 2003. Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. *Am. J. Hum. Genet.* 72 (1), 83–87. <https://doi.org/10.1086/345442>.
- Sun, A., Koelsch, G., Tang, J., Bing, G., 2002. Localization of beta-secretase memapsin 2 in the brain of Alzheimer's patients and normal aged controls. *Exp. Neurol.* 175 (1), 10–22. <https://doi.org/10.1006/exnr.2002.7875>.
- Tan, S.H., Karri, V., Tay, N.W.R., Chang, K.H., Ah, H.Y., Ng, P.Q., Ho, H.S., Keh, H.W., Candasamy, M., 2019. Emerging pathways to neurodegeneration: Dissecting the critical molecular mechanisms in Alzheimer's disease, Parkinson's disease. *Biomed. Pharmacother.* 111, 765–777. <https://doi.org/10.1016/j.biopha.2018.12.101>.
- Tian, J., Geng, F., Gao, F., Chen, Y.H., Liu, J.H., Wu, J.L., Lan, Y.J., Zeng, Y.N., Li, X.W., Yang, J.M., Gao, T.M., 2016. Down-regulation of neuregulin/ErbB4 signaling in the hippocampus is critical for learning and memory. *Mol. Neurobiol.* 54 (6), 3976–3987. <https://doi.org/10.1007/s12035-016-9956-5>.
- Ting, A.K., Chen, Y., Wen, L., Yin, D.M., Shen, C., Tao, Y., Liu, X., Xiong, W.C., Mei, L., 2011. Neuregulin 1 promotes excitatory synapse development and function in GABAergic interneurons. *J. Neurosci.* 31 (1), 15–25. <https://doi.org/10.1523/jneurosci.2538-10.2011>.
- Tsoutsoulas, C., Mulsant, B.H., Kumar, S., Ghazala, Z., Voineskos, A.N., Menon, M., Pollock, B.G., Rajji, T.K., 2017. Anticholinergic burden and cognition in older patients with schizophrenia. *J. Clin. Psychiatry* 78 (9), e1284–e1290. <https://doi.org/10.4088/jcp.17m11523>.
- Tyler, S.J., Dawbarn, D., Wilcock, G.K., Allen, S.J., 2002. Alpha- and beta-secretase: profound changes in Alzheimer's disease. *Biochem. Biophys. Res. Commun.* 299 (3), 373–376. [https://doi.org/10.1016/S0006-291X\(02\)02635-9](https://doi.org/10.1016/S0006-291X(02)02635-9).
- Unger, M.S., Marschallinger, J., Kaind, J., Höfling, C., Rossner, S., Heneka, M.T., Van der Linden, A., Aigner, L., 2016. Early changes in hippocampal neurogenesis in transgenic mouse models for Alzheimer's disease. *Mol. Neurobiol.* 53 (8), 5796–5806. <https://doi.org/10.1007/s12035-016-0018-9>.
- Vaillant-Beuchot, L., Mary, A., Pardossi-Piquard, R., Bourgeois, A., Lauritzen, I., Eysert, F., Kinoshita, P.F., Cazareth, J., Badot, C., Fragaki, K., Bussièrè, R., Martin, C., Mary, R., Bauer, C., Pagnotta, S., Paquis-Flucklinger, V., Buée-Scherrer, V., Buée, L., Lacas-Gervais, S., Checler, F., Chami, M., 2021. Accumulation of amyloid precursor protein C-terminal fragments triggers mitochondrial structure, function, and mitophagy defects in Alzheimer's disease models and human brains. *Acta Neuropathol.* 141 (1), 39–65. <https://doi.org/10.1007/s00401-020-02234-7>.
- Van Assche, L., Van Aubel, E., Van de Ven, L., Bouckaert, F., Luyten, P., Vandenbulcke, M., 2019. The neuropsychological profile and phenomenology of late

- onset psychosis: A cross-sectional study on the differential diagnosis of very-late-onset schizophrenia-like psychosis, dementia with Lewy bodies and Alzheimer's type dementia with psychosis. *Arch. Clin. Neuropsychol.* 34 (2), 183–199. <https://doi.org/10.1093/arclin/acy034>.
- Vincent, B., Checler, F., 2012. α -secretase in Alzheimer's disease and beyond: mechanistic, regulation and function in the shedding of membrane proteins. *Curr. Alzheimer Res.* 9 (2), 140–156. <https://doi.org/10.2174/156720512799361646>.
- de Vries, P.J., Honer, W.G., Kemp, P.M., McKenna, P.J., 2001. Dementia as a complication of schizophrenia. *J. Neurol. Neurosurg. Psychiatry* 70 (5), 588–596. <https://doi.org/10.1136/jnnp.70.5.588>.
- Vrillon, A., Mouton-Liger, F., Martinet, M., Cognat, E., Hourregue, C., Dumurgier, J., Bouaziz-Amar, E., Brinkmalm, A., Blennow, K., Zetterberg, H., Hugon, J., Paquet, C., 2022. Plasma neuregulin 1 as a synaptic biomarker in Alzheimer's disease: a discovery cohort study. *Alzheimers Res. Ther.* 14 (1), 71. <https://doi.org/10.1186/s13195-022-01014-7>.
- Walls-Bass, C., Liu, W., Lew, D.F., Villegas, R., Montero, P., Dassori, A., Leach, R.J., Almasy, L., Escamilla, M., Raventos, H., 2006. A novel missense mutation in the transmembrane domain of neuregulin 1 is associated with schizophrenia. *Biol. Psychiatry* 60 (6), 548–553. <https://doi.org/10.1016/j.biopsych.2006.03.017>.
- Wang, K.S., Xu, N., Wang, L., Aragon, L., Ciubuc, R., Arana, T.B., Mao, C., Petty, L., Briones, D., Su, B.B., Luo, X., Camarillo, C., Escamilla, M.A., Xu, C., 2014. NRG3 gene is associated with the risk and age at onset of Alzheimer's disease. *J. Neural Transm. (Vienna)* 121 (2), 183–192. <https://doi.org/10.1007/s00702-013-1091-0>.
- Willem, M., Garratt, A.N., Novak, B., Citron, M., Kaufmann, S., Rittger, A., De Strooper, B., Saftig, P., Birchmeier, C., Haass, C., 2006. Control of peripheral nerve myelination by the beta-secretase BACE1. *Science* 314 (5799), 664–666. <https://doi.org/10.1126/science.1132341>.
- Williams, N.M., Preece, A., Spurlock, G., Norton, N., Williams, H.J., Zammit, S., O'Donovan, M., Owen, M.J., 2003. Support for genetic variation in neuregulin 1 and susceptibility to schizophrenia. *Mol. Psychiatry* 8 (5), 485–487. <https://doi.org/10.1038/sj.mp.4001348>.
- Woo, R.S., Li, X.M., Tao, Y., Carpenter-Hyland, E., Huang, Y.Z., Weber, J., Neiswender, H., Dong, X.P., Wu, J., Gassmann, M., Lai, C., Xiong, W.C., Gao, T.M., Mei, L., 2007. Neuregulin-1 enhances depolarization-induced GABA release. *Neuron* 54, 599–610. <https://doi.org/10.1016/j.neuron.2007.04.009>.
- Woo, R.S., Lee, J.H., Yu, H.N., Song, D.Y., Baik, T.K., 2011. Expression of ErbB4 in the neurons of Alzheimer's disease brain and APP/PS1 mice, a model of Alzheimer's disease. *Anat. Cell Biol.* 44 (2), 116–127. <https://doi.org/10.5115/acb.2011.44.2.116>.
- Woo, R.S., Lee, J.H., Kim, H.S., Baek, C.H., Song, D.Y., Suh, Y.H., Baik, T.K., 2012. Neuregulin-1 protects against neurotoxicities induced by Swedish amyloid precursor protein via the ErbB4 receptor. *Neuroscience* 202, 413–423. <https://doi.org/10.1016/j.neuroscience.2011.11.026>.
- Xie, A., Gao, J., Xu, L., Meng, D., 2014. Shared mechanisms of neurodegeneration in Alzheimer's disease and Parkinson's disease. *Biomed. Res. Int.* 2014, 648740. <https://doi.org/10.1155/2014/648740>.
- Xu, J., de Winter, F., Farrokhi, C., Rockenstein, E., Mante, M., Adame, A., Cook, J., Jin, X., Masliah, E., Lee, K.F., 2016. Neuregulin 1 improves cognitive deficits and neuropathology in an Alzheimer's disease model. *Sci. Rep.* 6, 31692. <https://doi.org/10.1038/srep31692>.
- Yang, J.Z., Si, T.M., Ruan, Y., Ling, Y.S., Han, Y.H., Wang, X.L., Zhou, M., Zhang, H.Y., Kong, Q.M., Liu, C., Zhang, D.R., Yu, Y.Q., Liu, S.Z., Ju, G.Z., Shu, L., Ma, D.L., Zhang, D., 2003a. Association study of neuregulin 1 gene with schizophrenia. *Mol. Psychiatry* 8 (7), 706–709. <https://doi.org/10.1038/sj.mp.4001377>.
- Yang, L.B., Lindholm, K., Yan, R., Citron, M., Xia, W., Yang, X.L., Beach, T., Sue, L., Wong, P., Price, D., Li, R., Shen, Y., 2003b. Elevated beta-secretase expression and enzymatic activity detected in sporadic Alzheimer's disease. *Nat. Med.* 9 (1), 3–4. <https://doi.org/10.1038/nm0103-3>.
- Yin, D.M., Chen, Y.J., Lu, Y.S., Bean, J.C., Sathyamurthy, A., Shen, C., Liu, X., Lin, T.W., Smith, C.A., Xiong, W.C., Mei, L., 2013. Reversal of behavioral deficits and synaptic dysfunction in mice overexpressing neuregulin 1. *Neuron* 78 (4), 644–657. <https://doi.org/10.1016/j.neuron.2013.03.028>.
- Yoo, J.Y., Kim, H.B., Baik, T.K., Lee, J.H., Woo, R.S., 2021. Neuregulin 1/ErbB4/Akt signaling attenuates cytotoxicity mediated by APP-CT31 fragment of amyloid precursor protein. *Exp. Mol. Pathol.* 120, 104622. <https://doi.org/10.1016/j.yexmp.2021.104622>.
- Zhang, Z., Cui, J., Gao, F., Li, Y., Zhang, G., Liu, M., Yan, R., Shen, Y., Li, R., 2019. Elevated cleavage of neuregulin-1 by beta-secretase 1 in plasma of schizophrenia patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 90, 161–168. <https://doi.org/10.1016/j.pnpbp.2018.11.018>.
- Zhao, Q.F., Tan, L., Wang, H.F., Jiang, T., Tan, M.S., Tan, L., Xu, W., Li, J.Q., Wang, J., Lai, T.J., Yu, J.T., 2016. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J. Affect. Disord.* 190, 264–271. <https://doi.org/10.1016/j.jad.2015.09.069>.
- Zhong, C., Akmentin, W., Du, C., Role, L.W., Talmage, D.A., 2017. Axonal type III Nrg1 controls glutamate synapse formation and GluA2 trafficking in hippocampal-accumbens connections. *eNeuro* 4 (1). <https://doi.org/10.1523/euro.0232-16.2017>.
- Zhou, W., Cai, F., Li, Y., Yang, G.S., O'Connor, K.D., Holt, R.A., Song, W., 2010. BACE1 gene promoter single-nucleotide polymorphisms in Alzheimer's disease. *J. Mol. Neurosci.* 42 (1), 127–133. <https://doi.org/10.1007/s12031-010-9381-6>.