

# Clinical Profile of Alzheimer's Disease Non-Responder Patient

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## 1. Introduction

Alzheimer's disease (AD) is a disabling neurodegenerative disorder typical of old age. Recent advances led to the development of drugs which effectively alleviate cognitive symptoms. About one-third of patients however do not respond to current pharmacological treatment (Ryu et al., 2005). Reasons of such lack of efficacy of available drugs may represent a step ahead in the understanding of this disabling disorder. To define a non responder profile is the aim of this work.

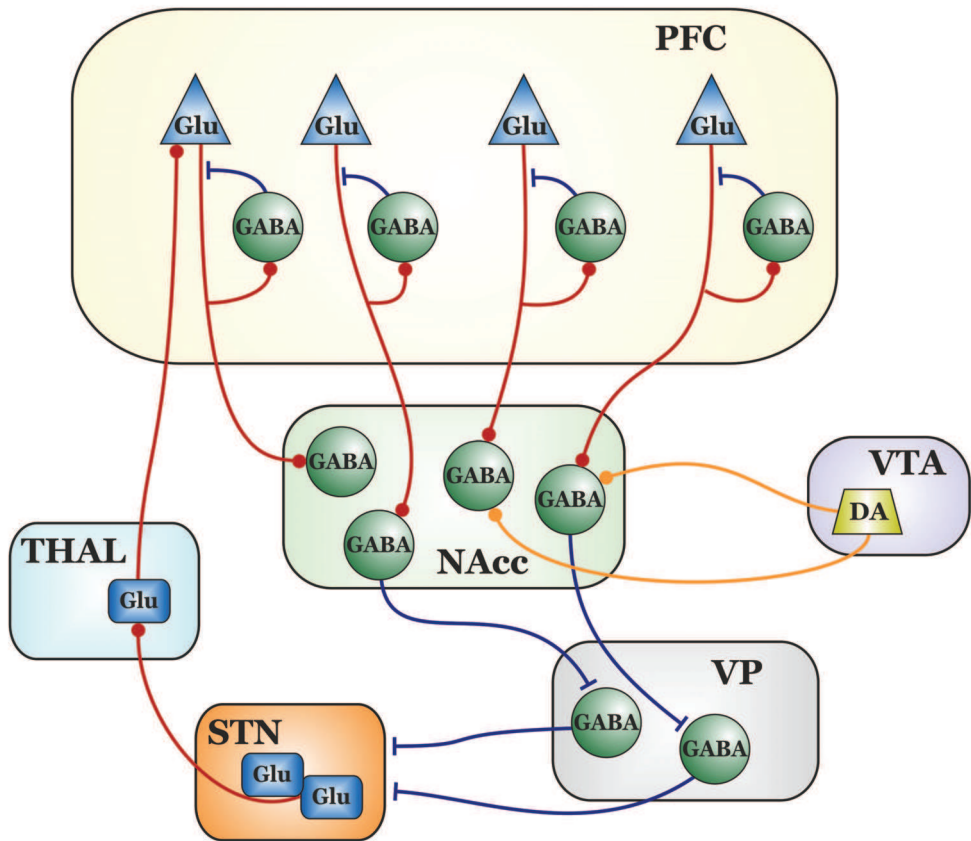
Accordingly, authors will deal with pathogenesis of AD, neuro-behavioural symptoms, brain imaging and CSF characteristics in order to extract from each section the most relevant features helpful for identification of non responder profile. Such work is difficult and may meet disagreement among specialists, however authors strongly believe that this work may represent a sort of starting point contributing to better understand AD pathophysiology.

### 1.1 Apathy and Alzheimer's disease

Apathy is a behavioural syndrome common in normal physiological aging, is also part of the psychiatric spectrum of mental illness, and often is part of clinical symptoms of neurodegenerative disorders like AD, fronto-temporal dementia, Parkinson's disease. The opportunity to discuss about its presence during AD lead to start from its definition and anatomical substrates, to better understand possible pathologic reasons of its occurrence.

Apathy is an observable behavioural syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behaviours (Levy and Dubois, 2006). Therefore, apathy occurs when the systems that generate and control voluntary actions are altered. In this view apathy can be defined as the quantitative reduction of self-generated voluntary and purposeful behaviour. Accordingly, apathy is not to be considered a clinical aspect of depression, although they may co-exist (Marin et al., 1993;1994).

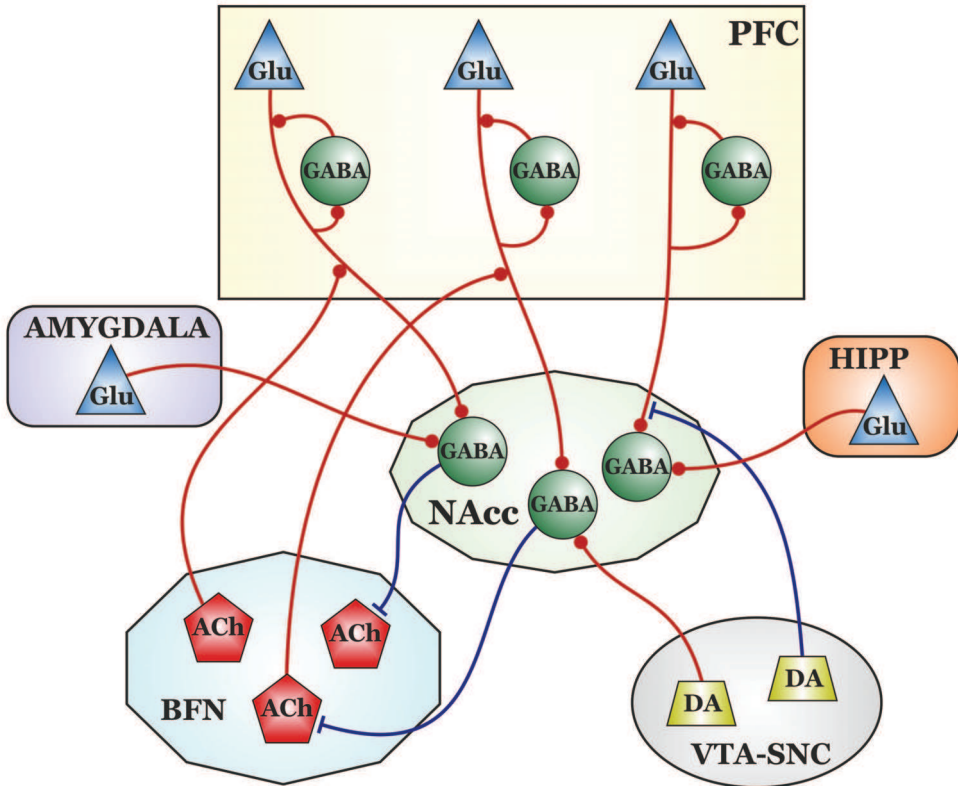
Anatomical circuits of apathy are generally represented by cortical areas like the prefrontal cortex (neo-, paleo- and archeo-cortex), amygdala and hippocampus and the ventral basal ganglia (limbic striatum or better the nucleus accumbens, midbrain ventral tegmental area, medial tip of subthalamic nucleus, centro-median and para-fascicular nuclei of the thalamus) (Haber et al., 1995; Deniau et al., 1997; Haber et al., 2010) (Fig. 1). In general, prefrontal cortex (PFC) has an essential role in cognitive and executive processes that involve



PFC: prefrontal cortex; NAcc: nucleus accumbens; VP: ventral pallidum; VTA: ventral tegmental area; STN: subthalamic nucleus; THAL: thalamus; Glu: glutamatergic excitatory neurons; GABA: GABA-ergic inhibitory neurons; DA: dopaminergic neurons.

Fig. 1. Schematic representation of ventral aspects of the cortical-basal ganglia circuit. Prefrontal cortex sends inputs to the main afferent nuclei of the system, the NAcc, which in turn sends inputs to the VP. Then information flow passes through the STN to the Parafascicular and Centro-Median nuclei of the thalamus and then again to the cortex.

motivation, emotion learning and memory. PFC integrates sensory and limbic information and promotes goal-directed behavior through efferent projections to the nucleus accumbens (NAcc). In addition, PFC sends outputs to other limbic areas such as the hippocampus and amygdala, which in turn modulate the activity of the NAcc through excitatory-glutamatergic projections. NAcc has been proposed to play a role in emotion, and more generally in limbic-motor integration (Nicola et al., 2007). This hypothesis has been based on the anatomical organization of the NAcc which suggests that this nucleus is an interface through which limbic (glutamatergic) structures influence motor activity, and that these limbic influences on behavior could in part be controlled by meso-limbic (dopaminergic structures) and cholinergic systems (Haber et al., 1997; Amalric et al., 1993) (Fig. 2).



PFC: prefrontal cortex; HIPP: hippocampus; NAcc: nucleus accumbens; SN-VTA: substantia nigra and ventral tegmental area; BFN: basal forebrain nucleus.

Fig. 2. Schematic representation of the complex relationship among NAC(nucleus accumbens) and cortical areas (amygdale, hippocampus and prefrontal cortex), dopamine-nuclei (substantia nigra and ventral tegmental area) and basal forebrain cholinergic neurons (Meinert's nucleus). NAC is in a position to modulate excitatory drive from cortical areas, cholinergic inputs to the cortex through basal forebrain neurons, modulated by dopamine inputs from the ventral midbrain

Inputs from the cortex convey through the multiple organization of the basal ganglia into the pallidum and then back to the cortex. Such arrangement is organized to extract (selection) relevant signals from background noise and to amplify it throughout the final pathway. The final selection is then transferred back to the PFC, which in turn generates inputs in output targets such as cognitive, limbic and even motor territories (Haber et al., 2010).

Over all, PFC and nucleus NAcc are considered the main structures responsible for apathy. In this view, apathy may be distinct at least in three different phenomena related to cortico-basal ganglia topography (Levy and Dubois, 2006): the first, that involves the affective-emotional processing, is topographically related to the ventral-medial PFC and its connection with NAcc and amygdala. This circuit integrates the affective or emotional value

of a given stimulus into ongoing behaviour. The second, involving cognitive processing, is topographically related to lateral PFC and to the dorsal caudate nucleus. This circuit is responsible for executive elaboration of a plan of action and involved in a goal-directed behaviour. The third, is observed in severe cases of apathy, is characterised by difficulties in self-initiating actions or thoughts, contrasting with relatively spared externally driven response. This pattern which was called the "auto-activation" deficit is the result of bilateral lesion of the pallidum (Starkstein et al., 1989; Lugaresi et al., 1990) or after extensive damage of the PFC (Kumral et al., 2002).

Within these perspectives, apathy observed in AD patients is more likely to be the result of a dysfunction of affective-emotional processing, thus involving the medial PFC and its connection with amygdala and NAcc.

During normal aging as well as during AD, it is conceivable to suppose that due to morphological and metabolic changes of cortical neurons and of subcortical nuclei, disorder of emotional-affective processing may appear. PFC and hippocampus has been demonstrated to show particular vulnerability during normal aging. Subtle regional changes of dendritic branching or altered mechanisms of neural plasticity has been experimentally demonstrated in lab animals and also in humans (Hof et al., 2004; Petanjek et al., 2008; Bloss et al., 2010; Juraska et al., 2011; Kalpouzos et al., 2011). These changes are also associated to reduced levels of neurotransmitters like acetylcholine, glutamate, GABA and dopamine with age (Chen et al., 2011). Such alterations may reasonably be responsible for appearance of apathetic behavior. Moreover, several reports showed that dopamine transmission is particularly vulnerable with age. In particular reduction of the accumbal dopamine transporter, and of cortical dopamine receptors (both D1-like and D2-like, where D2-like seem to be prevalent) in aged subjects (Volkow et al., 1994,1996; Ishibashi et al., 2009; Backman et al., 2009). These changes were related to PFC cognitive deficits and in particular were related to executive function impairment (Mizoguchi et al., 2009). Given the particular deficits of dopamine transmission and the role played by this transmitter in the control of PFC-basal ganglia circuit, it is conceivable to suppose that such changes could be responsible for apathetic behavior in old subject. Moreover, apathy increases with age in healthy old population (Brodsky et al., 2010), and its presence is considered an early sign of cognitive decline (Onyike et al., 2007). Contrarily to what expected bio-physical and also metabolic differences between AD brain and aged brain are very subtle (Hof et al., 2004). Myth of neuronal loss during aging is not confirmed, and pathologic metabolism of APP and hyper-phosphorylation of tau protein do represent the real difference with age related changes (Giannakopoulos et al., 2008 and 2009; Dickstein et al., 2010). Although many neurotransmitters dysfunction were found in AD brain, interest on dopaminergic transmission has been recently developed with relevant results (McNeil et al., 1984; Martorana et al., 2009; Martorana et al., 2010; Koch et al., 2011-b). However, apathy is usually recognized as part of AD symptoms, being considered the most common behavioral symptom in AD. Apathy increases with severity of AD (yet from conversion from MCI to AD) and has been associated with poorer initiative and executive functions (Drijgers et al., 2011). More importantly, apathy could be an early manifestation of a more aggressive AD phenotype, in which a faster cognitive decline occur (Starkstein et al., 2010). Studies of correlation between dopamine deficits and apathy in AD are needed to better interpret this behavioral syndrome. Of note is the concept that presence of apathy may render difficult the pharmacological approach to AD patients (See Boyle et al., 2004; Robert et al., 2010).

In conclusion, to define apathy simply a neuropsychiatric symptom common in AD, as well as in other dementias or degenerative disorders of the brain, or whether it may represent a clinical predictor of the turn-over (thus worsening) of a defined clinico-pathologic entity (like AD) actually represent a challenge for neurologists studying cognitive decline.

### 1.2 Neuroimaging morphometric predictors

The effectiveness of current pharmacological treatment of AD, by using AchEIs on cognitive decline symptoms can be highly variable. Genetic factors like the presence of 1 or 2 apolipoprotein E4 (APOE4) alleles are considered predictive of poorer response to therapy, while demographic factor like sex, or culture of the subject revealed some importance if related or associated to APOE status.

Recently, the development of neuro-morphometric measures of regional blood flow and also brain metabolism provided a new possible biomarker of the AD pathologic process. In particular, volumetric analysis of different brain regions showed that hippocampal volume loss is present in patients with mild AD, and the progression of volume loss parallels the worsening of clinical symptoms, and may also be used to predict to the pharmacological response of patients (Csernansky et al., 2005).

Moreover, during AD neuro-psychiatric symptoms are usually persistent, although with variable intensity, and can also be resistant to treatment (Ryu et al., 2005). The physiopathological and psychological mechanisms involved in the development of neuropsychiatric symptoms are still poorly understood. Thus, several neuro-anatomical correlative studies have been made, and association between discrete regional pathologies and psychiatric symptoms emerged (Mega et al., 2000; Sweet et al., 2003; Rosen et al., 2005; Sultzer et al., 2003; Shanks and Venneri, 2004; Migneco et al., 2001). Most of recent literature tried to correlate neuro-psychiatric symptoms to morphological features, particularly in early stages of AD. Delusions and agitation, more frequent at late stages of AD, are associated primarily with atrophy of the right fronto-parietal regions (matching with results obtained with metabolic and cerebral blood flow studies) (see Staff et al., 1999 ; Sultzer et al., 2003). Agitation was observed in about one third of AD patients and associated to atrophy of left insula and bilaterally of anterior cingulate cortex (Bruen et al., 2008).

Apathy which is the most frequent symptom of early AD, may be also an early indicator of the disease and is detectable in a high proportion of patients with mild cognitive impairment (Palmer et al., 2007; Lyketos et al., 2007). Presence of apathy was correlated with atrophy of sub-cortical nuclei like putamen bilaterally and of left caudate nucleus. Significant correlations were also found with atrophy of anterior cingulate cortex bilaterally, inferior frontal and orbito-frontal regions of both hemispheres (Gado et al., 1983; Jack et al., 2005; Shiino et al., 2006; Bruen et al., 2008). Apathy has also been linked to dysfunction or atrophy of ventral frontal areas (Rosen et al., 2005; Marshall et al., 2007). Apathy is often seen in early presentation of AD and is sometimes described even before memory deficits become noticeable.

In conclusion morphometric analysis of AD brains indicate that variable degrees of atrophy in selected brain regions could represent a potential and reliable predictor of clinical-type of presentation and may also be used as predictor of pharmacological response to treatment.

### 1.3 Cerebrospinal fluid analysis

Biochemical changes in the brain extracellular fluid are reflected in the cerebrospinal fluid (CSF). Levels of biological markers like A $\beta$ 42, total-tau (t-Tau) and hyper-phosphorylated

tau (p-Tau) are currently measured in clinical settings of many western countries, and used as diagnostic tool for diagnosis and for stratification of patients useful for pharmacological trials (Mattsson et al., 2009; Blennow and Zetterberg 2009). In AD patients typically levels of CSF A $\beta$ 42 is lower (370 ng/L in AD vs 670 ng/L in controls), while t-Tau (559 ng/L in AD vs 280 ng/L in controls) and p-Tau (82 ng/L in AD vs 51 ng/L in controls) are higher than in healthy controls (Blennow et al., 2007; Mattsson et al., 2009). Low levels of A $\beta$ 42 reflect a disturbance of the metabolism of this protein.

A $\beta$  is produced mainly in neurons and is secreted in the CSF 12 hs later, then excreted through the blood-brain barrier 24 hs later into blood (clearance of A $\beta$ ), and finally degraded in the reticulo-endothelial system (Shoij et al., 2001). These different phases are in equilibrium among them. In AD patients, A $\beta$ 42 forms insoluble aggregates and accumulates in form of fibrils in extracellular space of the brain (Bateman et al., 2009). The reason why A $\beta$ 42 levels are decreased in CSF of these patients is believed to be caused by the impairment of the physiologic clearance mechanism above described.

Major biological function of tau is to promote microtubule assembly and maintain the stability of the microtubules, play also crucial roles in signal transduction of neurons (Wang et al., 2008; Fanara et al., 2010), and in neural plasticity mechanisms (Avila et al., 2004; Boekhoorn et al., 2006). In AD patients, where plasticity mechanisms are altered, t-Tau levels increase three-fold than the age-matched controls. It's increase in CSF is considered as the result of degenerating process of neurones. Thus, increase of tau protein may leak from the degenerating neurons into the CSF as disease progresses (Blom et al., 2009; Mattson et al., 2009). P-Tau is considered a marker of NFT tangles production, and is strictly associated to the patho-physiological process of AD. Thus, p-Tau is increased in the CSF of AD in relation to neuronal degeneration degree (Blennow and Hampel, 2003).

Whether CSF biomarkers could be used as predictors for progression rate or treatment response was investigated only recently (Wallin et al., 2010; Blom et al., 2009; de Souza et al., 2011). In general, results of recent studies indicate that CSF biomarkers are not considered useful as predictors of treatment response (Wallin et al., 2009), nor were ever considered as markers for pharmacological response. From these studies has emerged that increased levels of t-Tau and p-Tau are associated to rapid progression rate of disease (Kester et al., 2009; Van Der Vlies et al., 2009), in particular for patients converting from MCI to AD (Blom et al., 2009), and also for patients with malignant form of AD (Wallin et al., 2010). In the latter condition was characterised by very high levels of t-Tau(> 800 ng/L) in the CSF, and by higher risk of mortality.

More recently high levels of tau (both total and hyper-phosphorylated) were also associated to hippocampal atrophy (de Souza et al., 2011), or with forms of pathologic neural plasticity (Koch et al., 2011a), indicating again for these proteins possible role as markers of rapid cognitive deficits observed in course of AD. Therefore, heterogeneity of AD patients reflects heterogeneity also in CSF biomarkers, thus the need to deepen the relationship between CSF biomarkers and different subgroups of AD emerges. Within these perspective, association between biomarkers and clinical and/or biochemical data could in turn provide new insight of our understanding of patho-physiology of AD and also of an appropriate pharmacological treatment.

## 2. Non responder profile

The current approach to cognitive deficits of AD patients derives from the so-called "cholinergic hypothesis", where major cholinergic deficit was suggested to characterise AD,

similarly to dopamine for Parkinson's disease. The cholinergic deficiency is currently a target of therapy since cholinesterase inhibitors treatment enhance the cholinergic transmission in AD and shows beneficial effects on cognition in both placebo controlled and open studies (Birks et al., 2006; Wallin et al., 2007). Despite several studies provided the efficacy of pharmacological treatment on cognition, however long-term treatment showed unsatisfactory results. Reasons of such interpretation of data were individuated in the progressive degeneration of cortical and sub-cortical neurons, as the consequence of the abnormal accumulation of A $\beta$ 42 and NFT formation.

Interestingly, during the treatment trials of the first cholinesterase inhibitor tacrine, heterogeneity in treatment response was observed. About one-third of the patients evaluated resulted to respond to treatment, one-third remained unchanged and one-third resulted to not respond to pharmacological treatment (Minthon et al., 1993; Egger and Harvey, 1995; Wallin et al., 2004). The discussion of these results showed clearly the need to define a treatment response, that was extended also to the AchEIs of second generation, however a consensus for how to define a response treatment do not exist.

Such difficulty may justify a sort of "lack of interest" for non responders and moreover may render obscure and hard to define the non responder profile. Many variables (genetic, metabolic, vascular, biochemical, etc) may be considered responsible for pharmacological treatment un-efficacy, and in recent years several studies investigated the importance of these factors. Among others, as possible predictors to treatment response were included cognitive impairment severity (Pakrasi et al., 2003; Van Der Putt et al., 2006; Wallin et al., 2005 and 2009), frontal lobe blood flow (Hanyu et al., 2003), age (Schneider et al., 1991; Evans et al., 2000), gender (Macgowan et al., 1998; Winblad et al., 2001), APOE genotype (Almkvist et al., 2001; Winblad et al., 2001). Unfortunately conflicting results were obtained, and reliable predictors are still unavailable.

However, taking in account the anatomical, clinical and biochemical consideration made above, a profile of "non responder" AD patients may be outlined.

In general patients that do not respond to treatment present with rapidly progressive cognitive decline, not dependent on age, gender, years of education, baseline instrumental activities of daily living, or APOE genotype. The neuropsychological assessment of these patients show involvement of executive functions associated to memory deficits, and the presence of severe apathy. No other behavioural symptoms do occur in these cases. CSF analysis show low levels of A $\beta$ 42, and very high levels of t-Tau (> 800 ng/L). Gross morphology remains unaltered in neuro-imaging assessment, although changes of grey matter volumes in frontal-temporal areas were recently described (Serra et al., 2010). It is interesting to note that such transition from responder to non responder state coincide with described changes occurring in MCI converters (Hansson et al., 2009; Mattsson et al., 2009; Blom et al., 2009; Palmer et al., 2010), and also in a subset of AD patients with moderate AD showing rapidly progressive rate of cognitive decline (van Der Vlies et al., 2009; Kester et al., 2009; Wallin et al., 2010; Musicco et al., 2011; Stepaniuk et al., 2011). Thus, from these results appear that the efficacy of current pharmacological treatment with AchEIs could depend on the rate of progression of cognitive decline (fast or slow), which in turn appear as to be associated to signs of frontal lobe dysfunction (indicative of faster decline), hence with the appearance of severe apathy and of executive functions alterations.

Impairment of executive functions and also neurobehavioral symptoms are often observed in course of AD. Their occurrence is typical of more advanced stages and is associated to greater impairment of daily activities in these patients (Boyle et al., 2003; Marshall et al.,

2011; Carter et al., 2011). In this view non responders might represent a clinico-pathological variant of AD (as identified by Back-Madruga et al., 2002), not rare, in which frontal lobe degeneration prevails. Moreover, the reason why the cognitive decline become faster may reside in the interaction between A $\beta$ 42 and Tau. Yet at intracellular level A $\beta$ 42 has been demonstrated to induce tau fragments formation, which are particularly toxic for mitochondria, leading rapidly to cell dysfunction (Amadoro et al., 2010; 2011). Such interaction would happen also at post-synaptic site leading to cell death via excitotoxic mechanisms (Ittner et al., 2010; Roberson et al., 2011). Such condition could be sufficient to explain the reason of AchEIs treatment un-effectiveness. As alternative hypothesis, it may be supposed that the frontal lobe dysfunction could be due to the direct interaction of A $\beta$  peptides with neurotransmitters system, leading to impairment of cross-talk between transmitters (Palop et al., 2010).

From the patho-physiological point of view, frontal lobe function depends on the anatomical integrity of neurotransmitters network and cross-talk (acetylcholine, dopamine, glutamate, GABA) which function regulating memory, behaviour and emotions (see Martorana et al., 2010). Recent experimental evidences show that such modulatory role is played by interaction between acetylcholine, and other major transmitters like glutamate or dopamine (Moore et al., 2009; Gullege et al., 2009; Dasari et al., 2011; Livingstone et al., 2010). Thus, frontal lobe dysfunction, particularly in cases of AD would be the result of an impairment among transmitters, particularly of acetylcholine, glutamate, and dopamine, thus likely responsible for faster cognitive decline. Interestingly, recent papers showed marked changes of glutamatergic as well as of dopaminergic systems in frontal lobe of AD brains (Kashani et al., 2008; Kirvell et al., 2007; Kumar and Patel, 2007), suggesting also that involvement of frontal lobe in AD might occur earlier than supposed. Moreover recent transcranial magnetic stimulation studies showed that in AD central cholinergic transmission was restored by L-dopa administration (Martorana et al., 2009), and further showed that L-dopa was unable to modulate neural plasticity mechanisms in AD patients (Koch et al., 2011-b). Within these perspectives it is conceivable to suppose that impaired neurotransmitter systems could account for lack of response to AchEIs.

Remain to be established whether frontal lobe dysfunction represent a reversible condition, and whether alternative treatments, like memantine or dopamine agonists could interfere with this event.

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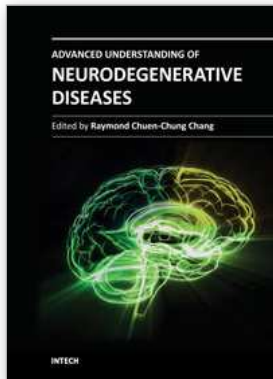
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## **Advanced Understanding of Neurodegenerative Diseases**

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Advanced Understanding of Neurodegenerative Diseases focuses on different types of diseases, including Alzheimer's disease, frontotemporal dementia, different tauopathies, Parkinson's disease, prion disease, motor neuron diseases such as multiple sclerosis and spinal muscular atrophy. This book provides a clear explanation of different neurodegenerative diseases with new concepts of understand the etiology, pathological mechanisms, drug screening methodology and new therapeutic interventions. Other chapters discuss how hormones and health food supplements affect disease progression of neurodegenerative diseases. From a more technical point of view, some chapters deal with the aggregation of prion proteins in prion diseases. An additional chapter to discuss application of stem cells. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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