rijksuniversiteit groningen / faculteit wiskunde en natuurwetenschappen / levenswetenschappen

Deep Brain Stimulation in Alzheimer's and Parkinson's disease

A.I.E. Faber
1725882

Behaviour and Neurosciences

July 2010

Supervisor: Prof. Dr. P.G.M. Luiten

Abstract

Both Alzheimer's disease and Parkinson's disease are characterized by neurodegeneration of the cholinergic system and cholinergic neurons in the nucleus basalis of Meynert. Those neurons are the source for the cholinergic innervation of the cortical mantle, olfactory bulb, hippocampus and amygdala. Loss of the cholinergic system and the neurotransmitter acetylcholine goes together with an impairment in many forms of memory, and early loss of episodic memory is the main character of Alzheimer's disease. Impairment of executive and attentional function are the initial and early prominent cognitive features of Parkinson's disease dementia. Inhibition of acetylcholinesterase, the enzyme that breaks down acetylcholine, is the most successful way to treat Alzheimer's disease until now. Unfortunately this therapy does not stop the degeneration of the cholinergic neurons in the nucleus basalis of Meynert. Perhaps electrical stimulation of these neurons via deep brain stimulation will prevent this neurodegeneration and improves the memory of Alzheimer's and Parkinson's patients. This suggestion is supported by a recent study in which memory tasks in a patient with Parkinson's disease dementia were improved after deep brain stimulation of the nucleus basalis of Meynert. Even though this approach of treating memory problems following loss of cholinergic neurons is new and little is known about the effects, the application of deep brain stimulation in Alzheimer's disease and Parkinson's disease dementia is very promising. Symptoms of cognitive impairment can be reduced and maybe even delayed by the prevention of cholinergic neuron cell death with electric stimulation.

Contents

Introduction

Since people become older and older, neurodegenerative diseases like Alzheimer's disease (AD), become more common. In the USA the number of people suffering of AD is estimated on 5 million. It is predicted that there will be an average of 50% increase in AD patients by the year 2025 (reviewed by Crews and Masliah, 2010). Because the prevalence of AD is strongly associated with increasing age, AD can become a great burden for health care in all countries (Fratiglioni et al. 2000). AD is mainly characterized by early loss of episodic memory (Mc Khann et al. 1984). Loss of functional capacities and activities of daily living, and a progressive involvement of other cognitive domains are also present (Petersen et al. 1999). Progressive accumulation of insoluble fibrous material is the neuropathological hallmark of AD (reviewed by Braak and Braak, 1991). Extracellular amyloid and intraneuronal neurofibrillary changes are the compounds of this material which is normally not present in the human central nervous system (reviewed by Braak and Braak, 1991). Multiple studies proved that the extracellular amyloid and intraneuronal neurofibrillary changes are not distributed at random but are present according a characteristic pattern (Braak and Braak, 1985; Braak and Braak, 1990; Braak and Braak, 1991; Braak et al. 1989; Hyman et al. 1984; Lewis et al. 1987; Rogers and Morrison, 1985; Van Hoesen and Hyman, 1990).
By performing memory tests, medical history and conversations with family members of the patient the diagnosis of Alzheimer's disease is established. Most of the time the exact diagnosis is determined after the death of a patient by examining the brain.
One of the affected brain areas in AD is the cholinergic basal forebrain. The neurons of this brain area are localized in the septal/diagonal band complex of Broca and in the nucleus basalis of Meynert (NbM), whose neurons send well developed projections to almost all layers of all cortical regions. Therefore they are the source for the cholinergic innervation of the cortical mantle, olfactory bulb, hippocampus and amygdala (Luiten et al. 1987).
Neurologically, AD is characterized by extracellular amyloid-β plaques, and intraneuronal tau neurofibrillary tangles. The exact mechanism behind the neurodegeneration in AD is still unknown.
Parkinson's disease (PD) is also known as a neurodegenerative disease. Currently there are around one million people in the USA that suffer from PD (Ruipérez et al. In press). The loss of dopaminergic neurons in the substantia nigra pars compacta is the main neuropathological characteristic next to the presence of Lewy bodies, which are cytoplasmatic inclusions (Ruipérez et al. In press). The small synaptic protein alpha-synuclein is the main component of these Lewy bodies (Spillantini et al. 1997). Uncontrollable tremor, muscular rigidity, slowness of movement and postural instability are the clinical characteristics of PD caused by the loss of dopaminergic neurons (Lees et al. 2009).
In both AD and Parkinson's disease dementia (PDD), the cholinergic system is affected. The enzyme choline acetyltransferase (ChAT) synthesizes the neurotransmitter acetylcholine (ACh) from choline and acetylcoenzyme A (ACoA) in the cholinergic neurons of the nucleus basalis of Meynert. Coenzyme A is formed as a by-product in this reaction (reviewed by Tuček, 1984). ACh is known to be involved in learning and memory processes. An impairment in many forms of memory is induced by pharmacologically blocking the cholinergic system (Deutsch, 1972; Flood et al. 1982; Power et al. 2003; Rudy, 1996). Cholinergic agonists and cholinesterase agonists are known to facilitate memory (Introini-Collison and McGaugh, 1988; Stratton and Petrinovich, 1963). In AD, strongly reduced levels of ChAT in the NbM show that there is a decreased state of the NbM cholinergic neurons

(Vogels et al. 1990), and reduction of neurons of the NbM was 70% for AD patients and 77% for PD patients (Vogels et al. 1990).
AD patients are treated with cholinesterase inhibitors to treat the cholinergic deficit and cortical ACh levels are thereby increased. The cholinesterase inhibitors tacrine and donepezil improved performance on cognitive tests (reviewed by Wilkinson et al. 2004). Levodopa is the most widely used and most effective drug for the symptomatic therapy of the motor defects in PD, but treatment with this drug can also develop motor complications (reviewed by Olanow et al. 2006). Deep brain stimulation (DBS) is a very effective surgical therapy to treat movement disorders. A lead just larger than 2 mm in diameter is implanted into a specific brain region and connected to a pulse generator typically placed in the chest (reviewed by Greenberg, 2002). Because of the positive results of DBS in PD, this technique can also be applied on neurons of the NbM in AD and PDD. By stimulating these neurons, neurodegeneration and thereby memory impairment might be delayed.

1. The nucleus basalis of Meynert

1.1 The cholinergic basal forebrain and the Nucleus Basalis of Meynert
The human cholinergic basal forebrain includes large (magnocellular) hyper chromic neurons. Those neurons are localized in the septal/diagnal band complex of Broca and in the nucleus basalis of Meynert. The nucleus basalis of Meynert (NbM), or nucleus basalis magnocellularis (MBN) as it is called in the rodent brain, is a structure in the basal forebrain which consists of cholinergic cellgroups that send well developed projections to fundamentally all layers of all cortical regions. Hereby it is the source for the cholinergic innervation of the cortical mantle, olfactory bulb, hippocampus and amygdala (Luiten et al. 1987).
The nucleus basalis of Meynert consists of three subpopulations: the nucleus septi medialis, the nucleus of the diagonal band of Broca and the NbM neurons in the substantia innominata (Jones et al. 1976; Wenk et al. 1981). More recently the cholinergic neurons of the basal forebrain were defined as Ch1-Ch4 neurons (reviewed by Amenta and Tayebati, 2008). Ten per cent of the basal forebrain consists of cholinergic neurons of the medial septum (Ch1). The diagonal band includes the Ch2 (vertical limb) and Ch3 (horizontal limb). The neurons situated here are fusiform in shape. Approximately 70 % of the neurons in the diagonal band are cholinergic neurons of the Ch2 group, and 1-2% of the Ch3 group. The Ch4 cells are fusiform to multipolar in shape and represent the neurons of the nucleus basalis of Meynert. Approximately 90 % of them are cholinergic. In the human brain their number is about 210.000 per hemisphere (reviewed by Amenta and Tayebati, 2008). The neurons of the Ch4 group are topographically separated into anterior (Ch4a), intermediate (Ch4i) and posterior (Ch4p) subfields. The anterior portion can then be further divided into medial (Ch4am) and lateral (Ch4al) sectors. The dorsal (Ch4id) and ventral (Ch4iv) portions are the subdivisions of the intermediate subfield (reviewed by Mufson et al. 2003). The hippocampal regions, including entorhinal cortex divisions, receive their cholinergic innervations from the medial septum, vertical limb and medial part of the horizontal limb of the diagonal band of Broca (Gaykema et al. 1990). The lateral part of the horizontal limb of the diagonal band of Broca provides the cholinergic innervations to the olfactory bulb. Further is the medial horizontal limb of the diagonal band of Broca a major cholinergic source of the prefrontal cortex (Gaykema et al. 1990).

1.2 The cholinergic system and acetylcholine

Acetylcholine (ACh) represents the first neurotransmitter of neuroscience history since it has been discovered in 1920 (reviewed by Amenta and Tayebati, 2008). In the central, peripheral, autonomic and enteric nervous system ACh plays an important role. In several vascular beds ACh is involved in the endothelium-dependent vasodilatation and it is present in different cell systems (reviewed by Amenta and Tayebati, 2008). In the mammalian nervous system ACh is responsible for the transfer of nerve-impulse-coded information from postganglionic parasympathetic nerve fibres to the heart, smooth muscles and glands, from motor nerves to skeletal muscles, from preganglionic fibres to neurons in the sympathetic and parasympathetic ganglia, from postganglionic sympathetic nerve fibres to sweat glands and some vascular smooth muscles, and from some nerve cells within the central nervous system to others. Next to that is also plays the role of synaptic transmitter in other vertebrates and in invertebrates only the type of synapses on which it is used may differ (reviewed by Tuček, 1984).

Figure 1 shows the specialized enzymatic systems that are needed for the process of ACh synthesis, storage and release.

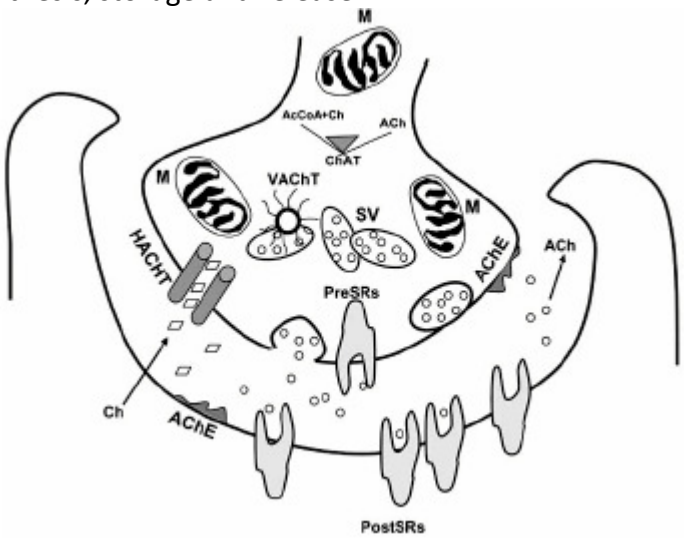

Figure 1. Schematic overview of a cholinergic synapse showing neurotransmitter synthesis, storage and release mechanisms (Amenta and Tayebati, 2008). ACh: acetylcholine; AChE: acetylcholinesterase; Acetyl-CoA: acetyl coenzyme A; Ch: choline; ChAT: choline acetyltransferase; HACHT: high affinity choline transporter; M: mitochondria; PreSRs: presynaptic receptors; PostSRs: postsynaptic receptors; SV: synaptic vesicle; VAChT: vesicular acetylcholine transporter.

First a high affinity Na^+-dependent uptake system takes up choline from the extracellular space (reviewed by Amenta and Tayebati, 2008). This choline originates from multiple sources, namely from free choline in the blood plasma, from ACh which was hydrolysed after its release from cholinergic neurons, from phosphatidylcholine that is synthesezed by methylation of phosphatidylethanolamine in the cells of the brain, and finally from the posphatidylcholine supplied to the cells of the brain by the blood plasma (reviewed by Tuček, 1984).

The choline uptake system was defined as Sodium-Dependent High-Affinity Choline Uptake (SDHACU) at the time of discovery and is located predominantly in terminals of cholinergic neurons (reviewed by Amenta and Tayebati, 2008). Multiple studies consider the transfer of choline by the SDHACU into the cholinergic terminals to be the rate-determining step for the ACh synthesis (reviewed by Amenta and Tayebati, 2008).

Most of the “classic” neurotransmitters are synthesized in the cytosol of nerve terminals. After that they are stored into synaptic vesicles prior to exocytotic release (reviewed by Amenta and Tayebati, 2008). ACh is synthesized by the enzyme choline acetyltransferase (ChAT) from choline and acetylcoenzyme (ACoA), that is produced in intraterminal mitochondria. ChAT is only present in the cholinergic neurons in the nervous system. In the equation coenzyme A is also formed next to ACh (reviewed by Tuček, 1984). The activity of the vesicular ACh transporter (VAChT), a 12-transmembrane domain protein, is responsible for the accumulation of ACh in synaptic vesicles. The VAChT exchanges two protons generated by a proton ATPase with one ACh molecule by electrochemical gradient (reviewed by Amenta and Tayebati, 2008). After the release of ACh during synaptic activity, ACh interacts with postsynaptic and presynaptic cholinergic receptors where it is hydrolysed by acetylcholinesterase (AChE) into acetate and choline (reviewed by Tuček, 1984). Research of Harkany et al. (2000b) showed that cholinergic terminals do not synapse directly on vascular endothelium or the surrounding basement membrane, but to adjacent perivascular astrocytic endfeet that are covered with muscarinic receptors. But before reaching the receptors, much of the ACh released is probably destroyed (reviewed by Tuček, 1984). There is almost no reuptake of the released ACh into the presynaptic neurons and reutilization of it is also rare (reviewed by Tuček, 1984).

1.3 Cholinergic receptors

There are two types of receptors that are activated by Ach, called the muscarinic (mAChR) and nicotinic (nAChR) receptors. The mAChR in the brain plays a role in the activation of a multitude of signalling pathways that are important for the modulation of neuronal excitability, synaptic plasticity and feedback regulation of ACh release. Next to that, these receptors are also involved in higher cognitive functions like learning and memory (reviewed by Wevers, in press). MAChR are members of the class of metabotropic receptors that act via G-protein signalling. NAChR belong to a superfamily of excitatory ligand-gated ion channels (reviewed by Wevers, in press).

Nowadays there are five mAChR subtypes that are genetically defined and been cloned and expressed in multiple types of cells. Those subtypes are termed as m1-m5. Besides those subtypes, there are also five subtypes of pharmacologically characterised mAChR, termed as M1-M5 (reviewed by Wevers, in press). Although each receptor subtype can couple to other signalling pathways, M1, M3 and M5 subtypes generally couple to Gq/11 protein and thereby activate phospholipase C. The M2 and M4 subtypes couple to Gi/o protein and associated effector systems as inhibition of adenylate cyclase and ion channels (Conn et al. 2009; Eglen et al. 2006). Research of Perry et al. (2003) has shown that both M1 and M2 are involved in cognitive function since Parkinson patients developed cognitive symptoms that are related to those seen in AD when they were treated for more than two years with antimuscarinic drugs, compared to patients who were not treated with these drugs. Using receptor autoradiography with N-[^{3}H]methyl-scopolamine ([^{3}H]NMS), which is a ligand that binds to all mAChR subtypes, Cortés et al. (1984 & 1986) demonstrated a widespread distribution of mAChR. The highest density was observed in the striatum (1100 fmol/mg protein) followed by the hippocampal formation (dentate gyrus, 700 fmol/mg protein) and areas of the neocortex (600 fmol/mg protein). The lower densities were found in most of the brainstem nuclei (Cortés et al. 1984; Cortés et al. 1986).

The other type of ACh Receptor, the nAChR, is in the central nervous system (CNS) important for processes like cell excitability, regulation of neurotransmitter release, intracellular

enzymatic processes and activity-dependent modulation of circuits (reviewed by Wevers, in press). Physiological functions as sleep, anxiety, arousal, central processing of pain, fatigue, food intake, and some cognitive functions as memory, learning and attention are influenced by nAChR through modulation of activity-dependent events (reviewed by Wevers, in press). Reviews of Dani et al. (2007) and Gotti et al. (2004) have shown that there is an association between disturbance of cholinergic nicotinic neurotransmission and diseases involving nAChR dysfunction during development, adulthood and ageing. Using binding assays with nicotinic radioligands in different brain areas of autopsy tissue, early studies characterized the nAChRs and thereby demonstrated at least two classes of putative nAChRs because of their high affinity for nicotine or the snake toxin α-bungarotoxin (α-Bgt) (reviewed by Wevers, in press). With molecular cloning of a family of genes encoding for different nAChR subunits the pharmacological heterogeneity was later confirmed and extended. In the CNS and ganglionic neurons, two types of subunits, α and non-α, were identified. Until now, nine α (α2-α10) and three non- α (β2-β4) subunits have been cloned from mammalian and chick neuronal tissue (reviewed by Wevers, in press). Six α subunits (α2-α7) and three β subunits (β2-β4) were cloned in the human nervous system so far. Five subunits form in various combinations the pentameric nAChR. This can be as a heterooligomer, which is a combination of α and β subunits, or as a homooligomer nAChR subtype. The (α4)2(β2)3 nAChR subtype represents 90% of the high-affinity nicotine-binding sites. The majority of α-Bgt binding sites in the human brain consists of the (α7)5 nAChR subtype (reviewed by Wevers, in press).

1.4 Acetylcholine in learning and memory

For more than 40 years the cholinergic system has been implicated in learning and memory. To discover the role of acetylcholine (ACh) in these processes pharmacological studies have been critical. Several studies showed an impairment in many forms of memory by pharmacologically blocking the cholinergic system (Deutsch, 1972; Flood et al. 1982; Power et al. 2003; Rudy, 1996). Cholinergic agonists and cholinesterase agonists are known to facilitate memory (Introini-Collison and McGaugh, 1988; Stratton and Petrinovich, 1963) and promote memory recovery from brain damage (Russel et al. 1994). Lesion studies showed that learning and memory are impaired in a variety of tasks when lesions in the brain reduce the levels of ACh or choline acetyltransferase (ChAT) and thereby demonstrated the involvement of cholinergic mechanisms in lesions (Bartus et al. 1985; Cabrera et al. 2006; Everitt et al. 1987; Mandel et al. 1989; McGaughy et al. 2002). Casamenti et al. (1988) showed that a long-lasting and significant decrease in cortical ACh together with disruption of a passive avoidance conditioned response are caused by excitotoxic lesions of the nucleus basalis. Also working memory was disrupted (Bartolini et al. 1996; Casamenti et al. 1998). Multiple studies in monkeys and rodents imply that cholinergic neurons may be required not for learning per se, but they could be important for specific aspects of attention (reviewed by Pepeu and Giovannini, 2004). A large increase in cortical and hippocampal ACh release is observed during acquisition of a rewarded operant behavior, but not when it is recalled (Orsetti et al. 1996). Other microdialysis experiments imply that when demands on attentional processing are high, cortical ACh increases during performance of simple operant tasks are limited to early acquisition stages (reviewed by Pepeu and Giovannini, 2004). In rats performing a visual attentional task cortical ACh increases (Dalley et al. 2001). Cortical ACh increases are also directly correlated with the attentional effort during an operant task that is designed to assess sustained attention (reviewed by Pepeu and Giovannini, 2004).

Research of Dashniani et al. (2009) has shown that the learning of NBM 192 IgG-saporin lesioned rats was slower than in a control group. No obvious differences were found between the groups in perception, motivation or motor abilities that could differentially influence acquisition of task. This indicates that there is a deficit in the place learning performance strategy in NBM lesioned rats (Dashniani et al. 2009). Next to that, NBM lesioned rats seized the visible platform version of the water maze task, but they failed to learn the platform location in space (Dashniani et al. 2009). This suggests that the NBM is essential for accurate spatial learning. It can be suggested that the NBM plays a role in processing information about the spatial environment. But it is also possible that behavioral deficits are caused by a lack of attentional function (Dashniani et al. 2009). A study of Miasnikov et al. (2009) found that stimulation of the nucleus basalis in rats can induce specific, associative memory. Memory that is induced by stimulation of the NBM has a lot of features, such as the fact that it is associative, highly specific, it can be induced in a single session, it becomes stronger over time, thus it consolidates, and it is retained for at least several days (Miasnikov et al. 2009).
It is clear that the cholinergic system and the nucleus basalis of Meynert are involved in processes of learning and memory. In diseases like Alzheimer's disease, this cholinergic system and the nucleus basalis of Meynert are affected leading to the symptoms of memory loss that characterizes those diseases.

2. Pathologies

In several neurodegenerative diseases as Alzheimer's disease, Parkinson's disease, Dow's syndrome, the Parkinsonism-dementia complex, progressive supranuclear palsy, Korsakoff's syndrome, olivoponto-cerebellar atrophy and pugilistic dementia, the basal forebrain cholinergic complex degenerates (reviewed by Amenta and Tayebati, 2008). In this chapter only Alzheimer's and Parkinson's disease are discussed. There are multiple possible causes for the neurodegeneration of the basal forebrain, for instance excitotoxic injury; growth factor deprivation; oxidative stress; inflammation; mitochondrial dysfunction and beta-amyloid toxicity (McKinney and Jacksonville, 2005). Even though there were extensive studies performed in the last years, the mechanisms underlying brain cholinergic vulnerability in human neurodegenerative diseases characterized by cognitive impairment are still unclear (McKinney and Jacksonville, 2005).

2.1 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is clinically characterized by early loss of episodic memory (Mckhann et al. 1984). Next to that a loss of functional capacities and activities of daily living and a progressive involvement of other cognitive domains are also present. The phase preceding AD is called mild cognitive impairment (MCI) and is characterized by memory impairment but patients have normal activities of daily living (Petersen et al. 1999). Most patients progress to a clinical and pathological diagnosis of AD when they are diagnosed with MCI (Jack et al. 2004; Jicha et al. 2006). Braak and Braak (1991) found that pathological changes in the brain, which include the presence of extracellular amyloid immunoreactive senile plaques and intraneuronal tau immunoreactive neurofibrillary tangles are associated with AD. Both plaques and tangles cause a decrease in neuronal density and atrophy of brain tissue which leads to a widening of the sulci and shrinkage of gyri. Brain weight is also significantly reduced. During life,

magnetic resonance imaging (MRI) can detect cerebral atrophy. In AD patients the medial temporal lobe, in particular the hippocampus and entorhinal cortex, the posterior cingulate, precuneus and the temporoparietal association neocortex are affected, and the ventricles are expanded (Baron et al. 2001; Fox et al. 1996; Jack et al. 1992; Whitwell et al. 2007b). Whitwell et al. (2007b) have found that atrophy starts in the medial temporal lobes and fusiform gyrus yet three years before patients are diagnosed with AD. From then it scatters to the posterior temporal lobes and parietal lobes around one year before AD diagnosis. When AD is diagnosed, the medial temporal lobe, temporoparietal cortices, and the frontal lobe are also affected and the pattern becomes more severe and widespread. The patterns of atrophy that are visible with MRI correlate to the distribution of neurofibrillary tangles (Whitwell et al. 2008b).

Dementia in AD is associated with neurodegeneration and starts with synaptic injury, followed by neuronal loss (reviewed by Crews and Masliah, 2010). This comes along with astrogliosis, microglial cell proliferation and the presence of neurofibrillary tangles composed of dystrophic neurites an hyperphosphorylated tau (reviewed by Crews and Masliah, 2010). Recently studies exposed evidence for another component of the neurodegenerative process in AD, namely the possibility of interference with the process of adult neurogenesis in the hippocampus (Boekhoorn et al.. 2006; Li et al. 2008). Multiple studies have shown significant alterations in the process of adult neurogenesis in the hippocampus in transgenic animal models of AD (reviewed by Crews and Masliah, 2010). The pathogenesis of AD is related to progressive accumulation of amyloid-β (Aβ) protein. This Aβ is derived from proteolysis of Aβ precursor protein (APP) (reviewed by Crews and Masliah, 2010). An imbalance between the levels of Aβ production, aggregation and clearance result in an abnormal accumulation of Aβ. The clearance of Aβ is mediated by proteolytic enzymes like neprilysin (Iwata et al. 2001), lysosomal and non-lysosomal pathways (reviewed by Crews and Masliah, 2010) and chaperone molecules as apoE (Kim et al. 2009). In familial forms of AD, an increased Aβ production or aggregation is a result of mutations. In sporadic AD, there might be a central role for failure of the clearance mechanisms (reviewed by Crews and Masliah, 2010). Aβ oligomers and fibrils are the prominent components of the plaques found in AD and formation results from progressive accumulation of Aβ (reviewed by Crews and Masliah, 2010). The idea that not the fibrils, but the Aβ oligomers are responsible for the synapto-toxic effects of Aβ is supported by most evidence (Klein et al. 2001; Walsh and Selkoe, 2004). Synaptic plasticity and neuronal integrity are disturbed in the progression of AD, but also during normal ageing (reviewed by Crews and Masliah, 2010). It is still not completely clear what mechanisms lead to neurodegeneration in AD, but the focus of most studies is on the role of Aβ precursor protein (PPP) and its products in the pathogenesis of AD (Selkoe, 1989; Selkoe; 1999; Vassar, 2005). Recent studies of Kamenetz et al. (2003) and Sinha et al. (2000) suggest that there might be a major role in the pathogenesis of AD for alterations in the processing of APP, which results in the accumulation of Aβ and APP C-terminal products. From this point of view, earlier studies have indicated that a proteolytic product of APP metabolism, Aβ1-42, accumulates in the neuronal endoplasmatic reticulum and extracellularly (reviewed by Crews and Masliah, 2010). Studies about the primary pathogenic event that triggers the synaptic loss and the selective neuronal cell death in AD do not agree with each other, but recent studies suggest that the conversion of normally non-toxic monomers to toxic oligomers results in nerve damage, while the larger polymers and fibres that most of the time form the plaques, might not even be as toxic (reviewed by Crews and Masliah, 2010). It is suggested that the synaptic

damage, and ultimately the neurodegeneration in AD are caused by the direct abnormal accumulation of Aβ oligomers in the nerve terminals (Selkoe, 1999). Recently also the investigation of the possibility that Aβ oligomers might interfere with synaptic function by altering synaptic proteins as post-synaptic density-95, scaffold proteins as Shank, and glutamate receptors has emerged (reviewed by Crews and Masliah, 2010). To conclude this part, it is clear that the potential role of neurotoxic Aβ oligomers is a hot topic and of considerable interest in the past few years.

But, the number of neurofibrillary tangles, and not the plaques, correlates best with the presence and or the degree of dementia in AD. This has been consistently demonstrated in studies on the clinical-to-pathological correlation (reviewed by Iqbal and Grundke-Iqbal, 2008). Aβ alone without the presence of neurofibrillary degeneration does not lead to AD clinically, so the neurofibrillary degeneration seems to be required for the clinical expression of AD. Some of the normal aged individuals even have as much Aβ plaques in the brain as typical AD patients. The only difference is the lack of dystrophic neurites with neurofibrillary changes surrounding the Aβ cores in the normal aged individuals (reviewed by Iqbal and Grundke-Iqbal, 2008). But, neurofibrillary degeneration of the type seen in AD without the presence of Aβ, is also seen in other diseases as Guan Parkinsonism dementia complex, dementia pugilistica and Pick disease. All of those disorders are clinically characterized by dementia and are neurogenerative disorders, collectively called tauopathies (reviewed by Iqbal and Grundke-Iqbal, 2008). Tau is a microtubule associated protein and is very hydrophilic. Therefore it is highly soluble and heat stable. In every known human tauopathy, including AD, the pathology of tau is about the abnormally hyperphosphorylated protein (reviewed by Iqbal and Grundke-Iqbal, 2008). In AD, truncation of tau (Cotman et al. 2005; Gamblin et al. 2003; Novak et al. 1991) and conformational changes (Jicha et al. 1997; Jicha, Berenfeld and Davies, 1999; Jicha et al. 1999) have been reported while the most established and compelling cause of dysfunctional tau in AD and other related tauopathies is abnormal hyperhposphorylation of the protein (reviewed by Iqbal and Grundke-Iqbal, 2008). In AD brains, tau is abnormally hyperphosphorylated and thereby the major protein subunit of the neurofibrillary tangles (reviewed by Iqbal and Grundke-Iqbal, 2008). Two important functions of tau that are known are its ability to promote assembly and to maintain the structure of microtubules (Weingarten et al. 1975). By the degree of phoshorylation, these functions are regulated (reviewed by Iqbal and Grundke-Iqbal, 2008). In brains of AD patients the amount of normal tau is the same as in age-matched control human brains, but the amount of abnormally hyperphosphorylated tau is 4-8 folded in the AD brain (Khatoon et al. 1992; Khatoon et al. 1994). Around 40% of the abnormally hyperphosphorylated tau is present in the cytosol and not polymerized into neurofibrillary tangles (Kopke et al. 1993). The tau that is polymerized into neurofibrillary tangles is seemingly inactive and does not bind to tubulin or promotes the assembly of tubulin into microtubules, it even inhibits assembly and disrupts microtubules (reviewed by Iqbal and Grundke-Iqbal, 2008). Besides this, the toxic feature of the pathological tau also involves sequestration of normal tau by the diseased tau. The hyperphosphorylated tau even sequesters the two other major neuronal microtubule associate proteins MAP1 A/B and MAP2 (reviewed by Iqbal and Grundke-Iqbal, 2008). It seems that only the abnormal hyperphosphorylation of tau is responsible for this toxic behavior since dephosphorylation of diseased tau converts it into a normal-like protein (reviewed by Iqbal and Grundke Iqbal, 2008). Next to this, *in vitro* dephosphorylation of neurofibrillary tangles disaggregates the filaments which results in the normal like protein behavior of the tau released in promoting microtubule assembly (Wang

et al. 1995). So, the two characteristics of abnormally hyperphosphorylated tau in AD are the sequestering of normal MAPs and thereby the disruption of microtubules, and the self-assembly into paired helical and or straight filaments (reviewed by Iqbal and Grundke-Iqbal, 2008).

2.2 Parkinson's disease

Parkinson's disease (PD) is among the aging human population the second most common neurodegenerative disorder after Alzheimer's disease. PD was first described in 1817 by James Parkinson. Motor symptoms such as uncontrollable tremor, muscular rigidity, slowness of movement and postural instability are the clinical characteristics of PD. Neuropathologically, the loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of cytoplasmic inclusions also known as Lewy bodies are the main characteristics (Lees et al. 2009). Spillantini et al. (1997) found that a small synaptic protein, alpha-synuclein, is the main component of the Lewy bodies found in brains of PD patients. Studies that showed three independent mutations in the alpha-synuclein protein provided a strong proof for the involvement of alpha-synuclein in the neurodegeneration in PD (reviewed by Ruipérez et al. in press). Those mutations, alanine to proline at position 30 (Krüger et al. 1998), alanine to threonine at position 53 (Polymeropoulos et al. 1997) and glutamate to lysine at position 46 (Zarranz et al. 2004) lead to the development of familial Parkinson's disease. Alpha-synuclein is a small, intrinsically unfolded cytoplasmic protein that is highly expressed in the central nervous system and concentrated in presynaptic terminals (Krüger et al. 2000). There are also some other factors that are necessary for the development and progression of PD. Mitochondrial dysfunction and oxidative stress seem to contribute to PD (reviewed by Ruipérez et al. in press). Impairment of dexterity is a common feature in the beginning of PD. Dragging of one foot is also a feature, but less common. The onset of PD is gradual and the first symptoms can be unnoticed or misinterpreted for quite some time. Symptoms as a lugubrious stiff face, a hangdog appearance, a monotonous quality to the speech, a flexion of one arm with lack of swing, and an extreme slowing down are rarely noticed by the patient (Lees et al. 2009). In the late stages of PD, the speech of patients is monotonous, festinant, and slightly slurred, the face is masked and expressionless, and the posture is flexed simian with a severe pill rolling tremor of the hands (Lees et al. 2009). All dextrous movements are done slowly and awkwardly. Assistance for dressing, bathing, feeding, getting out of chairs, and turning in bed might be needed. Also chewing and swallowing difficulties, constipation, urge incontinence of urine and drooling of saliva are common complaints (Lees et al. 2009). Next to the region-specific selective loss of dopaminergic, neuromelanin-containing neurons from the substantia nigra pars compacta, cell loss in the locus coeruleus, raphe nuclei, dorsal nuclei of the vagus and the nucleus basalis of Meynert are also present (Damier et al. 1999). The nerve cell loss is accompanied by three distinctive intraneuronal inclusions, namely the Lewy body, the pale body, and the Lewy neurite (Lees et al. 2009). The Lewy bodies can be subdivided into cortical and classical (brainstem) types based on their morphology (Lees et al. 2009). Pale bodies are large rounded eosinophilic structures that often displace neuromelanin. Those bodies are the predecessor of the Lewy bodies (Lees et al. 2009). Irrespective of disease duration, a constant proportion of nigral neurons, 3-4%, contain Lewy bodies. This is consistent with the idea that Lewy bodies are continuously forming and disappearing in the diseased substantia nigra, in contrast to neurofibrillary tangles (Greffard et al. 2010).

Next to the motor disorders, dementia is a common associated feature of PD. Dementia becomes more common as PD advances and age, early occurrence of levodopa-related psychosis, increased duration of PD, more severe motor symptoms and depression are the most significant risk factors (reviewed by Emre, 2003). For long it was thought that dementia in PD is caused by AD pathology, but more and more evidence suggests that PD dementia (PDD) is more closely associated with Lewy body pathology (reviewed by Farlow and Cummings, 2008). The characterization of PDD and AD are clinically distinct. Impairment of executive and attentional function are the initial and early prominent cognitive features of PDD which make it a dysexecutive syndrome, while characteristically AD is an amnestic disorder (reviewed by Emre, 2003). Presence of Lewy bodies is the most consistent pathological correlate of dementia in PD (reviewed by Farlow and Cummings, 2008). Research of Zarow et al. (2003) has shown that the basal forebrain pathway, extending from the nucleus basalis of Meynert is affected in PD. Research has shown that the degree of neuronal loss in the NbM correlates with the severity of cognitive deficit in PD patients (reviewed by Farlow and Cummings, 2008).

2.3 The Nucleus basalis of Meynert in Alzheimer's and Parkinson's disease

Multiple studies have shown deficits in specific neurotransmitters in AD (Arendt et al. 1983). Reduction of cholinergic parameters as the activity of ChAT, ACh content, and the activity of AChE in the cerebral cortex, are the most prominent abnormalities (Arendt et al. 1983). This matches with a decreased functional state of the NbM cholinergic neurons in AD, which is reflected by strongly reduced levels of ChAT in the NbM itself (Vogels et al. 1990). The study of Vogels et al. (1990) showed that there was significant neuron loss for the NbM as a whole, except for the Ch1 and Ch2 region, in AD patients compared with age-matched controls. Next to that, the length of both the left and right NbM was significantly reduced. The Ch4p subdivision accounted for this shortening, the other subdivisions, Ch4i, Ch4a, Ch3, Ch1 and Ch2 demonstrated no significant changes in length (Vogels et a. 1990). A study of Arendt et al. (1983) discovered a reduction in the number of neurons of the NbM of 70% in Alzheimer patients, in PD this reduction was 77%. The loss of the cholinergic projections from the NbM to other parts of the neocortex may be reflected in some of the cognitive, emotional, and motivational abnormalities seen in AD and PD (Arendt et al. 1983).

3. Treatment

3.1 Classic treatments

To treat the cholinergic deficit in AD, the initial strategy was the use of cholinergic precursors. Lecithin and phosphatidylcholine, both precursors of ACh, were tested. Unfortunately they failed to show consistent beneficial effects in the treatment of AD (Heyman et al. 1987; Levy et al. 1983). Using acetylcholine receptor agonists is an alternative method to increase cholinergic transmission. In laboratory animals, muscarinic receptor agonists as sabcomeline and cevimeline, improved cognition (reviewed by Wilkinson et al. 2004). Some muscarinic receptor agonists, like xanomeline, have demonstrated efficacy in treating the symptoms of AD (reviewed by Wilkinson et al. 2004). But other muscarinic receptor agonists failed (Thal et al. 2000). The same applies to the nicotinic receptor agonists (reviewed by Wilkonson et al. 2004). Until now, the most successful way to treat AD has been by inhibition of acetylcholinesterase. Preclinical experiments conducted in rats have shown that hypothermia and tremor can be induced by cholinesterase inhibitors, but cortical

ACh levels were increased. Performance on cognitive tests was improved after administration of tacrine and donepezil. The administration also led to partially reversed scopolamine-induced impairment in cognitive tasks (reviewed by Wilkinson et al. 2004). Treatment of AD patients with cholinesterase inhibitors has been associated with cognitive improvements from baseline, while the cognitive functions of untreated patient decline (reviewed by Wilkinson et al. 2004).
The most widely used and most effective drug for the symptomatic therapy of the motor defects in PD is levodopa (reviewed by Olanow et al. 2006). Unfortunately, treatment with levodopa is complicated by the development of other motor complications. Those complications can be disabling, are difficult to treat and even limit the usefulness of the drug itself (reviewed by Olanow et al. 2006). Because of this, medical therapy that provides the benefits of levodopa, but without motor complications would be a major advance in the treatment of Parkinson's disease (reviewed by Olanow et al. 2006). Treatment with levodopa unfortunately does not have a positive effect on the dementia and cognitive symptoms that are also associated with PD.
Another way to treat the motor complications in PD, are surgical therapies as pallidotomy and deep brain stimulation of the subthalamic nucleus and the internal segment of the globus pallidus. Those techniques can provide effective treatment for the motor complications induced by levodopa. On the other hand does surgery have risks, it is expensive, and it does not provide the antiparkinsonian benefits better than treatment with levodopa (reviewed by Olanow et al. 2006).

3.2 Deep brain stimulation

Deep brain stimulation (DBS) is a very effective surgical therapy for treating people with movement disorders. With DBS those patients are able to re-establish control over their motor function. Reversibility of the surgical outcome and the ability to adjust stimulation parameters postoperatively to optimize therapeutic benefit for the patient, and minimizing adverse side effects are the advantages of DBS (reviewed by Johnson et al. 2008). Each year, thousands of DBS implants are performed for a growing number of movement disorders (Kringelbach et al. 2007; Perlmutter et al. 2006; Wichmann et al.. 2006). With DBS a lead that is just larger than 2 mm in diameter is implanted stereotactically into specific brain targets. This implanting goes with submillimeter accuracy. Pulse generators typically placed in the chest, like cardiac pacemakers, are connected to the stimulation leads (reviewed by Greenberg, 2002). The pulse generators are connected to the stimulation leads in the brain via an extension wire that is tunneled under the skin. The anatomical extent of stimulation is adjustable because of the several independently programmable electrode contact sites of the leads. Frequency, pulse width and intensity are also programmable, of course within safety limits restricting the density of the electrical charge induced. The opportunity to optimize the therapy and a challenge to do so are provided by this large space (reviewed by Greenberg, 2002).
It is suggested that DBS in PD works by freeing thalamocortical and brainstem motor systems from abnormal and disruptive basal ganglia influences in movement disorders (reviewed by Wichmann and DeLong, 2006), but how electrical stimulation produces the therapeutic effects in PD and tremor is still unknown. High frequencies (around 100 Hz) has been proposed to inhibit transmission via depolarization blockade, neural jamming, imposing a physiologically meaningless pattern of activity within the affected circuits, or synaptic fatigue. These mechanisms would have the same effect as a lesion and thereby

mimicking the therapeutic effect of an actual lesion (reviewed by Greenberg, 2002). But the clinical effects of lesions and of DBS in movement disorders do not always correspond (reviewed by Greenberg, 2002). It could also be that the stimulation does not inhibit information flow within key neural pathways, but actually enhances it. Chaotic information processing is thereby reduced through stochastic resonance (Deuschl et al. 2002). DBS is also used in treating neuropsychiatric disorders. This use is based on findings suggesting that these conditions are, at least partly, due to abnormalities within the nonmotor basal ganglia circuits, of which the limbic circuitry is the most prominently (reviewed by Wichmann and DeLong, 2006). This limbic circuitry may play a role in motivated behavior and the modulation of emotional 'tone' under physiologic conditions (reviewed by Wichmann and DeLong, 2006). The most severe complication in stereotactic neurosurgery is intracranial hematoma, which is an inherent risk of the procedure. It is estimated to occur in 2-8% of all patients (Obeso et al. 1997). Adverse effects of surgery occur frequently, but those that induce permanent neurologic impairment are relatively rare, around 3% (Obeso et al. 1997). At least in severely disabled PD patients, the benefit to risk ratio of DBS seems favorable (Obeso et al. 1997).
A study of Freund et al. (2009) described a new DBS strategy for the modification of cognitive functions by stimulating the NbM in addition to the subthalamic nucleus (STN) in a patient with Parkinson's disease dementia (PDD). The tips of the NbM electrodes were directed into the laterodorsal portion of the intermediate (Ch4i) sector of the NbM.

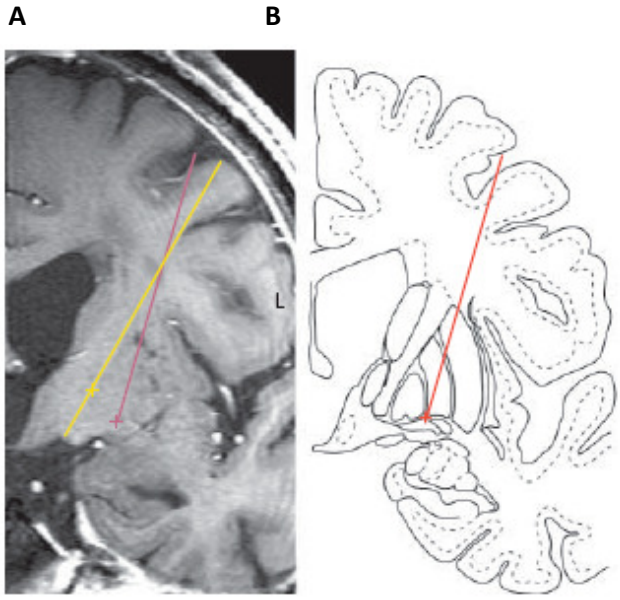

Figure 2. Anatomical and graphic presentation of the electrode trajectory (Freund et al. 2009). **A** Reconstructed electrode trajectories to the NbM (magenta line) and the STN (yellow line) superimposed on preoperative T1-weighted magnetic resonance image. **B** Structural outline of the coronal section at the level of the electrode tip in the NbM (red line). L indicates left side. (Freund et al. 2009).

Combined bilateral stimulation of the STN and the NbM lead to significantly and impressively improved memory tasks. Other remaining neuropsychological measures were enhanced and reached higher levels than using only STN stimulation (Freund et al. 2009). Major cognitive deterioration was observed after 24 hours without NbM stimulation. Cognitive functioning notably improved 24 hours after restarting NbM stimulation (Freund et al. 2009). There was no continuation of the cognitive decline that had been observed in the six months before

DBS. Clear improvements of various aspects of cognitive functioning following the NbM stimulation were observed instead (Freund et al. 2009). NbM-DBS in a patient with PDD led to a distinct improvement of the patient's quality of life (Freund et al. 2009).

4. Discussion

It is clear that in our society, where the proportion of elderly people becomes bigger, neurodegenerative diseases accompanied by memory dysfunction as Alzheimer's disease (AD) and Parkinson's disease dementia (PDD) will become a larger problem. Those diseases thereby become a great burden for health care around the world. In both AD and PD the number of neurons in the nucleus basalis of Meynert is reduced with 70 and respectively 77% (Arendt et al. 1983). The NbM is the major cholinergic source in the brain, and loss of cholinergic projections from the NbM to other parts of the neocortex may be reflected in some of the cognitive, emotional and motivational abnormalities seen in AD and PD (Arendt et al. 1983). A variety of studies were performed to demonstrate the involvement of the cholinergic system and the NbM in learning and memory processes. Inhibition of acetylcholinesterase with cholinesterase inhibitors is for now the most successful way to treat the cholinergic deficits in AD. The cholinesterase inhibitor galantamine leads to cognition-enhancing effects, but it does not prevent the neurodegeneration in the NbM. But still, adult onset dementia disorders that are characterized by cognitive impairment and brain cholinergic hypofunction have no adequate therapy. The hypothesis is raised that the depressed cortical glucose metabolic activity in senile dementia of Alzheimer's type may result primarily from diminished activity and loss of the cells in the NbM (Turnbull et al. 1985). The study of Turnbull et al. (1985) tested the hypothesis that electrical stimulation of the NbM would bring about clinical improvement and increase cortical glucose metabolic activity in SDAT. Positron emission tomography showed preservation of cortical glucose metabolic activity in the ipsilateral temporal and parietal lobes while elsewhere in the cortex the glucose metabolic activity declined. These results would suggest that electrical stimulation of the NbM leads to preservation of the cholinergic neurons. Results of a recent study of Freund et al. (2009) support this suggestion. Memory tasks in a patient with PDD treated with deep brain stimulation (DBS) were improved. Besides that, there was no continuation of the cognitive decline observed in the six months before DBS, and improvements of cognitive functioning were observed instead (Freund et al. 2009). Application of DBS in AD and PDD is promising. By preventing cholinergic neuron cell death with electric stimulation, symptoms of cognitive impairment can be reduced and maybe even delayed. In this manner the burden on people that live close to the patient, and even the burden on health care around the world can be decreased.

References

Amenta, F. and Tayebati, S.K. 2008. Pathways of Acetylcholine synthesis, Transport and Release as Targets for Treatment of Adult-Onset Cognitive Dysfunction. Current Medicinal Chemistry; 15: 488-498.

Arendt, T., Bigl, V., Arendt, A., Tennstedt, A. 1983. Loss of neurons in the Nucleus basalis of Meynert in Alzheimer's disease, Paralysis Agitans and Korsakoff's disease. Acta Neuropathologica (Berl); 61: 101-108.

Bartus, R.T., Flicker, C., Dean, R.L., Pontecorvo, M., Figueirede, J.C., Fisher, S.K. 1985. Selective memory loss following nucleus basalis lesions: Long term behavioral recovery despite persistent cholinergic deficiencies. Pharmacology, Biochemistry, and Behavior; 23(1): 125-135.

Baron, J.C., Chetelat, G., Desgranges, B., Perchey, G., Landeau, B., de la Sayette, V., Eustache, F. 2001. In vivo mapping of gray matter loss with voxel-based morphometry in mild Alzheimer's desease. Neuroimage; 14(2): 298-309.

Bartolini, L., Casamenti, F., Pepeu, G. 1996. Aniracetam restores object recognition impaired by age, scopolamine, and nucleus basalis lesions. Pharmacology, Chemistry and Behavior; 53: 277-283.

Boekhoorn, K., Joels, M., Lucassen, P.J. 2006. Increased proliferation reflects glial and vascular-associated changes, but not neurogenesis in the presenile Alzheimer hippocampus. Neurobiology of Disease; 24: 1-14.

Braak, H., Braak, E. 1985. On areas of transition between entorhinal allocortex and temporal isocortex in the human brain. Normal morphology and lamina-specific pathology in Alzheimer's disease. Acta Neuropathologica (Berl); 68: 325-332.

Braak, H., Braak, E. 1990. Neurofibrillary changes confined to the entorhinal region and an abundance of cortical amyloid in cases of presenile and senile dementia. Acta Neuropathologica; 80: 479-486.

Braak, H., Braak, E., 1992. Alzheimer's disease affects limbic nuclei of the thalamus. Acta Neuropathologica; 81: 261-268.

Braak, H., Braak, E. 1991. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica; 82: 239-259.

Braak, H., Braak, E., Kalus, P. 1989. Alzheimer's disease: areal and laminar pathology in the occipital isocortex. Acta Neuropathologica; 77: 494-506.

Cabrera, S.M., Chaves, C.M., Corley, S.R., Kitto, M.R., Butt, A.E. 2006. Selective lesions of the nucleus basalis magnocellularis impair cognitve flexibility. Behavioral Neuroscience; 120(2): 298-306.

Casamenti, F., Di Patre, P.L., Bartolini, L., Pepeu, G. 1988. Unilateral and bilateral nucleus basalis lesions: differences in neurochemical and behavioural recovery. Neuroscience; 24: 2009-215.

Casamenti, F., Prosperi, C., Scali, C., Giovanneli, L., Pepeu, G. 1998. Morphological, biochemical and behavioural changes induced by neurotoxic and inflammatory insults to the nucleus basalis. International Journal of Developmental Neuroscience; 16: 705-714.

Conn, P.J., Jones, C.K., Lindsley, C.W. 2009. Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders. Trends in Pharmacological Sciences; 30: 148-155.

Cortés, R., Probst, A., Palacios, J.M. 1984. Quantitative light micorscopic autoradiographic localization of cholinergic muscarinic receptors in human brain: brainstem. Neuroscience; 12: 1003-1026.

Cortés, R., Probst, A., Tobler, H-J., Palacios, J.M. 1986. Muscarinic cholinergic receptor subtypes in the human brain. II. Quantitative autoradiographic studies. Brain Research; 362: 239-253.

Damier, P., Hirsch, E.C., Agid, Y., Graybiel, A.M. 1999. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain; 122: 1437-1448.

Cotman, C.W., Poon, W.W., Rissman, R.A., Blurton-Jones, M. 2005. The role of caspase cleavage of tau in Alzheimer disease neuropathology. Journal of Neuropathology and Experimental Neurology; 64: 104-112.

Crews, L., Masliah, E., 2010. Molecular mechanisms of neurodegeneration in Alzheimer's disease. Human Molecular Genetics; 19: R12-R20.

Dalley, J.W., McGaughy, J., O'Connell, M.T., Cardinal, R.N., Levita, L., Robbins, T.W. 2001. Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and noncontingent performance of a visual attentional task. Journal of Neuroscience; 21:4908-4014.

Dani, J.A., Bertrand, D. 2007. Nicotinic acetylcholine receptors and nicotinic cholinergic mechanisms of the central nervous system. Annual Review of Pharmacology and Toxicology; 47: 699-729.

Dashniani, M., Burjanadze, M., Beselia, G., Maglakelidze, G., Naneishvili, T. 2009. Spatial memory following selective cholinergic lesion of the nucleus basalis magnocellularis. Georgian Medical News; 174: 77-81.

Deuschl, G., Bain, P. 2002. Deep brain stimulation for tremor (correction of trauma): patient selection and evaluation. Movement Disorders; 17(Suppl 3): S102-S111.
Deutsch, J.A. 1987. The cholinergic synapse and the site of memory. Science 174(11): 788-794.

Eglen, R.M. 2006. Muscarinic receptor subtypes in neuronal and non-neuronal cholinergic function. Autonomic and Autacoid Pharmacology; 26: 219-233.

Emre, M. 2003. Dementia associated with Parkinson's disease. Lancet Neurology; 2: 229-237.

Everitt, B.J., Robbins, T.W., Evenden, J.L., Marston, H.M., Jones, G.H., Sirkiä, T.E. 1987. The effects of excitotoxic lesions of the substantia innominata, ventral and dorsal globus pallidus on the acquisition and retention of a conditional visual discrimination: Implications for cholinergic hypothses of learning and memory. Neuroscience; 22(2): 441-469.

Farlow, M.R., Cummings, J. 2008. A modern hypothesis: the distinct pathologies of dementia associated with Parkinson's disease versus Alzheimer's disease. Dementia and Geriatric Cognitive Disorders; 25: 301-308.

Flood, J.F., Landry, D.W., Jarvik, M.E. 1981. Cholinergic receptor interactions and their effects on long-term memory processing. Brain Research 215(1-2): 177-185.

Fox, N.C., Freeborough, P.A., Rossor, M.N. 1996. Visualisation and quantification of rates of atrophy in Alzheimer's disease. Lancet; 348: 94-97.

Fratigklioni, L., Launer, L.J., Andersen, K., Breteler, M.M., Copeland, J.R., Dartigues, J.F., Lobo, A., Martinez-Lage, J., Soininen, H., Hofman, A. 2000. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology; 54(11 Suppl 5): S10-15.

Freund, H-J., Kuhn, J., Lenartz, D., Mai, J.K., Schnell, T., Klosterkoetter, J., Sturm, V. 2009. Cognitive functions in a patient with Parkinson-Dementia Syndrome undergoing deep brain stimulation. Archives of Neurology; 66(6): 781-785.

Gamblin, T.C., Chen, F., Zambrano, A., Abraha, A., Lagalwar, S., Guillozet, A.L., Lu, M., Fu, Y., Garcia-Sierra, F., LaPointe, N., Miller, R., Berry, R.W., Binder, L.I., Cryns, V.L. 2003. Caspase cleavage of tau: linking amyloid and neurofibrillary tangles in Alzheimer's disease. Proceedings of the National Acadamy of Sciences USA; 100: 10032-10037.

.

Gaykema, R.P., Luiten, P.G.M., Nyakas, C., Traber, J. 1990. Cortical projection patterns of the medial septum-diagonal band complex. Journal of Comparative Neurology; 293: 103-124.

Gotti, C., Clementi, F. 2004. Neuronal nicotinic receptors: from structure to pathology. Progress in Neurobiology; 74: 363-396.

Greenberg, B.D. 2002. Brain stimulation techniques. Update on deep brain stimulation. The Journal of ECT; 18(4): 193-196.

Greffard, S., Verny, M., Bonnet, A.M., Seilhean, D., Hauw, J.J., Duyckaerts, C. 2010. A stable proportion of Lewy body bearing neurons in the substantia nigra suggests a model in which the Lewy body causes neuronal death. Neurobiology of Aging; 31(1): 99-103.

Harkany, T., Penke, B., Luiten, P.G.M. 2000b. beta-Amyloid excitotoxicity in rat magnocellular nucleus basalis. Effect of cortical deafferentiation on cerebral blood flow regulation and implications for Alzheimer's disease. Annals of the New York Academy of Sciences; 903: 374-386.

Heyman, A., Schmechel, D., Wilkinson, W., Rogers, H., Krishnan, R., Holloway, D., Schultz, K., Gwyther, L., Peoples, R., Utley, C. et al. 1987. Failure of long term high-dose lecithin to retard progression of early-onset Alzheimer's disease. Journal of Neural Transmission; 24: 279-286.

Hyman, B.T., van Hoesen, G.W., Damasio, A.R., Barnes, C.L, 1984. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. Science; 25: 1168-1170

Intrioni-Collison, I.B. and McGaugh, J.L. 1988. Modulation of memory by post-training epinephrine: Involvement of cholinergic mechanisms. Psychopharmacology 94(3): 379-385.

Iqbal, K., Grundke-Iqbal, I. 2008. Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. Journal of Cellular and Molecular Medicine; 12(1): 38-55.

Iwata, N., Tsubuki, S., Takaki, Y., Shirotani, K., Lu, B., Gerard, N.P., Gerard, C., Hama, E., Lee., H.J., Saido, T.C. 2001. Metabolic regulation of brain Abeta by neprilysin. Science; 202: 1550-1552.

Jack, C.R. Jr., Petersen, T.C., O'Brien, P.C., Tangalos, E.G. 1992. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology; 42: 183-188.

Jack, C.R. Jr., Shiung, M.M., Gunter, J.L., O'Brien, P.C., Weigand, S.D., Knopman, D.S., Boeve, B.F., Ivnik, R.J., Smith, G.E., Cha, R.H., Tangalos, E.G., Petersen, R.C. 2004. Comparison of different MRI brain atrophy rate measures with clinical disease progressio in AD. Neurology; 62(4): 591-600.

Jicha, G.A., Lane, E., Vincent, I., Otvos, L. Jr., Hoffmann, R., Davies, P. 1997. A conformation- and phosphorylation-dependent antibody recognizing the paired helical filaments of Alzheimer's disease. Journal of Neurochemistry; 69: 2087-2095.

Jicha, G.A., Berenfeld, B., Davies, P. 1999. Sequence requirements for formation of confromational variants of tau similar to those found in Alzheimer's disease. Journal of Neuroscience Research; 55: 713-723.

Jicha, G.A., Rockwood, J.M., Berenfeld, B., Hutton, M., Davies, P. 1999. Altered conformation of recombinant frontotemporal dementia-17 mutant tau proteins. Neuroscience Letters; 260: 153-156.

Jicha, G.A., Parisi, J.E., Dickson, D.W., Johnson, K., Char R., Ivnik, R.J., Tangalos, E.G., Boeve, B.F., Knopman, D.S., Braak, H., Petersen, R.C. 2006. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. Archives of Neurology; 63(5): 674-681.

Johnson, M.D., Miocinovic, S., McIntyre, C.C., Vitek, J.L. 2008. Mechanisms and targets of deep brain stimulation in movement disorders. The American Society for Experimental NeuroTherapeutics; 5: 295-308.

Jones, E.G., Burton, H., Saper, C.B., Swanson, L.W. 1976. Midbrain, diencephalic and cortical relationship of the nucleus basalis of Meynert and associated structures in primates. Journal of Comparative Neurology 167: 385-397. Neuron; 63: 287-303.

Kamenetz, F., Tomita, T., Hsieh, H., Seabrook, G., Borchelt, D., Iwatsubo, T., Sisodia, S., Malinow, R. 2003. APP processing and synaptic function. Neuron; 37: 925-937.

Khatoon, S., Grundke-Iqbal, I., Iqbal, K. 1992. Brain levels of microtubule-associated protein tau are elevated in Alzheimer's disease: a radioimmuno-slot-blot assay for nanograms of the protein. Journal of Neurochemistry; 59: 750-753.

Khatoon, S., Grundke-Iqbal, I., Iqbal, K. 1994. Levels of normal and abnormally phosphorylated tau in different cellular and regional compartments of Alzheimer's disease and control brains. FEBS Letters; 351: 80-84.

Klein, W.L., Krafft, G.A., Finch, C.E. 2001. Targeting small Abeta oligomers: the solution to an Alzheimer's disease conundrum? Trends in Neuroscience; 24: 219-224.

Kopke, E., Tung, Y.C., Shaikh, S., Alonso, A.C., Iqbal, K., Grundke-Iqbal, I. 1993. Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. Journal of Biological Chemistry; 268: 24374-24384.

Kringelbach, M.L., Jenkinson, N., Owen, S.L., Aziz, T.Z. 2007. Translational principles of deep brain stimulation. Nature Reviews Neuroscience; 8: 623-635.

Krüger, R., Kuhn, W., Müller, T., Woitalla, D., Graeber, M., Kösel, S., Przuntek, H., Epplen, J.T., Schöls, L., Riess, O. 1998. Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. Nature Genetics; 18: 106-108.

Krüger, R., Müller, T., Riess, O. 2000. Involvement of alpha-synuclein in Parkinson's disease and other neurodegenerative disorders. Journal of Neural Transmission; 107; 31-40.

Lees, A.J., Hardy, J., Revesz, T. 2009. Parkinson's disease. Lancet; 373: 2055-2066.

Levy, R., Little, A., Chuaqui, P., Reith, M. 1983. Early results from double-blind, placebo controlled trial of high dose phosphatidylcholine in Alzheimer's disease. Lancet; 1(8331): 987-988.

Lewis, D.A., Campbell, M.J., Terry, R.D., Morrison, J.H. 1987. Laminar and regional distributions of neurofibrillary tangles and neuritic plaques in Alzheimer's disease: a quantitative study of visual and auditory cortices. Journal of Neuroscience; 7: 1799-1808.

Li, B., Yamamori, H., Tatebayashi, Y., Shafit-Zagardo, B., Tanimukai, H., Chen, S., Iqbal, K., Grundke-Iqbal, I. 2008. Failure of neuronal maturation in Alzheimer disease dentate gyrus. Journal of Neuropathology and Experimental Neurology; 67: 78-84.

Luiten, P.G.M., Gaykema, R.P., Traber, J., Spencer, D.G. Jr. 1987. Cortical projection patterns of magnocellular basal nucleus subdivisions as revealed by anterogradely transported Phaseolus vulgaris leucoagglutinin. Brain Research 413:229-250.

Mandel, R.J., Gage, F.H., Thal, L.J. 1989. Spatial learning in rats: Correlation with cortical choline acetyltransferase and imporvement with NGF following NBM damage. Experimental Neurology; 104(3): 208-217.

Miasnikov, A.A., Chen, J.C., Weinberger, N.M. 2009. Behavioral memory induced by stimulation of the nucleus basalis: effects of contingency reversal. Neurobiology of Learning and Memory; 91: 298-309.

McGaughy, J., Dalley, J.W., Morrison, C.H., Everitt, B.J., Robbins, T.W. 2002. Selective behavioral and neurochemical effects of cholinergic lesions produces by intrabasalis infusions of 192 IgG-saporin on attentional performance in five-choice serial reaction time task. The Journal of Neuroscience; 22(5): 1905-1913.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E.M. 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of department of Health and Human Services Task Force on Alzheimer's Disease. Neurology; 34(7): 939-44.

McKinney, M., Jacksonville, M.C. 2005. Brain cholinergic vulnerability: relevance to behavior and disease. Biochemical Pharmacology; 70(8): 1115-1124.

Mufson, E.J., Ginsberg, S.D., Ikonomovic, M.D., DeKosky, S.T. 2003. Human cholinergic basal forebrain: chemoanatomy and neurologic dysfunction. Journal of Chemical Neuroanatomy; 26: 233-242.

Novak, M., Jakes, R., Edwards, P.C., Milstein, C., Wischik, C.M. 1991. Difference between the tau protein of Alzheimer paired helical filament core and normal ta revealed by epitope analysis of monoclonal antibodies 423 and 7.51. Proceedings of National Acadamy of Sciences USA; 88: 5837-5841.

Obeso, J.A., Rodriguea, M.C., Gorospe, A., Guridi, J., Alvarez, L., Macias, R. 1997. Surgical treatment of Parkinson's disease. Baillieres Clincial Neurology; 6: 125-145.

Olanow, C.W., Obeso, J.A., Stocchi, F. 2006. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurology; 5: 677-687.

Orsetti, M., Casamenti, F., Pepeu, G. 1996. Enhanced acetylcholine release in the hippocampus and cortex during acquistion of an operant behavior. Brain Research; 724: 89-96.

Pepeu, G., Giovannini, M.,G. 2004. Changes in acetylcholine extracellular levels during cognitive processes. Learning and Memory; 11:21-27.

Perlmutter, J.S., Mink, J.W. 2006. Deep brain stimulation. Annual Review of Neuroscience; 29: 229-257.

Perry, E.K., Kilford, L., Lees, A.J., Burn, D.J., Parry, R.H. 2003. Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. Annals of Neurology; 54: 235-238.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E. 1999. Mild cognitive impairment: clinical characterization and outcome. Archives of Neurology; 56(3): 303-308.

Polymeropoulos, M.H., lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Rooth, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L. 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science; 276: 2045-2047.

Power, A.E., Vazdarjanova, A., McGaugh, J.L. 2003. Muscarinic cholinergic influences in memory consolidation. Neurobiology of Learning and Memory 80(3): 178-193.

Rogers, J., Morrison, J.H. 1985. Quantitative morphology and regional and laminar distributions of senile plaques in Alzheimer's disease. Journal of Neuroscience; 5: 2801-2808.

Rudy, J.W. 1996. Scopolamine administered before and after training impairs both contextual and auditory-cue fear conditioning. Neurobiology of Learning and Memory 65(1): 73-81.

Ruipérez, V., Darios, F., Davletov, B. *In press.* Alpha-synuclein, lipids and Parkinson's disease.

Russel, R.W., Escobar, M.L., Booth, R.A., Bermudez-Rattoni, F. 1994. Accelerating behavioral recovery after cortical lesions. II. In vivo evidence for cholinergic involvement. Behavioral and Neural Biology 61(1): 81-92.

Selkoe, D. 1989. Amyloid b protein precursor and the pathogenesis of Alzheimer's disease. Cell; 58: 611-612.

Selkoe, D. 1999. Translating cell biology into therapeutic advances in Alzheimer's disease. Nature; 399: A23-A31.

Sinha, S., Anderson, J., John, V., McConlogue, L., Basi, G., Thorsett, E., Schenk, D. 2000. Recent advances in the understanding of the processing of APP to beta amyloid peptide. Annals of the New York Acadamy of Science; 920: 206-208.

Spillantini, M.G., Schmidt, M.L., Lee, V.M., Trojanowski, J.Q., Jakes, R., Goedert, M. 1997. Alpha-synuclein in Lewy bodies. Nature; 388: 839-840.

Stratton, L. and Petrinovich, L. 1963. Post-trial injections of an anti-cholinesterase drug and maze learning in two strains of rats. Psychopharmacologia 5: 47-54.

Thal, L.J., Forrest, M., Loft, H., Mengel. H. 2000. Lu 25-109, a muscarinic agonist, fails to improve cognition in Alzheimer's disease. Neurology; 54: 421-426.

Tuček, S. 1984. Problems in the organization and control of acetylcholine synthesis in brain neurons. Progress in Biophysics and Molecular Biology 44(1): 1-46.

Turnbull, I.M., McGeerR, P.L., Beattie, L., Calne, D., Pate, B., 1985. Stimulation of the basal nucleus of Meynert in senile dementia of Alzheimer's type. A preliminary report. Applied neurophysiology; 48: 216-221.

Van Hoesen, G.W., Hyman, B.T. 1990. Hippocampal formation: anatomy and the patterns of pathology in Alzheimer's disease. Progress in Brain Research; 83: 445-457.

Vassar, R. 2005. b-Secretase, APP and Abeta in Alzheimer's disease. Subcellular Biochemistry; 38: 79-103.

Vogels, O.J.M., Broere, C.A.J., Ter Laak, H.J., Ten Donkelaar, H.J., Nieuwenhuis, R., Schutle, B.P.M. 1990. Cell loss and shrinkage in the Nucleus basalis Meynert complex in Alzheimer's disease. Neurobiology of Aging; 11: 3-13.

Walsh, D.M., Selkoe, D.J. 2004. Oligomers on the brain: the emerging role of soluble protein aggregates in neurodegeneration. Protein and Peptide Letters; 11: 213-228.

Wang, J.Z., Gong, C.X., Zaidi, T., Grundke-Iqbal, I., Iqbal, K. 1995. Ephosphorylation of Alzheimer paired helical filaments by protein phosphatase-2A and –2B. Journal of Biological Chemistry; 270: 4854-4860.

Weingarten, M.D., Lockwood, A.H., Hwo, S.Y., Kirschner, M.W. 1975. A protein factor essential for microtubule assembly. Proceedings of the National Acadamy of Sciences USA; 72: 1858-1862.

Wenk, H., Bigl, V., Meyer, U., Biesold, D. 1981. Cholinergic pathways to the cerebral cortex in rats. In: Pepeu, G., Ladinsky, H. (eds). Cholinergic mechanisms. Phylogenetic aspects, central and peripheral synapses, and clinical significance. Plenum Press, New York London: 763-683.

Wevers, A. 2010. Localisation of pre- and postsynaptic cholinergic markers in the human brain. Behavioural Brain Research; in press.
Whitwell, J.L., Jack, C.R. Jr., Parisi, J.E., Knopman, D.S., Boeve, B.F., Petersen, R.C., Jack, C.R. Jr. 2007b. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from MCI to AD. Brain; 130:1777-1786.

Whitwell, J.L., Josephs, K.A., Murray, M.E., Kantarci, K., Przybelski, S.A., Weigand, S.D., Vemuri, P., Senjem, M.L., Parisi, J.E., Knopman, D.S., Boeve, B.F., Petersen, R.C., Dickson, D.w., Jack, C.R. 2008b. MRI correlates of neurofibrillary tangle pathology at autopsy: a voxel-based morphometry study. Neurology; 71: 743-749.

Wichmann, T., Delong, M.R. 2006. Deep brain stimulation for neurologic and neuropsychiatric disorders. Neuron; 52: 197-204.

Wilkinson, D.G., Francis, P.T., Schwam, E., Payne-Parrish, J. 2004. Cholinesterase inhibitors used in the treatment of Alzheimer's disease. The relationship between pharmacological effects and clinical efficacy. Drugs Aging; 21(7): 453-478.

Zarranz, J.J., Alegre, J., Gomez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atarés, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Muñoz, D.G., de Yebenes, J.G. 2004. The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. Annals of Neurology; 55: 164-173.