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Neural Basis of Object Recognition

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1. Introduction

Interaction between environment and human beings, as well as each living organism, is essential for survival. Indeed, in nature every interaction among different living species is not possible without the integrity of central nervous system (CNS), which generates brain activity such as arousal, attention, learning and memory. Moreover, face perception and recognition of face are fundamental brain processes for human relationship. The ability to hold objects in memory is essential to intelligent behavior, but its neural basis still remains poorly understood.

Many studies running in the last decades in neuroscience researches have contributed to clarify the intricate puzzle about brain recognizes objects [Ungerleider and Haxby, 1994].

Now, questioning is: "How does brain recognize? What is the neural basis of objects recognition?".

Here, we briefly review neuroanatomical substrates and neurophysiological correlates which could explain the neural basis of object recognition; we also describe our contribution in this field of neuroscience reporting own pharmacological data.

2. Neurophysiopathology of attention, learning and memory

What is knowledge? How is knowledge acquired? How do we know what we know?

Starting from these essential questions, much of the epistemological debate has focused on analyzing the neurophilosophical and neuropsychological nature of knowledge in living species and how it relates to connected neurobiological aspects.

Thinking about neural basis of recognition memory it means to imagine how biological systems integrate functional information that provide reference knowledge for successive recognition.

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In brain, recognition of objects depends from interaction between visual system and cognitive processes such as attention and learning [Desimone and Duncan, 1995].

It is well known that there is not learning without attention as well as there is no learning without memory. Prefrontal cortex (PFC) in brain is an important area known to be involved in attention and action recognition-dependent behaviour. It also is central to active short-term memory maintenance too [Warden and Miller, 2010]. In fact, PFC, promoting attention mechanism, allows learning and memory.

The terms *Attention*, *Learning* and *Working Memory*, respectively, refer to systems that provide for selective prioritization for processing of information, short-term maintenance and manipulation of information necessary for performance of complex tasks.

Although there is still little direct evidence how brain remembers and discriminates objects, most neurophysiological researches on memory suggest that multiple items may be held in memory by oscillatory activity across neuronal populations. Neuronal activity, recorded from the prefrontal cortices of primate remembering two visual objects over a brief interval, has shown that oscillatory neuronal synchronization mediates a phase-dependent coding of memorized objects in the prefrontal cortex. [Funahashi et al., 1989; Buschman and Miller, 2009; Fries et al., 2007]. Moreover, neuronal information about two objects held in short-term memory is enhanced at specific phases of underlying oscillatory population activity in hippocampus.

With the advent of modern brain imaging techniques, considerable progress has been made in understanding the organization of the human brain. Above all, the further development of functional brain imaging, including PET (positron emission tomography) and fMRI (functional magnetic resonance imaging), has given great impulse and fervor to map the functional organization of the human brain with far greater precision than is possible both in physiological conditions and in humans subjected to brain injury.

The neural system, responsible for working memory, involves a large number of brain regions, but abundant neurophysiological evidence and lesion studies in nonhuman primates indicate that prefrontal cortex is a critical component [Fuster 1990; Goldman-Rakic 1990].

In fact, brain-imaging studies, using PET and fMRI, have also demonstrated that the human prefrontal cortex is implicated in working memory [Jonides et al. 1993; Petrides et al. 1993; Cohen et al. 1994; McCarthy et al. 1994; Ungerleider and Haxby, 1994; Ungerleider, 1995; D'Esposito et al. 1995, 1998; Fiez et al. 1996; Owen, 1997; Courtney et al. 1997].

Although, some questions and some dispute, about the functional organization of the human prefrontal cortex and its exact role in working memory, still remain, at present day, computational neuroscience suggests that in recognition tasks two main learning processes can be distinguished: identification and categorization. Therefore, object perception and recognition are strongly related with experience and learning.

In human studies, event-related potentials (ERPs) have been enlightening for understanding the neural basis of object recognition. Results of these researches indicate that an early ERP component, the N170 wave, is significantly larger when subjects view image with face than when they view other objects [Allison et al., 1999; Eimer, 2000]. On the contrary, patients

with prosopagnosia, who have lost the ability to recognize faces, fail to demonstrate an enhanced N170 [Eimer and McCarthy, 1999].

The prefrontal area, studied by fMRI, demonstrates neuronal activity during a face recognition memory. Many findings suggest that the prefrontal attention/working memory systems are already impaired in Alzheimer's disease.

3. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder clinically characterized by progressive decline in memory and cognitive functions. AD is associated with a dramatic loss of cholinergic neurons in the basal forebrain; specifically, those emerging from the nucleus basalis magnocellularis (NBM) [Whitehouse et al., 1981, 1982]; that causes a marked hypofunction in cholinergic transmission mainly innervating the neocortex and, in a lesser degree, the hippocampus (Fig. 1) [Mesulam et al., 1983; Coyle et al., 1983; Francis et al., 1999]. As a consequence of loss of cholinergic neurotransmission, impairment of attention, learning and memory function is produced and, furthermore, many other behavioural and cognitive capacities are also affected [Bartus et al., 1982; Collerton, 1986; Everitt and Robbins, 1997; Mufson et al., 2003].

A correct input from NBM to neocortex is essential for brain mechanisms such as arousal, attention, learning as well as working memory; whereas input from septal cholinergic neurons to hippocampus results important in memory processes such as spatial navigation.

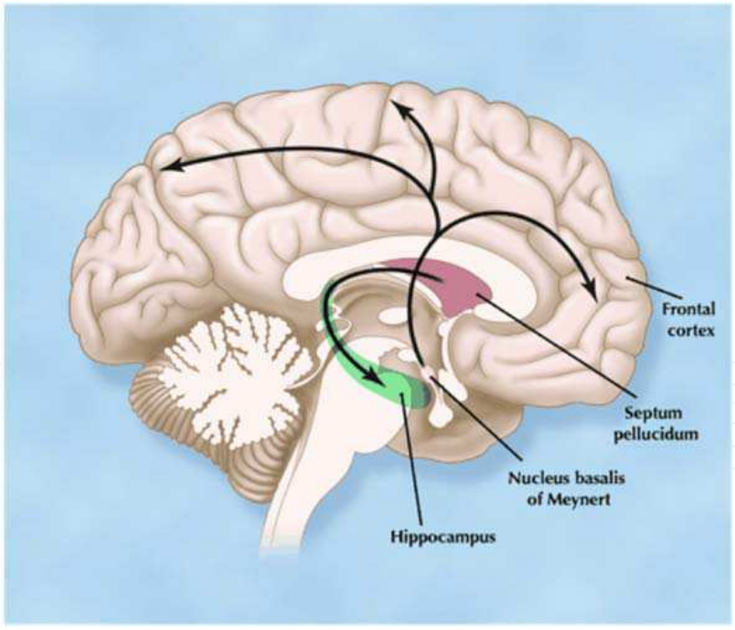


Fig. 1. Cholinergic transmission in brain.

From electrophysiological viewpoint, it is well known that basal cholinergic neurons can generate a spontaneous firing rate to control neocortical neurons; then neocortical activation generates desynchronization of electroencephalogram (EEG) and behavioural states related to alertness and attention [Rasmusson et al., 1994].

In patients with AD, the profound cognitive deficits, following loss of basal cholinergic neurons, is likely due to disrupted cortex-hippocampus neuronal network [Whitehouse e al., 1981; Coyle et al., 1983; Davies et al., 1987].

Although in the last decades there has been considerable progress in understanding the molecular and cellular changes associated with Alzheimer's disease, to date, treatment of AD is merely palliative. In fact, medication with cholinergic drugs can only alleviate clinical symptoms, even if recent fMRI studies have shown the importance of cholinesterase inhibitors (AChEIs) in treating AD [Miettinen et al., 2011].

The recent understanding in AD pathogenesis has resulted in identification of a large number of new possible drug targets. These targets include therapies that aim to prevent production or remove the amyloid-β protein that accumulates in neuritic plaques, to prevent the hyperphosphorylation and aggregation into paired helical filaments of the microtubule-associated protein tau and, finally, to keep neurons alive and functioning normally.

On which basis can we build an experimental model of Alzheimer's disease?

Experimental approach to pathophysiological comprehension of human disease, as well as to new therapeutics, has ethical limitations in medicine. For this reason, design and development of acceptable *in vivo* experimental animal models is important in research.

However, many different experimental approaches and behavioral testing have been suggested to study learning and memory. In particular, neuropharmacological research, involved in discovery of new antidementia agents, needs good experimental models of disease as well as good behavioral tests, which are important to validate pharmacological activity of drugs.

3.1 EEG and EP

Several quantitative electroencephalography (qEEG) studies have reported a progressive slowing of EEG and significant increased power in lower frequencies (delta and theta) in patients with AD [Prichep et al., 1994; van der Hiele et al., 2007]. In normal brain, correct performance in cognitive tasks implicate high levels of alertness and attention [Sala and Courtney, 2009], both dependent on the occurrence of fast EEG rhythms [Steriade, 2000, 2006].

EEG architecture shows great similarities across species. As above described, alertness is associated with fast frequencies in the EEG (e.g., beta activity), whereas non-REM sleep and drowsiness are characterized by slower waves (synchronized firing of cortical neurons).

Many experimental works have shown that drugs affect EEG characteristics in humans and rodents in a similar manner [Dimpfel et al., 1992; Jongsma et al., 1998a,b Coenen and Van Luijtelaar, 2003; Dimpfel, 2005]. In addition, a substantial body of studies suggest a relation between memory performance and EEG. For example, scopolamine decreases arousal level, which in turn increases EEG theta activity and impairs cognitive performance in object recognition in rodents. On the contrary, cholinergic agonists are able to decrease theta power and increase arousal.

Moreover, evoked potentials (EPs) show great correspondence between different species. In fact, auditory stimuli reveal a strong correspondence between rats and humans [Sambeth et al., 2003, 2004]. In both species, the short latency EP components are related to the processing of the physical properties of a stimulus, whereas the later components are associated with more endogenous processing (e.g., the psychological processes involved in the stimulus event) [Sambeth et al., 2003].

A particular aspect fascinate researchers: how does brain encode novel experiences, which are the intricate neural basis of learning and memory?

3.2 Theta oscillation underlies hippocampal novelty detection and learning

Although brain imaging has given important functional information about brain learning and memory, it cannot reveal how the brain works at level of individual neurons.

However, understanding of object recognition and its neural basis, it necessarily means to focus on a first-order question: how individual neurons represent individual memories. This has led to theoretical models of short-term memory such as sustained spiking activity by single neurons that typically reflects a single memorandum [Fuster and Alexander, 1971; Fuster and Jervey, 1982; Hopfield, 1995]. In other words, there is increasing evidence that information encoding may also depend on the temporal dynamics between neurons; for example, from relative spikes to rhythmic activity across the neural population generating local field potential (LFP) [Metha et al., 2002; Ninokura et al., 2003; Warden and Miller, 2007; Siegel et al., 2009; Kayser et al., 2009; Warden and Miller, 2010].

It is well documented that central cholinergic system plays a crucial role in cognitive functions; therefore, from an electrophysiological and neurochemical point of view, the integrity of the frontal cortex and hippocampus circuitry is essential for brain cognitive processes. In fact, it is well known that neuronal loss, following basal cholinergic degeneration, shows a close correlation with neuronal death in another vulnerable region of the brain such as the hippocampus.

Hippocampus is another brain area important for learning and memory and it exhibits relevant theta (4-7 Hz) frequency oscillations *in vivo* during behavioural activity. In fact, neural action can vary during different cognitive processes, becoming rhythmic during such a brain activity; in particular, in brain, hippocampal theta rhythmicity could contribute to learning and memory [Lee et al., 2005]. In rat, spatial memory is supported by interaction between hippocampus and cortical areas, frontal cortex mainly, which is critically involved in attention and learning [O'Keefe and Recce , 1993; Morris, 2001; Monosov et al., 2010].

Different studies indicate that hippocampus plays an essential role in novelty detection. These researches show that an important electrophysiological mechanism, by which hippocampus learn and discriminate objects in novelty detection, is the hippocampal theta activity [König et al., 1995]. Recently, new findings offer an insight into the mechanisms underlying hippocampal novelty detection stimulating new questions within the debate: theta peak or theta power?

It was proposed a link between the hippocampal theta and the detection of novel contexts. Some authors reported that in rats, exposed to familiar and novel environments, the peak

hippocampal theta frequency dropped (by about 0.6 Hz) when the rats were tested in a novel environment [Jeewajee et al., 2008]. This change in theta frequency might function as a novelty signal because hippocampal theta frequency is the same in the whole hippocampus [Buzsaki, 2002], and they suggested that the reduction in theta frequency would have implications for memory encoding. The authors speculate that novelty leads a low-frequency theta depending on acetylcholine release. In fact, it is well known that new experience and novel environment induces in brain increase in cholinergic input to the hippocampus and increase in ACh release which affects hippocampal theta activity [Givens and Olton, 1994, 1995; Podol'skii et al., 2001]. On the other hand, other authors did not find any change in peak theta frequency when animals were stimulated by a novel environment; they instead reported a change in theta power that differentiated active from passive behavior, with novelty increasing power at both levels of activity [Sambeth et al., 2009].

Nevertheless, taken together both findings suggest that theta oscillations in hippocampus are affected by novelty, and that this probably gives reasons for hippocampal learning.

3.3 Novelty-induced realese of acetylcholine

Historically, ACh has been implicated in cognitive functions such as learning and short-term memory, as well as dysfunction in central cholinergic transmission was linked to learning and memory impairment present in patients with Alzheimer's disease and other forms of dementia [Bartus et al., 1982; Bartus et al., 1985; Coyle et al., 1983; Collerton, 1986; Davies et al., 1987; Blokland, 1995; Muir, 1997; Francis et al., 1999].

However, brain areas, which are supposingly most important for attentional processing in both animals and humans, appear to be the prefrontal, parietal and somatosensory (especially visual) regions, where ACh plays an essential role in the control of attentional orienting and stimulus discrimination. In addition, cholinergic signaling in the septohippocampal system is suggested to be involved in memory processes.

Trait d'union between cortical areas and hippocampus in attention and cognition is the *basal forebrain cholinergic system* [Mesulam et al., 1983]. To this purpose a lot of studies have been carried out in animals and humans, investigating the role of ACh in attention and cognition. Animal behavioral studies have been performed both in intact and in compromised brain cholinergic transmission, such as in animals subjected to specific cholinergic lesions by toxins or pharmacologically induced amnesia using muscarinic or nicotinic antagonists [Dunnett et al., 1990]. Human studies, which can give some indication on the link between central cholinergic signaling and cognition, are obviously confined to less invasive imaging methods such as fMRI.

Therefore, a large body of researches has contributed to elucidate better the role of ACh in cognitive functions. In contrast to a general role in learning and memory, recent insights have refined the function of cortical ACh more specifically in attentional effort and orienting, and detection of behavioral significant stimuli [Sarter and Bruno, 1997].

Since both ACh release and theta oscillations are affected by a range of factors, testing animals in more settings may be needed to elucidate the nature of novelty effects on hippocampal theta oscillations and phasic ACh release.

In conclusion, some indications can be given. Prefrontal cortex regions are involved in short-term memory and object discrimination. Cholinergic signaling, coming from basal forebrain to frontal cortex, septum and hippocampus, are implicated in short-term memory; in addition, the hippocampus could be important for discrimination processes in cognition.

3.4 The object recognition test

In laboratory, cognitive tasks have shown a good reliability in many experimental models of human neurodegenerative diseases. Specifically, a lot of laboratory studies have shown that the object recognition task in rodents is highly sensitive to psychoactive drug. For example, this is the case of drugs such as acetylcholinesterase inhibitors (AChEIs) which can improve object memory performance in rats [Prickaerts et al., 2002; Hornick et al., 2008; Goh et al., 2009]. In fact, in rats these ACh enhancers can reverse drug-induced memory impairments [Bejar et al., 1999; van der Staay and Bouger, 2005; Yamada et al., 2005]. This has encouraged researchers that such drugs may also be useful in treating memory impairments in patients with dementia. On the other hand, to date, clear evidence for a reliable memory enhancing effect of these drugs in humans is lacking and controversial [Snyder et al., 2005; Wezenberg et al., 2005]; that might probably be related to the discrepancy between the large numbers of animal studies and only a limited number of human studies showing memory enhancing effects of these drugs.

Object discrimination requires the integrity of cortical cholinergic system; in rodents the cortex-hippocampus circuitry consents to distinguish individual objects such as different shapes [Hauser et al., 2009].

The novel object test or object recognition test (ORT) was first described by Ennaceur and Delacour (1988). Rats or mice are exposed first to two identical objects and then one of the objects is replaced by a new object. The time spent exploring each of the objects is measured. The test has become popular for assessing the effects of amnesic drugs in rodents in general and, after that, to test new compounds enhancing attention and memory [Bartolini et al., 1996]. The test is based on spontaneous behavior with no reinforcement such as food or shock. Non-amnesic animals will spend more time exploring the novel object than the familiar one. An absence of any difference in exploration time can be interpreted as a memory defect or, in case an amnesic drug is tested, a non-effective drug.

Although the novel object recognition task has shown high sensibility and it can be a simple approach to test new potential antidementia drugs, researchers need a stronger experimental tools to test *in vivo* pharmacological activity before clinical trials. From our point of view, an electrophysiological approach together with novel object recognition task can probably be useful.

3.5 An experimental model of AD

Discovering the cause of Alzheimer's disease should imply the ultimate hope of developing safe and effective pharmacological treatments [Francis et al., 1999].

Most researches on working memory, carried out in experimental models of AD, have been modelled on those conducted in physiological studies of monkeys.

On basis of these data, in the last decades many attempts have been done to alter central cholinergic neurotransmission. The two major approaches contemplate substances pharmacologically altering central cholinergic neurotransmission or toxins, directly injected in brain and disrupting cholinergic system. Commonly, the aim is to produce highly selective lesions of cholinergic neurons with none or marginal effects on other neurons [Torres et al., 1994; Perry et al., 2001].

Our group is involved in preclinical research investigating new therapeutical approaches to AD (Fig. 2). To this purpose, in the last decade, we developed an experimental model of Alzheimer's disease to investigate the pharmacological effects of drugs with putative antidementia activity. Original compounds, likely thought to enhance central cholinergic activity, were designed, synthesized and firstly studied in our molecular modeling laboratory; after that, their pharmacological properties on both EEG brain activity and novelty object recognition were tested; finally, the relation between the EEG architecture and performance measures was studied too.

Fig. 2. Laboratory for Preclinical Researches in Neuropharmacology and Neurodegenerative Diseases at the Department of Pharmacological Sciences, University *Magna Græcia* of Catanzaro. Surgery room (left) and Behavioural Lab (right) with Noldus Ethovision® XT 8.0 apparatus for novel object recognition are here depicted.

In this AD model, we selectively damaged portion of NBM which targets the frontal cortex, producing in rat a significant deficit in attention and working memory (Fig. 3), [Rispoli et al., 2004a,b, 2006, 2008]. Further, in this experimental model, attention, learning and working memory can be evaluated monitoring cortico-hippocampal qEEG activity during object recognition task [Rispoli et al., 2011, data in progress].

The brain lesion produces a significant reduction of cholinergic neuronal population in the NBM (45%; $p<0.01$ vs control; Fig. 3, panel B). Immunohistochemistry was performed to quantify the neuronal loss in the NBM by ChAT immunoreactive neurons. Quantitative analysis of ChAT-positive neurons in NBM was carried out using a computerized image analysis system (Axiophot Zeiss microscope equipped with a Vidas Kontron system). Notably no spontaneous recovering of ChAT immunoreactive neurons has been found by us, not even after several weeks post NBM lesion.

To validate our AD model, we compared it with other well validated experimental models producing dysfunction in cognitive processes: the scopolamine-induced amnesia, a classical pharmacological model of amnesia, and that in which cholinergic neurons in the basal forebrain are subjected to immunolesion by IgG-saporin.

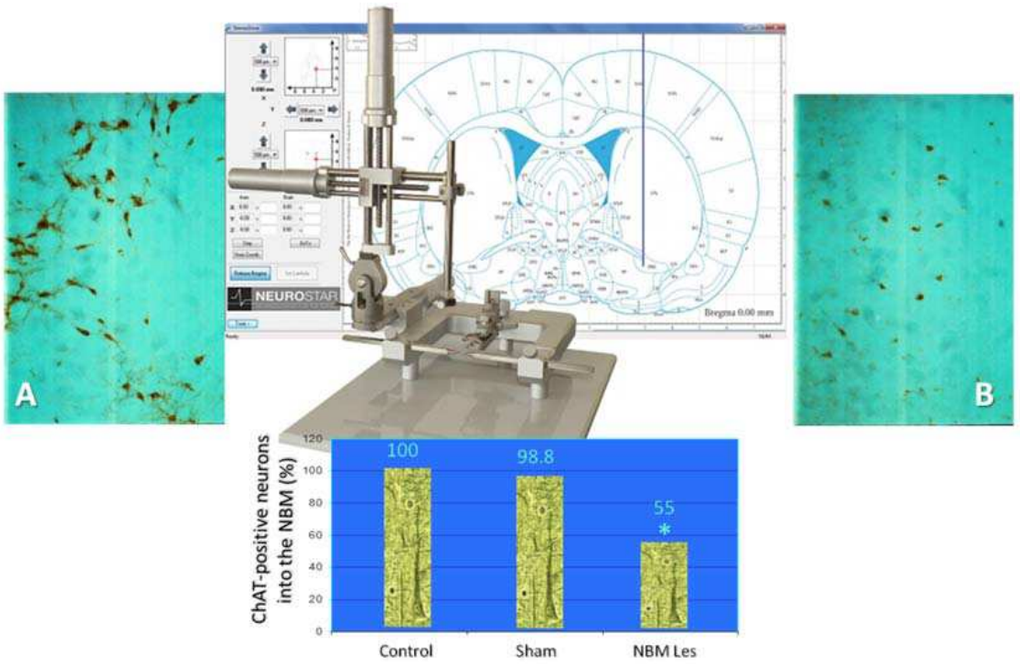


Fig. 3. Stereotaxic lesion of the Nucleus Basalis of Meynert.

Scopolamine impairs object recognition and increases theta frequency in the EEG. In this experimental model it is suggested that scopolamine likely caused a decrement in arousal. However, the effects of scopolamine on mnemonic paradigms can be characterized as disrupting acquisition and encoding information rather than retrieval processes. Most experiments used a relatively low dose of scopolamine (ranging 0.1 to 0.2 mg/kg). In fact, it must be noted that high doses of the muscarinic antagonist may not only have an effect on the muscarinic receptors, but also on the nicotinic receptors [Schmeller et al., 1994,1995]. Methyl–scopolamine, which only differs from scopolamine in that it does not cross the blood brain barrier, is generally used as a control.

Therefore, to target this aim an *in vivo* study, using our model of AD, was designed to test pharmacological properties of new compounds. With this purpose, a set of experiments was planned to evaluate them on cortex- and hippocampus-dependent memory. Attention, learning and working memory, with respect to cortical and hippocampal EEG theta rhythm, recorded during novel object recognition task in animals with lesion,of the nucleus basalis of Meynert, were studied. In NBM-lesioned animals, compared with control, an increased theta power in the cortex and a reduced theta rhythm oscillation in the hippocampus was found. These EEG changes were correlated with a worse performance in learning and memory tasks. In rats with damaged NBM, novel compounds were able to restore EEG architecture, producing cortical desynchronization and reduction in theta power [Rispoli et al., 2004a, 2006, 2008], while in the hippocampus the drugs increased theta oscillation and reduced the impairment in attention/working memory in the behavioural tasks [Rispoli et al., 2011, data in progress].

Here, we report data supporting this experimental model of AD in testing nwe compounds as putative antidementia drugs.

3.6 Novel object recognition test

The current studies investigated attention/memory for novel object recognition, according to Ennaceur and Delacour [1988] and Bartolini and coll. [1996]. Rats, placed in a white arena (70 X 60 X 30 cm) were trained to discriminate objects of different shapes (cubes, pyramids and cylinders). The day before testing, animals were placed in the arena and allowed to explore for 2min. The day after, rats were tested on a task involving two exploratory trials for 5 min with a 60-min delay between each sessions. In the first trial (T1) two identical objects were presented in two opposite corners of the arena and rats were left there until criterion was reached. Exploration was defined as directing the nose at a distance < 2cm to the object and/or touching it with the nose. Following, the second exploratory trial (T2) was conducted where the rat was presented with one object from the first exploratory trial and one novel object (Fig. 4). The time spent exploring the familiar (F) and the novel object (N) was recorded separately and the difference between the two exploration times was taken as the discrimination index (DI, a measure of novelty preference).

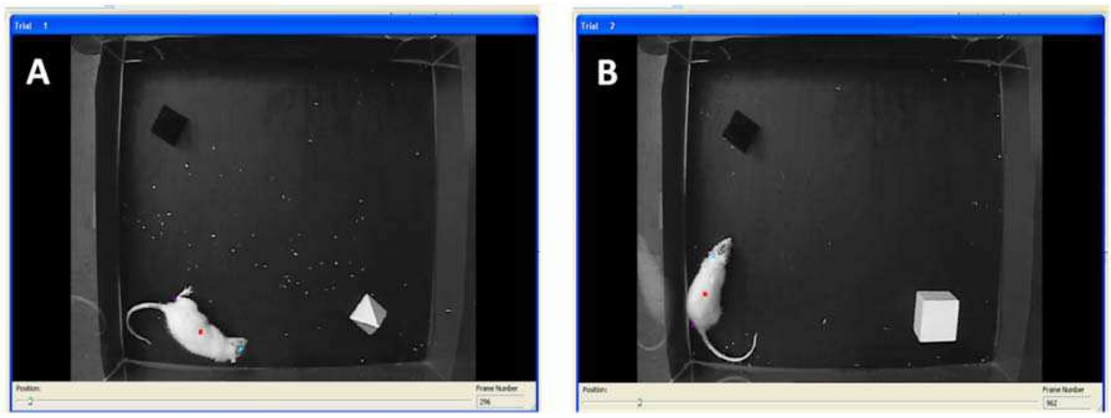


Fig. 4. Novel Object Recognition Test. A. Trial 1; B. Trial 2 (see text for details).

Intact rats, as well as sham-operated, were able to discriminate between the familial and novel object (DI = 0.33 and 0.29 respectively). In NBM-lesioned animals, values of DI were significantly lower than those in intact rats (DI = 0.07; $p<0.001$ vs intact and sham). Administration of our compounds, as well as cholinergic drugs, established discrimination in lesioned animals again, and they displayed a larger DI when compared with NBM-lesioned and saline-treated group. EEG activity in neocortex and hippocampus correlated directly with DI. Ability in novel object discrimination was evaluated as large DI, decreased theta power in neocortex and increased theta oscillation in hippocampus.

Results from the exploratory trials showed a significant impairment in exploration and discrimination in novel object in NBM-lesioned animals when compared with sham and intact group (Fig. 5). The test demonstrated that NBM-lesioned rats spent significantly less time exploring the novel object compared to familial object, indicating that lesioned rats showed disturbed attention and memory. However, NBM-lesioned rats showed no preference for novel object and spent a relatively equal amount of time exploring novel and familial objects. The results suggest that changes in attention and recent memory declines were a result of NBM-related neuronal loss and disruption in cholinergic central neurotransmission in the rodent brain. The findings also may reflect differences in

attraction to objects in NBM-lesioned animals. These differences were not due to decreased exploration, motivation, or locomotion, but they likely were due to decresed cholinergic transmission arising from the NBM.

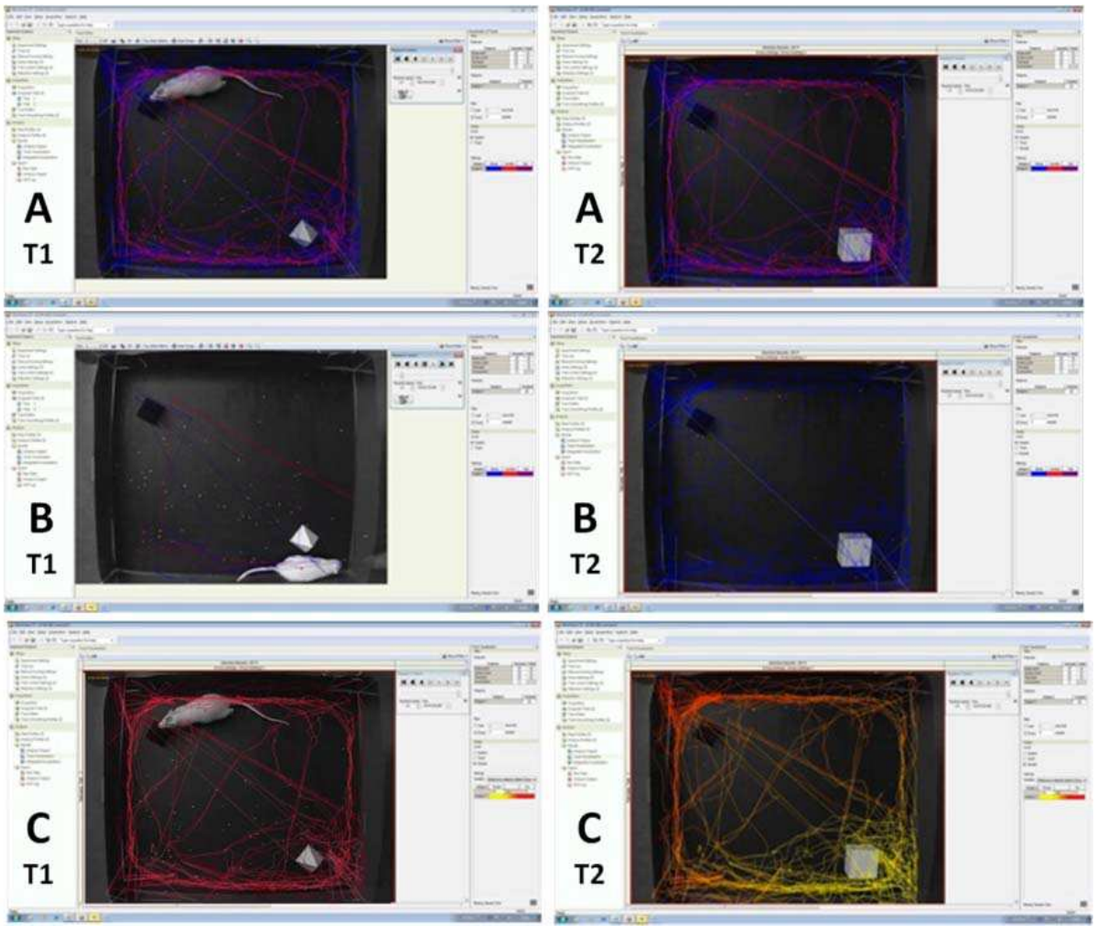


Fig. 5. Typical example of video tracking showing performance of rat with NBM lesion in novel object recognition (Noldus Ethovision® XT 8.0).

Performance in **A.** control animal (intact and sham-operated); **B.** NBM lesioned rat and **C**. NBM lesioned animal treated with AC1. Note the increased traces in T2 around the novel object in control (A) and NBM lesioned and AC1 treated animal (C).

3.7 EEG recording

Rats were equipped with neocortical electrodes to record EEG from cerebral cortex while an other electrode was implanted into the dorsal hippocampus to register hippocampal theta activity, since previous work has shown the last brain area to be involved in object recognition [Prickaerts et al., 2002; Broadbent et al., 2004].

In intact as well as in NBM-lesioned rats, EEG activity, derived from neocortex and hippocampus, was continuously monitored and recorded when animals were exposed to familiar and novel environments.

For statistical purpose, bipolar signals, derived from each neocortical area in both brain hemispheres as well as in the hippocampus, were analysed. qEEG analysis was performed on the theta range both in the hippocampus and on the whole EEG spectrum in the cerebral cortex. Five artifact-free epochs, of 10 s each, selected from EEG baseline and that recorded during the performance in behavioural tasks, were processed using Fast Fourier Transform (FFT) as previously described [Rispoli et al., 2004b]. Statistical analysis of the data was performed on the EEG signal amplitude (μV).

Neocortical EEG architecture and hippocampal theta activity was dramatically changed in NBM-lesioned rats when compared with sham-operated and intact animals. In NBM-lesioned animals, EEG baseline activity resulted significantly increased in total power (Fig. 6); in detail, quantitative analysis of EEG spectrum showed a marked raise in theta power; while neocortical high voltage spindle (HVS) appeared. No significant EEG difference was reported in sham group when compared with intact control one. No significant EEG change was also reported in lesioned animals during behavioural performance.

In NBM lesioned animals, during object recognition performance, our compounds produced desynchronisation and evidenced a marked decrease in the energy of the whole EEG power; a further analysis of the EEG spectrum showed a significant reduction of theta energy (Fig. 7). Incidence of HVS activity was also significantly reduced in NBM-lesioned animals. Moreover, in this AD model statistical analysis revealed very significant correlation between EEG changes and ORT performance.

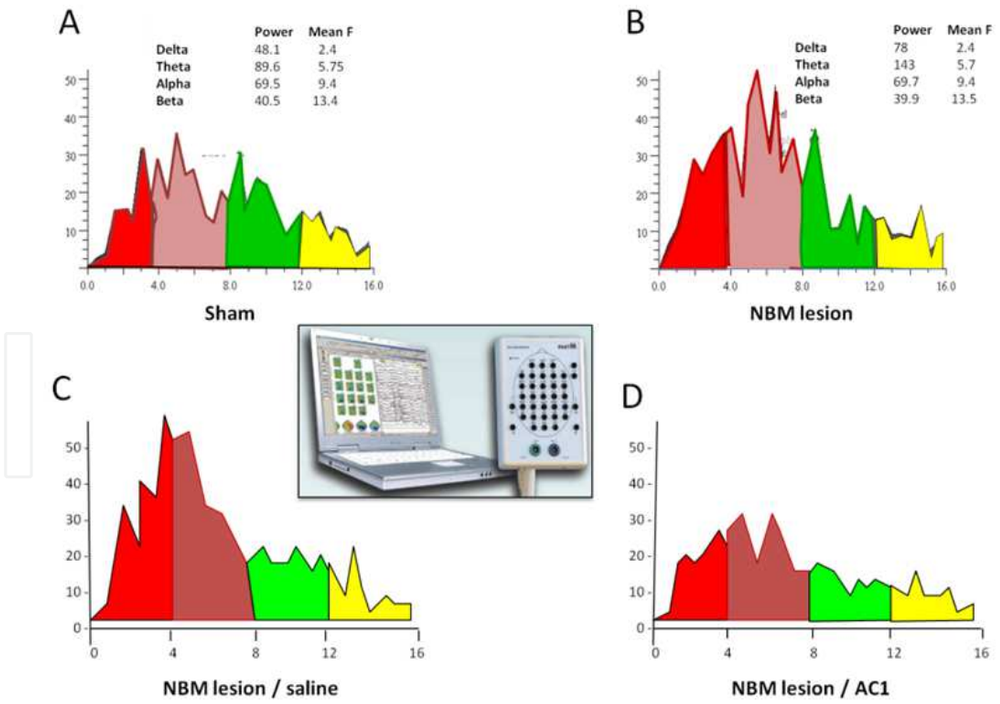


Fig. 6. Quantitative EEG and Spectral Analysis.

A typical example of neocortical EEG activity recorded in sham-operated (**A**) and NBM-lesioned animals (**B**). In NBM-lesioned animals, EEG architecture was altered; in fact, qEEG

analysis showed a strong increase in total as well as delta and theta power (p<0.001 vs sham). **C.** and **D.** depict EEG spectrum power recorded in NBM lesioned animal after systemic administration of saline (C) or AC1 (D). The cholinergic agonist dramatically modified EEG power when compared with EEG baseline activity. A significant (p<0.001) fall in total voltage power, as well as in the power of lower frequency bands (0.25-3 and 4-7 Hz) is here highlighted. No EEG effect was reported after saline administration. Sham group showed no significant difference in EEG activity when compared with intact animals (data not shown). Each experiment: n =7. AC1 (12.5 mg/kg i.p.), saline (2 ml i.p.). Ordinates show the voltage power expressed in arbitrary values, abscissae show the frequency range (0.25-16 Hz).

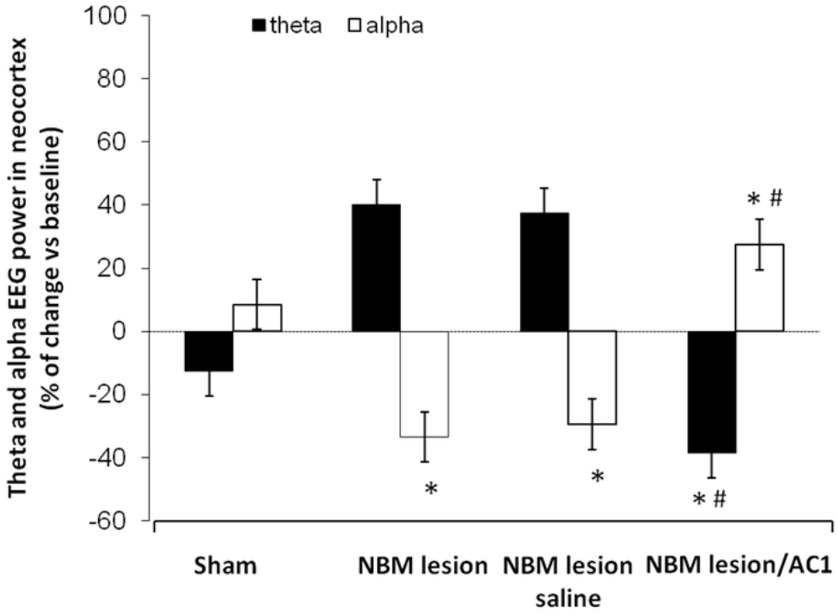


Fig. 7. Theta and alpha EEG power recorded in neocortex of rat subjected to lesion of the NBM during ORT performance.

In NBM lesioned animals, theta power resulted dramatically increased while alpha power was reduced (*p<0.001 vs sham). Treatment with AC1 was able to reverse the neocortical EEG activity producing a significant increase in alpha power and a marked reduction in theta power (*p<0.001 vs NBM lesion; #p<0.001 vs baseline). Values in mean ± SEM.

3.8 Hippocampal activity and ORT

The effects of these new compounds on learning and memory consolidation were investigated by hippocampal activity and in novel object recognition. Using the spectral analysis of the EEG, theta band (4-7 Hz) was directly recorded in rats by hippocampal depth electrode (Fig. 8). Theta oscillation was continuously monitored and recorded before and during exploration. In control animals, exploratory behaviour was correlated with an increase in hippocampal theta oscillation activity. In NBM-lesioned rats, no change in hippocampal theta frequency oscillations was observed during familial and novel recognition (Fig. 9).

The hippocampal theta oscillation, recorded in NBM-lesioned animals during the task, increased after drug treatment. In fact, compared to NBM-lesioned and not treated group, NBM-lesioned animals, which received the cholinomimetics, showed a significant increase in the duration and number of episodes of hippocampal theta activity (increase in frequency of theta rhythm) (Fig. 8).

The amount in hippocampal theta oscillations was correlated to performance in novel exploration (Fig. 10).

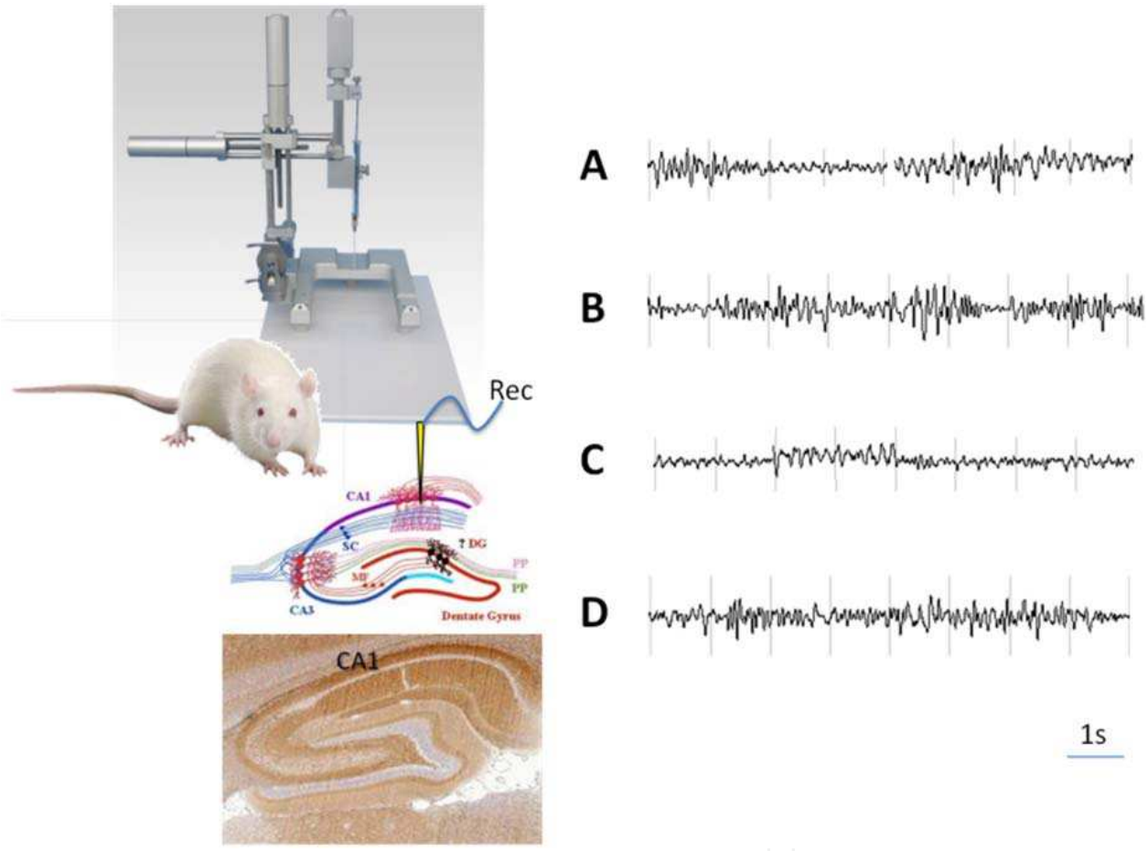


Fig. 8. Hippocampal Theta Oscillation in rats during exploration in ORT.

A bipolar electrode, stereotaxically implanted, was directly inserted into the CA1 area of the hippocampus to permit EEG recording. Theta rhythm was recorded during exploration in ORT and oscillatory activity (frequency) was studied. **A.** Control rat (intact and sham operated); **B.** Intact rat treated with AC1; **C.** Rat with lesion of the NBM and **D.** NBM lesioned rat injected with AC1. AC1 (12,5 mg/kg i.p.); seven animals for each experiment.

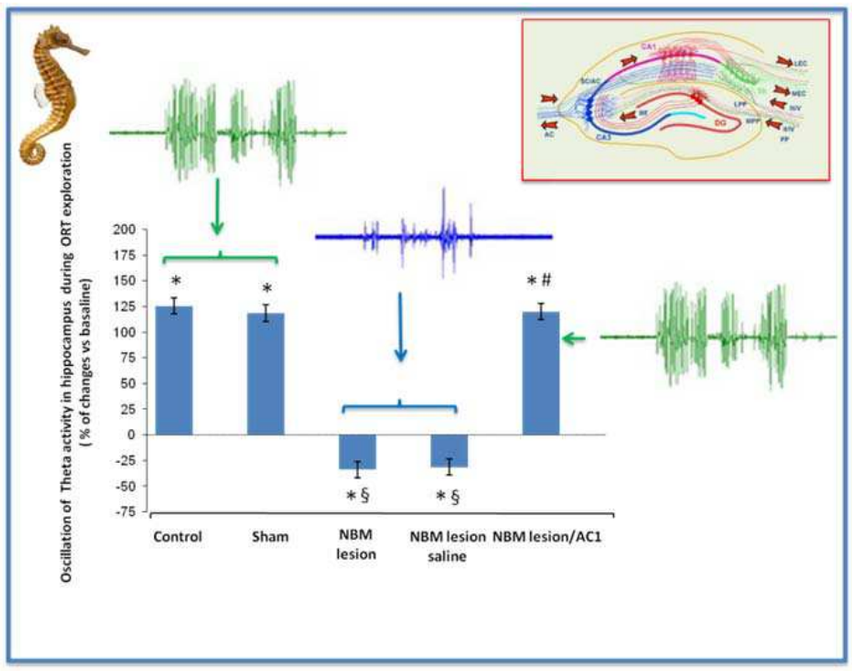
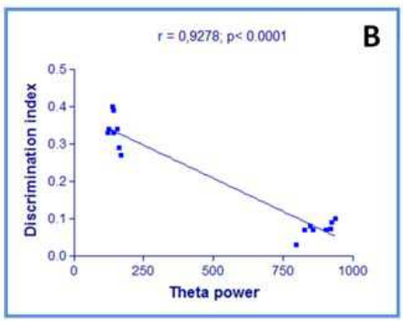


Fig. 9. Quantitative changes in hippocampal theta (3 -7 Hz) activity (frequency in theta oscillations) recorded during ORT exploration in rat with NBM lesion.

Theta activity in hippocampus was significantly reduced in animals with disrupted NBM. Theta oscillation, in this group of rats, was restored after intraperitoneal injection of AC1 (12.5 mg i.p.). Data are expressed as percent change (mean ± SEM); *p<0.0001 vs baseline; ; §p<0.0001vs control and sham; #p<0.0001 vs NBM lesion and NBM lesion/saline.

A

	Trial T2		D
	Familial (s + SEM)	*Novel (s + SEM)*	
Control (intact)	5.2 ± 1.6	10.0 ± 1.3*	0.31
Sham	6.0 ± 1.5	12.5 ± 2.3*	0.29
Lesion	12.6 ± 2.6	11.6 ± 1.5	0.06†
Not treated	10,5 ± 1.9	8.6 ± 2.9	0.09†
Saline	12.0 ± 1.6	12.6 ± 1.9	0.03†
AC1	7.2 ± 1.3	13.5 ± 2.3**	0.32 #



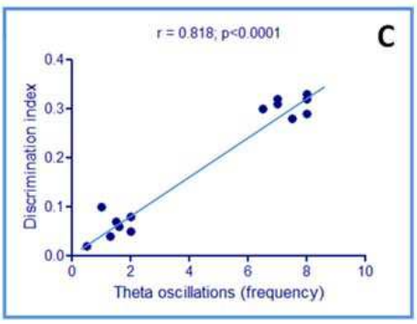


Fig. 10. Correlation between ORT performance and Theta activity in neocortex and hippocampus in rat subjected to NBM lesion.

A. Table reporting data on performance of rats in novel object recognition. NBM lesioned animals lost the ability to discriminate between the object getting a lower discrimination index (DI) than control group. **B.** Correlation between EEG theta power, recorded from neocortex in NBM-lesioned rats, and learning performance in ORT task. Damage of the cholinergic area caused a robust increase in theta power and a lower DI. AC1, in this group of animals, produced a reduction in theta power correlated with a higher DI. There was an extremely significant correlation (r= 0.9278, p<0.0001) between theta power and DI. **C.** Correlation between performance in novel object recognition and hippocampal theta oscillation (frequency) in rat with NBM lesion. The frequency of theta activity correlates to cognitive deficits in NBM-lesioned animals. Animals subjected to NBM-lesion scored a lower DI than control and showed reduced frequency in theta oscillation. AC1 administration was able to reduce the impairment in novel object recognition and restore the hippocampal theta rhythm during ORT. Theta oscillation correlates with DI (r = 0.818; p<0,0001). ORT. Spearman correlation between theta power and oscillation activity during object exploration performance evaluated as DI. Data are expressed as mean ± SEM (time (s) in object exploration). *p<0.01 N vs F (two-tailed Student's t-test). †p<0.001 vs intact-control and sham. #p<0.001 vs lesioned and not-treated and saline-treated (Tukey-Kramer test for multiple comparison). T2 = exploration session, DI = Discrimination index (N-F/N+F). F = exploration time. AC1 (12.5 mg/kg i.p.). In each set of experiments 7 animals were used.

In conclusion, this Alzheimer's model, likely to other models, in animals produced memory deficit, worsening in behavioural performance and failing discrimination in novel object; moreover, changes in the architecture of EEG is also generated, such a significant increase in EEG theta power. Another interesting finding, coming from such an approach, was that selective cholinergic lesions of the nucleus basalis impaired spatial learning in the Morris water escape task [Rispoli et al., 2004, 2006, 2008]. The deficit in attention, learning and memory, highlighted in this experimental AD, shows a close correlation between changes in cortex-hippocampus neuronal network and novelty recognition of objects. Indeed, like AD, in this experimental model, produced by selective bilateral lesion of the NBM, normal EEG activity and cognitive function are progressively restored after administration of drugs enhancing central cholinergic transmission.

In conclusion, taken together, the present data suggest that these new drugs are able to restore the cholinergic cortico-hippocampal functional connectivity.

4. Conclusions

In brain, working memory selectively maintains a limited amount of currently relevant information in an active state to influence future perceptual processing, thought and behavior. The representation of information held in working memory is still unknown. In action recognition, distinguishing individual objects in a scene is so important for living organism because it can allow survival.

Although at present our knowledge about the precise neurobiological, neurophysiological and neuropsychological mechanisms of object recognition is not yet whole complete, many evidence indicate that the framework for investigating the neural system underlying awareness of stimuli, memories and knowledge can not be pictured without the cholinergic basal forebrain →cerebral cortex → hippocampus neural circuitry. In fact, object memory

deficits point to the frontal cortex and hippocampus as early targets of functional disruption following loss of cholinergic neurons in the basal forebrain.

Alzheimer's disease is a progressive neurodegenerative disease for which no cure exists. Accordingly, there is a substantial need for new therapies that offer improved symptomatic benefit and disease-slowing capabilities. Therefore, although no cure for Alzheimer's disease are available presently, a large number of potential therapeutic interventions have emerged, designed to correct loss of cholinergic function. A few of these compounds have confirmed efficacy in delaying the deterioration of symptoms of Alzheimer's disease.

Indeed, we addressed the question of how we could contribute to alleviate cognitive decline in Alzheimer's disease.

Because human brain imaging cannot reveal the work of any brain structure at the level of individual neurons, EEG characteristics in animals may be used to predict central activity of drugs in humans. Clearly, such an approach can also be used if first a relation between EEG and memory performance can be found in animals.

In our opinion, EEG and object recognition well interface each other to study cognitive function in brain such as recognition and discrimination memory. To date, according to our experience, EEG and object recognition task still remain the best experimental approach to test pharmacological activity of potential new antidementia drugs.

The animal model of AD here presented was designed for assessing the pharmacological efficacy of original compounds, thought enhancing central cholinergic transmission, on object recognition task combined with the EEG study of neocortical and hippocampal activity. On basis of the data obtained, we believe that this Alzheimer's disease model could be reliable because a significant disturbance in attention was produced. Furthermore, results from qEEG and object recognition correlation confirm that. Moreover, cholinergic drug treatment recovered functionality in that saliency-based brain region.

Although we limit our experiments to a particular attention system, we believe that our results can be generalized to other system configurations. If this is indeed the case, more experimental testing would be required to verify this speculation, for example, a tools for measuring phasic ACh release in the hippocampus.

In conclusion, some remarks can be drown. First, we have considered the relationship between prefrontal cortex, important for working memory, and hippocampus processing information associated with object recognition. We then presented, evidence from electrophysiological, pharmacological and brain-imaging studies demonstrating that prefrontal cortex shows sustained activity during acquisition of information in working memory tasks; that indicates that this area maintains on-line representations of stimuli after they are removed. Furthermore, we discussed the possibility that the cholinergic basal forebrain → cortex → hippocampus network plays an essential role in working memory during the acquisition and maintenance of information, monitoring and manipulating the engaged novelty. Finally, we also proposed an innovative experimental model of AD which might be used to test new antidementia drugs; moreover, we reported data from our pilot study in which evidence for a contribute in this field of research have been produced.

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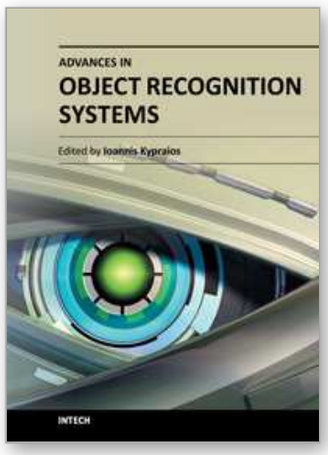

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An invariant object recognition system needs to be able to recognise the object under any usual a priori defined distortions such as translation, scaling and in-plane and out-of-plane rotation. Ideally, the system should be able to recognise (detect and classify) any complex scene of objects even within background clutter noise. In this book, we present recent advances towards achieving fully-robust object recognition. The relation and importance of object recognition in the cognitive processes of humans and animals is described as well as how human- and animal-like cognitive processes can be used for the design of biologically-inspired object recognition systems. Colour processing is discussed in the development of fully-robust object recognition systems. Examples of two main categories of object recognition systems, the optical correlators and pure artificial neural network architectures, are given. Finally, two examples of object recognition's applications are described in details. With the recent technological advancements object recognition becomes widely popular with existing applications in medicine for the study of human learning and memory, space science and remote sensing for image analysis, mobile computing and augmented reality, semiconductors industry, robotics and autonomous mobile navigation, public safety and urban management solutions and many more others. This book is a "must-read" for everyone with a core or wider interest in this "hot" area of cutting-edge research.

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