Supplementary Table. The overall neurochemical landscape of AD

System	System alterations and AD pathophysiology	Receptors alterations	Ligand alterations	Interaction with the AChergic systems
Glutamate	Increased sensitivity and/or activity of the GLUergic system to Aβ. GLUergic dynamic alterations overtime are tightly linked to Aβ-induced toxic pathways (GLUergic excitotoxity).	Post-synaptic NMDAr induce the LTP, which is essential for synaptic transmission/plasticity. Increased sensitivity / activity of NMDAr with a vicious cycle in with an abnormal turnover of the receptor leads to Aβ-induced toxic pathways as those involving the PrPc-Fyn-k and the caspase3-mediated apoptotic signalling (Um et al., 2012)	GLU uptake/recycling mechanisms, at the synaptic cleft, become progressively impaired during AD with increased both background and action-induced synaptic levels	There is a dual ACh-mediated regulation of GLU release: ▪ presynaptic α7 N may facilitates GLU release ▪ M are associated to decreased both release and concentration of GLU in the synaptic cleft (Higley *et al*., 2009). Moreover, α7 N stimulation lead to internalization of NMDAr thus lowering GLUergic-mediated neuronal Ca2+ influx (Kim *et al*., 2017). Early loss of presynaptic AChergic neurons is associated to a prolonged GLUergic excitatory response though an ineffective adaptive response consisting in a downregulation of the NMDAr (Um *et al.*, 2012) AChergic neurons express glutamatergic metabotropic receptor which, once activated in AChergic neurons, enhance the release of ACh (Ikonomovic *et al*., 2000).
Serotonin	Progressive serotoninergic neuronal loss (i.e. rafe nuclei) (Beaulieu, 2012) and widespread impairment of serotoninergic networks of the temporal-entorhinal cortex (Meltzer *et al*., 1998). No definitive data are available on the relationship between serotoninergic alteration and AD pathophysiology	5-HT 2A, 4 and 6 subtypes are upregulated as potential compensatory mechanism due to loss of serotonin and other neurochemical changes in CNS, during AD. Over stimulation of 5-HT 2A receptors lead to maladaptive GSK3-mediated pathways (Beaulieu, 2012) 5-HT6 activation, increases cAMP, activating the Fyn-k/ERK 1-2 axis which is associated to increased somatodendritic levels of hyperphosphorilated tau.	Progressive decline in both brain stem and cortical serotonin levels (Meltzer *et al*., 1998)	Cortical AChergic firing can be potentiated trough the blockade of 5-HT6 receptors, stimulating the Glu release and reducing the GABAergic inhibitory firing (Riemer *et al*., 2003).
Dopamine	Spatiotemporal re-configuration of brain DAergic networks with concurrent mechanisms of up-downregulation (McNamara *et al*., 2014). No definitive data are available on the relationship between serotoninergic alteration and AD pathophysiology	Not totally disclosed yet. However, GSK3 is recognized as a key mediator in the subcellular integration of the DAergic transmission (Beaulieu *et al*., 2004)	Controversial data have been reported so far even though a trend toward a progressive lowering of cerebral DA levels due to midbrain neuronal loss is likely to be the most probable scenario (Nobili *et al*., 2017)	AChergic projections finely regulate the presynaptic release of DA (Rice and Cragg, 2004), mainly through N. There is a striatal AChergic (both M and N) modulation of the DA release, particularly in the nucleus accumbens (Collins *et al*., 2016). A AChergic-mediated cerebral loss of DA has been linked to impair mesolimbic, prefrontal and striatal circuits. AChergic-mediated cerebral loss of DA homeostasis may contribute to aberrant cells signaling as GSK3 overactivation leading to Aβ accumulation, neurofibrillary pathology and neuroinflammation (Beaulieu *et al*., 2004).
Noradrenaline	There is a progressive NAergic degeneration and dysfunction overtime with extensive loss of NAergic terminals(Andres-Benito et al., 2017) It is well known that a pre-cortical tau-deposition in the LC occurs (pre-tangle stage of AD). Given the widespread NAergic projections from LC to limbic,	Higher expression levels of hippocampal and amygdala α2A NAergic post-synaptic receptor (representing a potential compensatory mechanism while enhancing dendrite sprouting)	Progressive decline in NA cortical levels mostly due to loss of cortical projections arising from neurons in the LC. Such a decline is initially compensated by upregulation of TH gene expression and NA transporter binding sites (Chalermpalanupap *et al*., 2013)	Adrenergic modulation of hippocampal AChergic neurons, through α2A NAergic post-synaptic receptors. These receptors contribute to the recruitment of AChergic neuronal networks relevant in cognition *(Andres-Benito et al., 2017)* Thus, brain regions, as hippocampi, receiving projections from the LC could lose a NAergic-mediated positive effect on the AChergic neuronal activation *(Andres-Benito et al., 2017)*. Whether AChergic neurons of basal forebrain modulate NAergic neurons of LC or its

	prefrontal and entorhinal areas as well as to AChergic basal nuclei, a potential prominent role in early stages of AD cannot be ruled out (Andres-Benito *et al*., 2017; Ehrenberg *et al*., 2017)			cortical projections is still matter of debate.
GABA	Impaired inhibitory GABAergic firing that are essential to balance the glutamatergic and AChergic excitatory synaptic effect. No definitive data are available on the relationship between serotoninergic alteration and AD pathophysiology	Down-regulation of GABA receptors in the temporal cortex associated to the glutamatergic excitotoxic cascade signatures (Limon *et al.*, 2012)	Progressive reduction of overall cerebral levels of GABA has been reported while recent works have shown increased levels of GABA in hippocampi (Rissman *et al.*, 2007)	GABAergic modulation of AChergic BF neurons, with a major inhibitory effect on the rate of ACh release.(Rissman *et al.*, 2007; Limon *et al.*, 2012) Functional re-modelling of the GABAergic system occurs during AD displaying a regional-pattern modality. These changes could represent a set of compensatory mechanisms facing AChergic decline(Limon *et al.*, 2012)
Astrocytes	Astroglial progressive loss and morpho-functional shift to pro-inflammatory phenotype affect synaptic transmission and plasticity (Osborn *et al.*, 2016). Astrocytes provide a relevant contribution to hippocampal synaptic transmission and plasticity, through Ca2+ -mediated intracellular signalling	n.a.	n.a.	Astrocytes surface has a high density of both M and N receptors: The stimulation of M leads to intracellular Ca2+ elevations from the background level. This, in turn, positively impact on downstream cellular processes as LTP. Hence, the M receptors are essential for the spatial-temporal coordination of astrocytes with the post-synaptic activity (Takata *et al.*, 2011). Recent evidences have shown that the astrocytic glutamate and serotonin synthesis and re-uptake may be regulated by AChergic stimulation *via* N receptors (Osborn *et al.*, 2016). Astrocytic and microglial N receptors activate cell signalling involved in the stimulation of autophagic processes, including Aβ oligomers, as well as modulating neuroinflammatory response (Vincent *et al.*, 2010).

Abbreviation: GLU: Glutamate; CNS: central nervous system; AD: Alzheimer's disease; NMDAr: N-methyl-D-aspartate receptor; LTP: long-term potentiation; ACh: acetylcholine; N: nicotinic receptor; M: muscarinic receptor; 5-HT: 5-hydroxytryptamine; GSK3: glycogen synthase kinase-3; DA: dopamine; cAMP: Cyclic adenosine monophosphate; ERK1/2: extracellular signal-regulated kinase ½; PrPc: cellular prion protein; Fyn-k: Proto-oncogene tyrosine-protein kinase Fyn, member of the Src family of kinase; Aβ: amyloid beta; LC: locus coeruleus; TH: tyrosine hydroxylase; GABA: Gamma-aminobutyric acid; n.a.: not applicable.

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