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REVIEW

# Cholinergic receptor subtypes and their role in cognition, emotion, and vigilance control: An overview of preclinical and clinical findings

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**Abstract**
*Rationale* The cholinergic system has long been linked to cognitive processes. Two main classes of acetylcholine (ACh) receptors exist in the human brain, namely muscarinic and nicotinic receptors, of which several subtypes occur.
*Objectives* This review seeks to provide an overview of previous findings on the influence of cholinergic receptor manipulations on cognition in animals and humans, with particular emphasis on the role of selected cholinergic receptor subtypes. Furthermore, the involvement of these receptor subtypes in the regulation of emotion and brain electrical activity as measured by electroencephalography (EEG) shall be addressed since these domains are considered to be important modulators of cognitive functioning.
*Results* In regard to cognition, the muscarinic receptor subtypes have been implicated mainly in memory functions, but have also been linked to attentional processes. The nicotinic α7 receptor subtype is involved in working memory, whereas the α4β2* subtype has been linked to tests of attention. Both muscarinic and nicotinic cholinergic mechanisms play a role in modulating brain electrical activity. Nicotinic receptors have been strongly associated with the modulation of depression and anxiety.
*Conclusions* Cholinergic receptor manipulations have an effect on cognition, emotion, and brain electrical activity as measured by EEG. Changes in cognition can result from direct cholinergic receptor manipulation or from cholinergically induced changes in vigilance or affective state.

**Keywords** nAChR · Nicotinic receptor · Acetylcholine receptor · Vigilance · Cognition · Working memory · Attention · Depression · Anxiety

**Abbreviations**

| | |
|---|---|
| 5-CSRT | Five-choice serial reaction time |
| ACh | Acetylcholine |
| CPT | Continuous performance task |
| EEG | Electroencephalography |
| FDG | Fluoro-2-deoxy-D-glucose |
| HVS | High-voltage spindle |
| mAChR | Muscarinic acetylcholine receptor |
| MPTP | Methylphenyltetrahydropyridin |
| nAChR | Nicotinic acetylcholine receptor |
| PET | Positron emission tomography |

## Introduction

The observation that cholinergic markers in the cerebral cortex such as choline acetyltransferase or acetylcholinesterase are reduced in patients with Alzheimer's disease sparked the interest in the relationship between the

The asterisk used in the receptor nomenclature indicates that the receptor complex may contain additional subunits.

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cholinergic system and cognition, particularly due to the fact that this decrease correlates with cognitive performance deficits (Bowen et al. 1976; Perry et al. 1978). Since these first findings, more extensive knowledge about the cholinergic system and the different cholinergic receptors has been gained. Meanwhile, multiple cholinergic receptor subtypes have been identified, and investigations into the involvement of the specific subtypes in cognition have advanced.

This review seeks to provide an overview of previous findings on the influence of cholinergic receptor manipulations on cognition, with particular regard to the role of selected cholinergic receptor subtypes. Furthermore, the involvement of these receptor subtypes in the regulation of brain electrical activity as measured by electroencephalography (EEG) shall be addressed in order to evaluate the relationship between the cholinergic system and vigilance regulation.

The term vigilance is used with various different definitions depending on the scientific field, in which it is used. Psychologists often refer to vigilance as sustained attention. Here, we use the term "vigilance" not to describe an attentional concept but to refer to neurophysiological arousal as measured by EEG. With vigilance stages, we refer to different global states of brain function which can be delineated not only during sleep but also during wakefulness as transition states from high alertness to drowsiness. We consider this additional focus important since cognition and vigilance (in terms of neurophysiological arousal) are interrelated. However, it is not quite clear how this interrelation is organised, i.e. whether both cognition and vigilance are directly influenced by the cholinergic system or whether cognitive changes upon cholinergic manipulation are only a result of a cholinergically induced change in vigilance regulation.

Cognitive aspects are not only influenced by a person's vigilance state either, but also by his or her affective state. Therefore, it seems most appropriate to think of an individual's cognition, EEG vigilance and affective state as partly overlapping and interacting domains, all of which are also influenced by cholinergic interference. For example, vigilance and the affective state influence cognition. In turn, cognitive processing has also been suggested to have an influence on affect (e.g. Schachter and Singer 1962). Furthermore, there seems to be a link between vigilance and affective state since vigilance patterns differ between various affective spectrum disorders (Hegerl et al. 2008b).

This article shall provide an overview of clinical and preclinical findings concerning the influence of the brain cholinergic system on these three domains, namely brain electrical activity (as a measure of vigilance), cognition and emotion.

## The cholinergic system

In the central nervous system, neurons that use the neurotransmitter acetylcholine (ACh) form the so-called cholinergic system. Cholinergic neurons form a contiguous aggregate of cells running from the cranial nerve nuclei of the brain stem to the medullary tegmentum and pontomesencephalic tegmentum, continuing rostrally through the diencephalon to the telencephalon (Woolf 1991). There are three major cholinergic subsystems in the brain, two of which are projection systems with broad, diffuse and rather sparse innervation to wide areas of the brain. In these two projection systems, cholinergic neurons originate either from (1) various basal forebrain nuclei (particularly, the nucleus basalis Meynert), from where they innervate mainly the cortex (e.g. neocortex, cingulate cortex) and hippocampus, or (2) from brainstem nuclei (e.g. the pedunculopontine and laterodorsal tegmental nucleus), from where they provide widespread innervation to the thalamus and midbrain dopaminergic areas and also descending innervation to the caudal pons and brain stem (Dani and Bertrand 2007; Everitt and Robbins 1997; Thiel and Fink 2007). The laterodorsal tegmental nucleus projects mainly to the ventral tegmental area; the pedunculopontine nucleus innervates both the ventral tegmental area and the substantia nigra (see also Maskos 2008; Mena-Segovia et al. 2008; Sesack and Grace 2010). The cholinergic modulation of the midbrain dopamine system has been connected to nicotine self-administration in rats and hence is thought to support drug reinforcement (see Maskos 2008, but see also Levin and Rose 1995 for interactions of the cholinergic and dopaminergic system in terms of working memory performance).

The third cholinergic subsystem arises from a collection of cholinergic interneurons in the striatum, which provides very dense local innervation. These interneurons contribute about 1–3% of the striatal neurons and interact with the rich dopaminergic innervation of the striatum arising from the substantia nigra pars compacta and the ventral tegmental area (Zhou et al. 2002).

There are two main classes of ACh receptors: muscarinic (mAChR) and nicotinic receptors (nAChR).

### Muscarinic receptors

Apart from being responsive to ACh, muscarinic receptors also have a high affinity for muscarine. They are metabotropic receptors that act by coupling to G proteins (Caulfield 1993) and belong to a multigene family that also includes serotonin, norepinephrine, and dopamine receptors (Blake et al. 1991).

Until now, cloning studies have identified five different genes (m1–m5) putatively encoding muscarinic receptor

subtypes. Consequently, it is assumed that there are also five mAChR subtypes, $M_1$ to $M_5$ (Caulfield 1993; Hulme et al. 1990), although only $M_1$ to $M_4$ could be verified by pharmacological binding studies (Eglen et al. 1994). M1/m1 is the most abundant subtype in cortex and hippocampus, while M2/m2 can be found mainly in brainstem, cerebellum and thalamus. Within the striatum, M4/m4 is most often found (Levey 1993). For further details on the distribution of the muscarinic subtypes in the brain, see Flynn et al. (1997) or Caulfield (1993). This review will focus on the $M_1$ and $M_2$ subtypes since previous studies have almost exclusively dealt with their implication in cognitive functions.

Besides ACh and muscarine, other agonists can also activate mAChR subtypes, e.g. carbachol or oxotremorine. All mAChR are antagonised by atropine. However, there are also selective antagonists that inactivate only certain subtypes, e.g. pirenzepine selectively antagonises $M_1$.

### Nicotinic receptors

As their name suggests, nAChR are easily activated by nicotine. In contrast to mAChR, nicotinic receptors are ionotropic and not metabotropic. That means they form ligand-gated cation channels, which do not need G proteins as second messengers. nAChR are members of a different supergene family, which also comprises glycine, $GABA_A$, $GABA_C$, and 5-$HT_3$ receptors (Gay and Yakel 2007; Sargent 1993). A nicotinic receptor is composed of five subunits arranged symmetrically around a central ion-conducting pore (Gay and Yakel 2007). So far, 12 subunits are known to exist in the central nervous system, α2–α10 and β2–β4 (Mudo et al. 2007; Picciotto et al. 2001). Different combinations of these subunits occur: A nAChR can be either homomeric, i.e. made up of α subunits only (α7–α9 subtype), or it can be heteromeric, i.e. composed of a combination of α and β subunits (e.g. the α4β2* subtype). The distribution of these nAChR subtypes differs for the various subunits. The most common nAChR subtypes in the brain are the α4β2* and the α7 subtypes. In rats, α4 and β2 subunits occur virtually in the entire brain (Wada et al. 1989), whereas the α7 subunit is mainly expressed in certain structures like hippocampus, hypothalamus, amygdala and restricted layers of the cerebral cortex (Seguela et al. 1993). Agonists and antagonists of heteromeric nicotinic receptors cannot distinguish the α4β2* combination from subtypes containing the β4 subunit (which is restricted to the medial habenula, the fasciculus retroflexus and the interpeduncular nucleus). Furthermore, α4β2* receptors may also contain α5 and α6 subunits. Therefore, we will use an asterisk in the receptor nomenclature to indicate that the receptor complex may contain additional subunits. For more extensive information concerning the nicotinic acetylcholine receptors, refer to the book by Changeux and Edelstein (2005).

## Vigilance regulation

In parallel to the transition from active wakefulness to deep sleep, the human brain takes on different global functional states. These functional states are reflected in the spectral composition and topography of the EEG and have been termed vigilance stages. Vigilance in this context is not a synonym for behaviourally measured sustained attention, but a neurophysiologic term indicating states of brain function. Behaviourally, these states correspond to different levels of alertness.

Several EEG vigilance stages can be observed not only during sleep but also during the transition from tense to relaxed wakefulness to drowsiness and sleep onset. Based on Bente (1964a), Roth (1961) and others (e.g. Cantero et al. 2002; Corsi-Cabrera et al. 2006; De Gennaro et al. 2001; Loomis et al. 1937; Tsuno et al. 2002), an algorithm has been developed, which automatically classifies EEG segments into vigilance stages and thus can be used for the quantification of vigilance regulation (Hegerl et al. 2008b; Olbrich et al. 2009).

Figure 1 provides an overview of the EEG-vigilance stage classification in humans. The A stages are states of higher vigilance (i.e. stronger neurophysiological arousal) characterised by rhythmic alpha activity while B stages are lower vigilance states observed with increasing subjective drowsiness and characterised by a lack of alpha in favour of increased low frequency activity (delta, theta). EEG stage C is characterised by the appearance of sleep spindles and K-complexes and marks the onset of sleep.

When interpreting findings concerning cognition and vigilance, several aspects are of importance:

1. It is already known (and will be elaborated later in this article) that cholinergic receptor manipulations can influence cognition. However, it is not quite clear how this cholinergic influence on cognition is exerted. For instance, the cholinergic system could have direct effects on cognition. However, the effect of cholinergic and anticholinergic substances—having arousing and sedating properties—on cognitive task performance might also be mediated by the modulation of EEG vigilance and vigilance regulation.
2. Vigilance level and vigilance regulation have to be distinguished. Both can have different effects on an individual's cognitive performance:
    a. The *vigilance level* in the sense of the central nervous arousal level at a certain point in time can be expected to be related to cognitive performance;

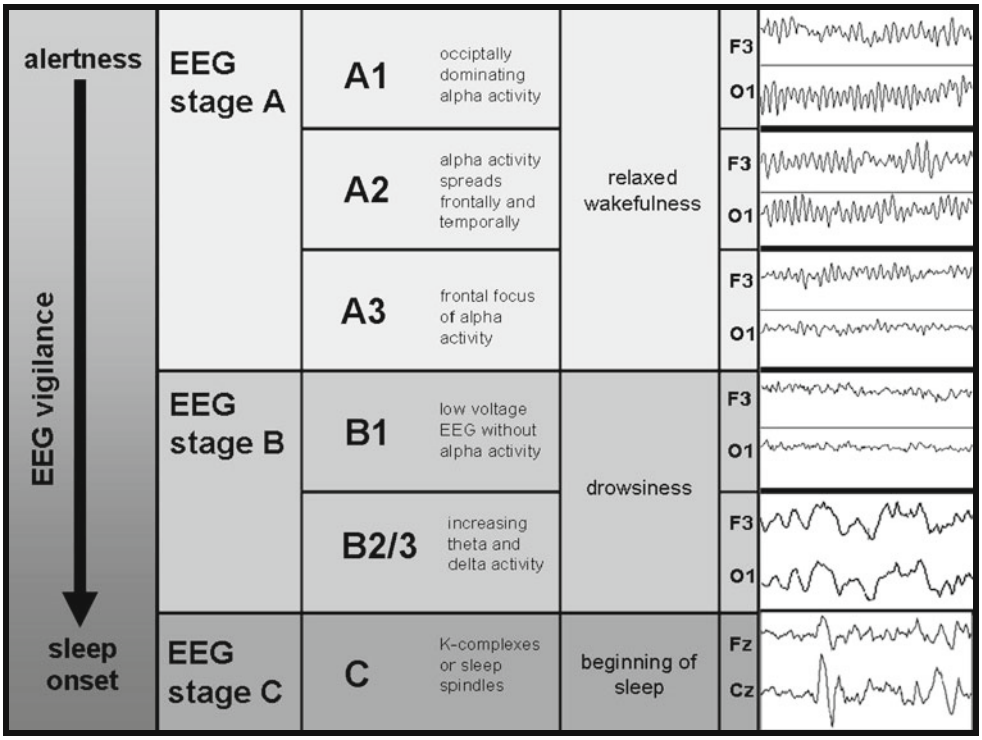


**Fig. 1** Vigilance states between wakefulness and sleep (modified from Hegerl et al. 2008a; Olbrich et al. 2009)

however, not in a linear manner. Based upon previous work by Yerkes and Dodson (1908) or Arent and Landers (2003), an inverted-U function between vigilance/arousal and cognitive performance has to be expected, with the optimal performance at medium arousal levels, while extreme levels (hypo- or hyperarousal) are likely to affect performance adversely (see Fig. 2).

b. The precise regulation of vigilance is crucial for all higher organisms. In humans, stable interindividual differences in *vigilance regulation* can be observed. For example, under quiet resting conditions with eyes closed, most subjects show decline to low EEG-vigilance stages or even sleep onset within 15 min. Others, however, show a tonically high vigilance level or a rapid decline to low vigilance levels (B2/3) already during the first minute (e.g. Bente 1964b; Small et al. 1999). Although being a trait (Bente 1964b; Ulrich 1994), this regulation of vigilance is modulated by psychoactive drugs, e.g., many recreational drugs like caffeine (Barry et al. 2005; Dimpfel et al. 1993) or nicotine (see the following paragraph) and state factors like sleep deficits. Vigilance regulation can therefore be thought of as a state-modulated trait.

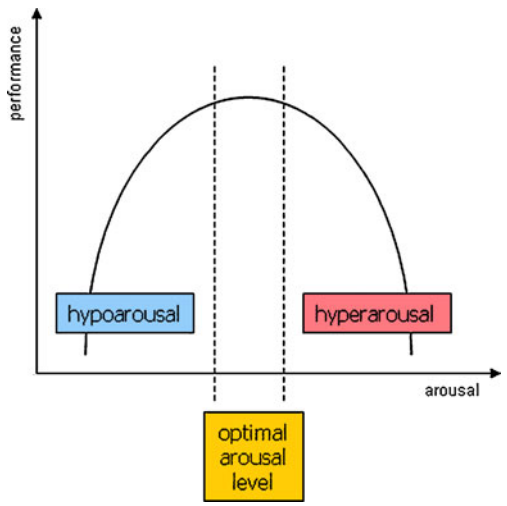


**Fig. 2** Assumed inverted-U relationship between arousal level and cognitive performance

Specific patterns of vigilance regulation occur in several mental disorders, e.g. hyperstable vigilance regulation in patients with major depression and unstable vigilance regulation in manic patients or patients with ADHD (Bschor et al. 2001; Hegerl et al. 2008a, b, 2010; Small et al. 1999; Ulrich and Furstenberg 1999).

Vigilance regulation might have an impact on cognitive performance, e.g. an unstable vigilance regulation with a strong tendency to drops to lower vigilance states (an extreme form of which is seen in patients with mania) should be associated with deficits especially in long-lasting monotonous cognitive tasks. Indeed, sustained attention impair-

ments have been reported for manic patients (Fleck et al. 2005; Strauss et al. 1984) but not for patients suffering from unipolar depression (Clark et al. 2005; Liu et al. 2002; Maalouf et al. 2010), i.e. patients characterised by a rather hyperstable vigilance regulation.

3. An individual's arousal level during the performance of a task is dependent on their baseline level of arousal before the start of the task but also on the arousing qualities of the task and the testing situation itself. Cognitive tasks can be more or less challenging, emotional and arousing. In subjects with low vigilance levels or an unstable vigilance regulation, arousing tasks with vigilance-stabilising properties may induce comparably little deficits whereas this might not be the case in subjects with an intrinsically high and stable vigilance, in whom even opposite effects may be observed. Very arousing tasks might push these subjects to a dysfunctional hyperaroused state (cf. Fig. 2: inverted-U relationship between vigilance/arousal and cognition).

The emotions generated during task performance (e.g. stress, anxiety) may have an influence on the subject's arousal and EEG as well (e.g. Umryukhin et al. 2002). Therefore, it should be kept in mind that cholinergic substances do not only influence cognition, EEG vigilance or affective state separately, but that there are also interactions between these domains.

## Cholinergic receptor subtypes and vigilance regulation—influence on the EEG

Both muscarinic and nicotinic receptors have been implicated in changes in the EEG. The vast majority of studies have investigated the influence of the muscarinic antagonist scopolamine and the nAChR agonist nicotine. The main outcome of these studies was that scopolamine has a slowing effect on the EEG with increased theta and delta activity while nicotine evokes an increased occurrence of activity in the alpha band. Bearing the vigilance concept in mind, these changes could partly reflect effects on vigilance regulation. The vigilance stabilising substance nicotine results in a higher percentage of vigilance stages A with high alpha and low theta and delta whereas more non-alpha stages (vigilance stages B) occur after scopolamine:

- In healthy human volunteers, administration of scopolamine causes an increase in delta and theta power (Ebert and Kirch 1998; Neufeld et al. 1994; Sannita et al. 1987), but a decrease in alpha and beta frequencies (Sloan et al. 1992) and in absolute and relative alpha amplitude (Neufeld et al. 1994).
- In a study by Knott et al. (1997), scopolamine as opposed to placebo administration increased relative power not only in theta, but also beta frequency bands. The same study also investigated the effects of the nAChR antagonist mecamylamine and found a decrease in absolute and relative beta power, but an increase in relative theta power.
- Pickworth et al. (1997) reported that mecamylamine in smokers and non-smokers caused dose-related decreases in alpha frequency and increases in delta frequency. Beta frequency increased only with mecamylamine doses up to 10 mg.

The effects of nicotine application on the EEG have often been studied in overnight deprived smokers (e.g. Domino et al. 1992; Lindgren et al. 1999). In general, a slowing of EEG frequency has been seen in deprived smokers (Gilbert et al. 2004; Gilbert et al. 1999). Nicotine readministration dose-dependently decreased delta and theta power and increased alpha-2 power and alpha peak frequency, while alpha-1 and beta remained unaffected (Lindgren et al. 1999). Domino et al. (1992) observed a shift from alpha-1 to alpha-2 frequencies with alpha-2 increase occurring mainly in occipital, parietal and frontal regions. Kadoya et al. (1994) reported that an increase in plasma nicotine of more than 10 ng/ml leads to a significant decrease in alpha-1 and an increase in beta activity, whereas an increase of plasma nicotine of more than 15 ng/ml results in a significant decrease in delta activity. Foulds et al. (1994) studied the effect of subcutaneous nicotine injections in non-smokers and found an increase in alpha frequency. Nicotine administered to Alzheimer's disease patients brought about a shift of EEG measures towards normal values, specifically a reduction of relative delta and theta power and an increase in relative alpha-1, alpha-2 and beta power (Knott et al. 2000).

The $\alpha 4\beta 2^*$ receptor agonist, TC-1734, led to an acceleration of the alpha centroid and alpha peak and decreased slow wave activity in young, healthy, male volunteers (Dunbar et al. 2007), arguing for an involvement of this nAChR subtype in EEG modulation. However, it has to be noted that this has been an exploratory study and that no statistical correction for multiple testing has been applied.

When conducting studies in overnight deprived smokers, it has to be considered that nicotine deprivation might be perceived as stressful, which may have an influence on the subjects' arousal and consequently might be reflected in the EEG. However, similar results have been achieved both in smokers and non-smokers, namely that, in general, cholinergic receptor agonists (e.g. nicotine) lead to an increase in higher frequency bands (alpha and beta) and to a decrease in low frequency bands (theta, delta) while cholinergic

receptor antagonists (e.g. scopolamine, mecamylamine) show the opposite pattern with decreasing alpha and beta but increasing theta and delta activity.

The influence of cholinergic agonists/antagonists on electrical brain activity has also been investigated in animal experiments, especially in experiments with rats and mice. However, it is important to note that the abovementioned vigilance classification (EEG stages A, B and C) has been developed for the description of human vigilance states only and cannot be applied to animals. Nevertheless, the study of cholinergic agents on electrophysiological measures in animals can help to investigate the involvement of specific cholinergic receptor subtypes in the modulation of brain electrical activity.

A partial agonist to the muscarinic M1 receptor, CS-932, has been reported to counteract scopolamine-induced slow waves in rat cortical EEG. It also increased the power of alpha and beta waves, but decreased delta waves of the cortical EEG in monkeys (Iwata et al. 2000). In rats, nicotine reversed the theta increment caused by scopolamine administration (Sambeth et al. 2007) and suppressed the duration and frequency of high-voltage spindle (HVS) occurrence (Riekkinen et al. 1993), thus providing supportive evidence for the vigilance-enhancing properties of nicotine. HVS are spontaneous; 6–8 Hz neocortical spike wave discharges generated in thalamocortical networks and occurring during waking immobility in rats (Radek et al. 1996). HVS are therefore typical for low arousal and low vigilance states, e.g. drowsiness (Jakala et al. 1996). The nAChR antagonist mecamylamine was found to increase HVS activity when administered in doses of at least 15 μmol/kg (Radek 1993), whereas Radek et al. (1996) pointed out that not only nicotine but also the α4β2* agonist ABT-418 dose-dependently reduced HVS incidence in rats. Further support for the importance of the β2 nAChR subunit—at least in rodents—comes from a study that investigated the sleep-EEG in β2-knockout mice. In contrast to wild type mice, nicotine did not increase wakefulness in these knockouts (Lena et al. 2004). Consequently, the authors reasoned that β2-containing nAChR mediate the arousing properties of nicotine.

From the existing studies, it can be assumed that both muscarinic and nicotinic cholinergic mechanisms play a role in modulating brain electrical activity. To date, however, only few studies have investigated the role of selected cholinergic receptor subtypes. The studies reviewed here argue for an involvement of the muscarinic M1 and nicotinic β2* component.

## The role of cholinergic receptor subtypes in cognition

The investigation of changes in cognition emerging after cholinergic receptor manipulation has strongly focused on the fields of memory and attention. Even though several different models exist about the way memory is structured and organised, most researchers agree on a time- and content-based division of memory. Time-based distinctions include the sensory, short-term and long-term memory (Atkinson and Shiffrin 1968). A special case is the so-called working memory, which some researchers equate with the short-term memory. However, working memory does not only require the storage of information for a restricted time. Rather, it refers to tasks that require the simultaneous storage and manipulation of information and therefore, lies at the crossroad between memory, attention and perception (Baddeley 1992). The content-based division of memory refers only to long-term memory, which it differentiates into declarative (or explicit) and non-declarative (or implicit) memory processes (Anderson 1976; Cohen and Squire 1980). Declarative memory includes semantic memory (i.e. factual knowledge) and episodic memory (i.e. information acquired in a particular temporal or spatial context, life experiences). Non-declarative memory comprises skills and habits, simple non-associative learning, conditional learning and priming (e.g. Kandel et al. 2000). There are also a few special concepts within memory research like, for example, prospective memory (i.e. remembering to perform an intended action in the future) as an extension of the time-based division, recognition memory (falling in the episodic memory category) and recall of learned information either immediately or delayed and with or without external help or cueing (e.g. Markowitsch 1998).

Non-declarative, semantic and prospective memory remain quite stable across the lifespan while declines in working memory and episodic memory occur frequently with increasing age or in neurodegenerative diseases like Alzheimer's disease. Attentional processes are less likely to be impaired in these cases. The following sections will outline findings about the involvement of cholinergic receptor subtypes in memory and attention.

### Memory and learning

#### *Working memory—studies in humans*

There is evidence for an involvement of cholinergic mechanisms in human working memory functions. It has been shown, for instance, that the acetylcholinesterase inhibitor physostigmine, which leads to a general enhancement of cholinergic function, has a positive impact on working memory (Furey et al. 1997; Kirrane et al. 2001).

Unselective blockade of the muscarinic receptors by scopolamine has been found to impair working memory performance in a number of tasks, whereas unspecific blockade of nicotinic receptors by mecamylamine had no

effect (Ellis et al. 2006; Green et al. 2005; Koller et al. 2003; see Table 1). However, the combined administration of scopolamine and mecamylamine produced deficits greater than the ones seen after scopolamine administration alone. Therefore, it appears that muscarinic and nicotinic receptors might interact functionally to have synergistic effects on working memory performance.

In an fMRI study with abstinent smokers, Loughead et al. (2010) reported increased working memory-related brain activity after administration of varenicline, a nicotinic receptor agonist, as compared with placebo. Varenicline is a high-affinity partial agonist at α4β2* receptors but also binds at α3β4*, α3β2* and α6-containing receptors (though with a somewhat lower affinity). Moreover, it is a full agonist at homomeric α7 receptors, for which it shows a lower affinity than for α4β2* receptors (Mihalak et al. 2006). The results by Loughead and colleagues therefore argue for an involvement of the nicotinic receptor subtypes in working memory, whilst they do not allow inferences about any one particular receptor subtype.

In sum, studies of working memory function in human subjects argue for an involvement of both muscarinic and nicotinic receptors. However, based upon these studies, an identification of specific cholinergic receptor subtypes is not possible.

*Working memory—studies in animals*

Animal studies offer better possibilities to examine specific receptor subtypes involved in cognitive functioning by means of genetic knockout studies or administration of subtype-selective ligands. In animals, working memory is often investigated by means of matching-to-sample tasks and maze tasks, particularly the radial arm maze task in rats. The radial arm maze apparatus consists of a central platform, from which several equidistantly spaced arms protrude. At the end of each arm is a food site and in order to check for food on all arms, the rat has to keep coming back to the central platform before choosing a new arm. Therefore, spatial working memory is required to remember which arms have already been visited.

The involvement of both muscarinic and nicotinic receptors in working memory functions in animals has been proven by a number of studies, which investigated the effects of non-selective muscarinic and nicotinic antagonists (see Table 1 for details). Both scopolamine and mecamylamine were found to impair working memory functions of rats and monkeys in maze tasks (Beatty and Bierley 1985; Kay et al. 2010; Kobayashi et al. 1995; Levin et al. 1987; Ohno et al. 1993; Okaichi et al. 1989; Tatsumi et al. 2006; Wirsching et al. 1984) and delayed matching tasks (e.g. Granon et al. 1995; Spinelli et al. 2006). However, on spatial alternation tasks, only scopolamine led to impairment while mecamylamine had no effect (Bymaster et al. 1993; Wilson and King 2000).

In regard to specific muscarinic receptor subtypes, a lot of evidence argues for the involvement of the M1 receptor, especially in maze tasks (Anagnostaras et al. 2003; Brandeis et al. 1995; Iwata et al. 2000; Nakahara et al. 1989; Ohno et al. 1994). Bymaster et al. (1993) linked the M1 subtype also to spatial alternation performance. In contrast, Wilson and King (2000) reported that—even though scopolamine disrupted spatial alternation performance in rats—the M1-selective antagonist pirenzepine did not impair their rats' performance on the task.

The three-panel runway task also seems to rely not exclusively on the M1 receptor since the administration of the M2-selective antagonist methoctramine caused impairment in this task in male Wistar rats (Ohno et al. 1994).

The investigation into the nicotinic receptor subtypes that are involved in working memory functions has mainly focused on radial arm maze performance in rats. Deteriorating effects of both the α4β2* antagonist DHβE and the α7-specific antagonist methyllycaconitine (MLA) have been reported (Addy et al. 2003; Arthur and Levin 2002; Bancroft and Levin 2000; Bettany and Levin 2001; Chan et al. 2007; Felix and Levin 1997; Levin et al. 2002; Nott and Levin 2006). Conversely, working memory improved after administration of nicotinic agonists (Chan et al. 2007; Gatto et al. 2004; Levin et al. 1999; Lippiello et al. 1996; Tatsumi et al. 2006). A study with knockout mice substantiates these results further: both β2* and α7 knockouts have been connected to radial arm maze performance (Levin et al. 2009). In a recent study, Rushforth et al. (2010) have underlined the involvement of both the α4β2* and the α7 subtype in rats' working memory using not a maze task, but an odour span task.

For delayed matching-to-sample tasks, results are somewhat mixed with Granon et al. (1995) being unable to find an effect of the α4β2* antagonist DHβE in rats, whereas the α4β2* agonist ABT-418 was found to improve performance on this task in monkeys (Buccafusco et al. 1995). Neuronal bungarotoxin, an antagonist to heteromeric nicotinic receptors (which targets primarily the α3β2* and, to a lesser extent, the α4β2* subtype), impaired the performance of rats on a delayed matching-to-sample task (Granon et al. 1995).

In sum, important roles for the muscarinic receptors and the nicotinic α7 receptor subtype in working memory performance can be assumed. The α4β2* subtype has been implicated in certain tasks but not others. Performance on the radial arm maze and the three-panel runway task seems to be mediated rather unspecifically by nicotinic (α4β2*, α7) and muscarinic (M1, partly M2) receptors. Spatial alternation tasks, however, seem to rely more specifically on muscarinic receptors.

**Table 1** Cholinergic influence on working memory in humans and animals

| Affected receptor | Compound | Species | Task/paradigm | Effects | References |
|---|---|---|---|---|---|
| Muscarinic | Scopolamine | Human | Delayed matching-to-sample | − | Koller et al. 2003 |
| Muscarinic | Scopolamine | Human | Modified Sternberg paradigm, numeric matching-to-sample, n-back task | − | Ellis et al. 2006; Green et al. 2005 |
| Muscarinic + nicotinic | SCOP + MEC | Human | | − | Ellis et al. 2006; Green et al. 2005 |
| Nicotinic | Mecamylamine | Human | | No effect | Ellis et al. 2006; Green et al. 2005 |
| Nicotinic | *Varenicline* | Human (smokers) | n-back task | + | Loughead et al. 2010 |
| Muscarinic | Scopolamine | Rat | Delayed matching | − | Granon et al. 1995 |
| Muscarinic | Scopolamine | Marmoset | Delayed matching | − | Spinelli et al. 2006 |
| Muscarinic | Scopolamine | Rat | Radial arm maze | − | Beatty and Bierley 1985; Kay et al. 2010; Okaichi et al. 1989; Tatsumi et al. 2006; Wirsching et al. 1984 |
| Muscarinic | Scopolamine | Rat | Spatial alternation task | − | Bymaster et al. 1993; Wilson and King 2000 |
| Muscarinic | Scopolamine | Rat | Three-panel runway task | − | Kobayashi et al. 1995 |
| M1 | *AF150(S)* | Rat | Radial arm maze | + | Brandeis et al. 1995 |
| M1 | *FKS-508* | Rat | Radial arm maze | + | Nakahara et al. 1989 |
| M1 | *CS-932* | Rat | Three-panel runway | + | Iwata et al. 2000 |
| M1 | Knockout | Mouse | Radial arm maze | − | Anagnostaras et al. 2003 |
| M1 | Pirenzepine | Rat | Spatial alternation task | −/no effect | Bymaster et al. 1993; Wilson and King 2000 |
| M1 | Pirenzepine | Rat | Three-panel runway | − | Ohno et al. 1994 |
| M2 | Methoctramine | Rat | Three-panel runway | − | Ohno et al. 1994 |
| nicotinic | Mecamylamine | Rat | Radial arm maze | − | Levin et al. 1987 |
| nicotinic | Mecamylamine | Rat | Spatial alternation task | No effect | Bymaster et al. 1993 |
| nicotinic | Mecamylamine | Rat | Three-panel runway task | − | Ohno et al. 1993 |
| α4β2* | *5-Iodo-A-85380* | Rat | Radial arm maze | + | Chan et al. 2007 |
| α4β2* | *ABT-418* | Macaque | Delayed matching-to-sample | + | Buccafusco et al. 1995 |
| α4β2* | DHβE | Rat | Delayed matching-to-sample | no effect | Granon et al. 1995 |
| α4β2* | DHβE | Rat | Radial arm maze | − | Nott and Levin 2006; Addy et al. 2003; Arthur and Levin 2002; Levin et al. 2002; Bettany and Levin 2001; Bancroft and Levin 2000; Felix and Levin 1997; Chan et al. 2007 |
| α4β2* | *Metanicotine* | Rat | Odour span task | + | Rushforth et al. 2010 |
| α4β2* | *RJR-2403* | Rat | Radial arm maze | + | Lippiello et al. 1996 |
| α4β2* | *TC-1734* | Rat | Radial arm maze | + | Gatto et al. 2004 |
| β2* | Knockout | Mouse | Radial arm maze | − | Levin et al. 2009 |
| α7 | *AR-R17779* | Rat | Radial arm maze | + | Levin et al. 1999 |

| | | | | | |
|---|---|---|---|---|---|
| α7 | *Compound 23* | Rat | Radial arm maze | + | Tatsumi et al. 2006 |
| α7 | *Compound A* | Rat | Odour span task | + | Rushforth et al. 2010 |
| α7 | Knockout | Mouse | Radial arm maze | – | Levin et al. 2009 |
| α7 | MLA | Rat | Radial arm maze | – | Addy et al. 2003; Levin et al. 2002; Bettany and Levin 2001; Nott and Levin 2006; Felix and Levin 1997; Chan et al. 2007 |
| α7 | *PNU-282987* | Rat | Radial arm maze | + | Chan et al. 2007 |
| α3β2*, (α4β2*) | κ-bungarotoxin | Rat | Delayed matching-to-sample | – | Granon et al. 1995 |

Compounds in italics have agonistic effects

*SCOP* scopolamine, *MEC* mecamylamine, *DhβE* dihydro-beta-erythroidine, *MLA* methyllycaconitine, – impaired performance, + improved performance

*Declarative memory—studies in humans*

In healthy volunteers, the muscarinic antagonist scopolamine has been shown repeatedly to impair episodic memory performance on a number of verbal tasks (Bishop et al. 1996; Ellis et al. 2006; Huff et al. 1988; Kamboj and Curran 2006a, b; Koller et al. 2003; Kopelman and Corn 1988; Litvan et al. 1995; Mintzer et al. 2010; Terry and Buccafusco 2003; Vitiello et al. 1997; see Table 2 for details) as well as in visual recognition memory tasks (Koller et al. 2003; Sherman et al. 2003).

The effect of scopolamine on semantic memory seems less pronounced. Only two studies reported deteriorating effects of scopolamine on a semantic sentence verification (Bishop et al. 1996) and a lexical semantic memory (i.e. category fluency) task (Tröster et al. 1989), while several studies reported neither impairments nor improvements after scopolamine administration (e.g. Dunne 1990; Huff et al. 1988; Mintzer et al. 2010). Scopolamine, therefore, seems to spare semantic memory functions to some extent. Moreover, scopolamine seems to have a stronger effect on acquisition of new information than on retrieval of contents that have been acquired before administration of the drug (Ghoneim and Mewaldt 1975, 1977; Koller et al. 2003).

There are hardly any studies that have investigated muscarinic subtype-specific agonists or antagonists in human declarative memory. One exception is a study by Wezenberg et al. (2005), which linked the M1 subtype to episodic memory performance in healthy elderly subjects.

Only few studies focused on the role of the nicotinic receptors in human declarative memory. While Ellis et al. (2006) found no effect of the unselective nicotinic antagonist mecamylamine, Kitagawa et al. (2003) reported memory enhancing properties of the α7-selective agonist GTS-21. Moreover, nicotine enhanced the prospective memory performance in minimally deprived smokers (Rusted et al. 2005).

In sum, declarative memory performance in humans, especially episodic memory but not so much semantic memory, seems to be mediated primarily by muscarinic receptors with some evidence pointing to an involvement of the M1 subtype. There is a lack of studies investigating the role of nicotinic receptors in declarative memory performance in humans. From the few studies that exist, it appears that nicotinic receptors might be less relevant for these kinds of tasks. However, the α7 subtype may be involved to some extent.

*Declarative memory—studies in animals*

Maze tasks like the radial arm maze and the Morris water maze are applied to investigate spatial reference memory in rats and mice. The radial arm maze, which has been

**Table 2** Cholinergic influence on declarative memory in humans and animals

| Affected receptor | Compound | Species | Task/paradigm | Effects | References |
|---|---|---|---|---|---|
| Muscarinic | Scopolamine | Human | Story recall | − | Bishop et al. 1996; Kamboj and Curran 2006a, b; Kopelman and Corn 1988 |
| Muscarinic | Scopolamine | Human | Free word recall | − | Bishop et al. 1996; Kopelman and Corn 1988 |
| Muscarinic | Scopolamine | Human | Cued word recall | − | Kopelman and Corn 1988; Mintzer et al. 2010 |
| Muscarinic | Scopolamine | Human | Wordlist learning | − | Bishop et al. 1996; Ellis et al. 2006; Huff et al. 1988; Koller et al. 2003; Vitiello et al. 1997 |
| Muscarinic | Scopolamine | Human | Paired associate learning | − | Kopelman and Corn 1988; Terry and Buccafusco 2003 |
| Muscarinic | Scopolamine | Human | Selective reminding | − | Litvan et al. 1995; Terry and Buccafusco 2003 |
| Muscarinic | Scopolamine | Human | Visual recognition memory | − | Koller et al. 2003; Sherman et al. 2003 |
| Muscarinic | Scopolamine | Human | Semantic sentence verification | − | Bishop et al. 1996 |
| Muscarinic | Scopolamine | Human | Category fluency | − | Tröster et al. 1989 |
| Muscarinic | Scopolamine | Human | Semantic memory | No effect | Dunne 1990; Huff et al. 1988; Mintzer et al. 2010 |
| M1 | Biperiden | Human | Verbal memory | − | Wezenberg et al. 2005 |
| Nicotinic | Mecamylamine | Human | Immediate and delayed word recall | No effect | Ellis et al. 2006 |
| Nicotinic | *Nicotine* | Human (smokers) | Prospective memory | − | Rusted et al. 2005 |
| α7 | *GTS-21*[a] | Human | Immediate word recall and recognition | + | Kitagawa et al. 2003 |
| Muscarinic | Atropine | Rat | Water maze | − | Whishaw 1985 |
| Muscarinic | Scopolamine | Rat | Radial arm maze (reference memory) | − | Okaichi and Jarrard 1982; Okaichi et al. 1989 |
| Muscarinic | Scopolamine | Rat | Radial arm maze (reference memory) | No effect | Beatty and Bierley 1985; Wirsching et al. 1984 |
| Muscarinic | Scopolamine | Rat | Object recognition memory | − | Sambeth et al. 2007 |
| Muscarinic | Scopolamine | Rat | social recognition memory | − | van Kampen et al. 2004 |
| M1 | Pirenzepine | Rat | Three-panel runway (reference memory) | No effect | Ohno et al. 1994 |
| M1 | Knockout | Mouse | Water maze | No effect | Anagnostaras et al. 2003 |
| M2 | Methoctramine | Rat | Three-panel runway (reference memory) | No effect | Ohno et al. 1994 |
| Nicotinic | *Nicotine* | Rat | Object recognition memory | + | Puma et al. 1999 |
| Nicotinic | *Nicotine* | Rat | Water maze | + | Hernandez and Terry 2005 |
| Nicotinic | Mecamylamine | Rat | Radial arm maze (reference memory) | − | Brown et al. 2002 |
| Nicotinic | Mecamylamine | Rat | Three-panel runway (reference memory) | No effect | Ohno et al. 1993 |
| α4β2* | DHβE | Rat | Radial arm maze (reference memory) | − | Levin et al. 2002 |
| α4β2* | *TC-1734* | Rat | radial arm maze (reference memory) | + | Gatto et al. 2004 |
| α4β2* | *RJR-2403* | Rat | Radial arm maze (reference memory) | + | Lippiello et al. 1996 |
| α4β2* | *TC-1734* | Mouse | Object recognition memory | + | Obinu et al. 2002 |
| α4β2* | *ABT-418* | Macaque | Delayed recall | + | Prendergast et al. 1998 |

| | | | | | | |
|---|---|---|---|---|---|---|
| β2* | knockout | Mouse | Water maze | – | | Zoli et al. 1999 |
| α7 | *GTS-21* | Rat | Radial arm maze (reference memory) | + | | Arendash et al. 1995 |
| α7 | *PNU-282987* | Rat | Radial arm Maze (reference memory) | + | | Chan et al. 2007 |
| α7 | *A-582941* | Rat | Social recognition memory | + | | Tietje et al. 2008 |
| α7 | *AR-R17779* | Rat | Social recognition memory | + | | van Kampen et al. 2004 |

Compounds in italics have agonistic effects; [a] GTS-21is a selective α7 nAChR agonist that antagonises α4β2* nAChRs
*DHβE* dihydro-beta-erythroidine, – impaired performance, + improved performance

described already as a measure of working memory, can be used to test both working and (declarative) reference memory. Usually, not all arms of the maze are baited and if the task is performed for several trials in a row, reference memory describes the rat's memory about which of the arms have been baited in previous trials while working memory is the rat's memory of the arms that it has visited already during the current trial. In the water maze task, another test of spatial reference memory, a rat is placed into a pool of water, in which a hidden platform is located a few millimetres below the water surface. Over several trials, the rat has to learn to find this escape platform using visual cues around the pool.

Apart from reference memory, recognition memory is another test of declarative memory in animals.

Interestingly, the involvement of muscarinic receptors in declarative memory appears to be less pronounced in animals than it is in humans (see Table 2). The non-selective muscarinic antagonist atropine impaired rats' performance on the water maze (Whishaw 1985). However, Cain (1998) argued that those deficits are not connected to memory impairment per se but to motor impairments caused by atropine: After being given the opportunity of a non-spatial pre-training, rats showed no impairment on this task anymore.

One group of authors reported that the antimuscarinic drug scopolamine increased the number of reference memory errors in rats tested on the radial arm maze (Okaichi and Jarrard 1982; Okaichi et al. 1989), whereas other studies found no effect of scopolamine on reference memory for this task (Beatty and Bierley 1985; Wirsching et al. 1984). As for recognition memory, scopolamine was found to impair object (Sambeth et al. 2007) and social recognition memory in rats (van Kampen et al. 2004).

Not only are there inconsistencies about the effects of scopolamine on declarative memory, but there is also a lack of effect of selective muscarinic antagonists (Ohno et al. 1994) or genetic deletion of the M1 receptor subtype (Anagnostaras et al. 2003).

The involvement of the nicotinic receptors in declarative memory functions in rats appears to be better documented (Brown et al. 2002; Hernandez and Terry 2005; Puma et al. 1999). Nicotine doses administered over a period of 14 days did not only improve water maze performance in Wistar rats but also caused an upregulation of α4β2* and α7 receptors, arguing for an involvement of those receptor subtypes in the water maze task (Hernandez and Terry 2005).

Several studies have confirmed the involvement of specific nicotinic receptor subtypes in declarative memory across different species, e.g. for the α4β2* subtype (Gatto et al. 2004; Levin et al. 2002; Lippiello et al. 1996; Obinu et al. 2002; Prendergast et al. 1998; Zoli et al. 1999) and the

α7 subtype (Arendash et al. 1995; Chan et al. 2007; Tietje et al. 2008; van Kampen et al. 2004).

In sum, in contrast to studies in humans, studies investigating declarative memory in rodents and monkeys highlight the role of the nicotinic receptors for these memory processes. There is a notable number of studies linking both the α4β2* and the α7 subtypes to reference and recognition memory. The role of the muscarinic receptors, which seemed so pronounced in studies with human subjects, appears hence comparably smaller in animals. Whether this is an actual difference between human and animal cognition or just a consequence of the restricted possibilities to study subtype-specific ligands in humans, remains an unresolved issue.

*Non-declarative memory—studies in humans*

There are only a limited number of studies that have looked at the impact of cholinergic receptor manipulations on non-declarative learning in humans and the general results suggest that cholinergic, especially muscarinic, mechanisms are of little relevance for this kind of learning (Bishop and Curran 1998; Kopelman and Corn 1988; Nissen et al. 1987; see Table 3 for details).

Rasch and colleagues examined the effects of a combined administration of the muscarinic antagonist scopolamine and the nicotinic antagonist mecamylamine on the performance of young, male volunteers in a finger sequence tapping task (Rasch et al. 2006, 2009). The subjects' immediate learning performance was not different from that of a placebo group, but the combined antagonists were found to have an impairing effect on motor skill consolidation. However, this effect was specific to sleep-dependent consolidation and did not occur during a wake-retention interval. Moreover, the effect was only seen in the reaction time measure but not the error rate.

*Non-declarative memory—studies in animals*

Non-declarative memory as defined by Milner et al. (1998) comprises—amongst others—emotional learning (e.g. fear conditioning and passive avoidance learning) and classical conditioning, paradigms which have been studied in animals with regard to cholinergic receptor involvement.

Avoidance behaviour is the result of an instrumental training procedure, in which a predictable aversive event does not take place contingent upon the occurrence or non-occurrence of a specified response by the animal. In the passive form, the aversive event is avoided by suppressing certain behaviour while, in the active form, a certain response (e.g. flight, lever press) has to be shown to avoid the aversive stimulus. Both the muscarinic M1 and M2 receptor subtypes have been implicated with passive avoidance learning (Brandeis et al. 1995; Fornari et al. 2000; Tzavara et al. 2003; see Table 3 for details).

Fear-conditioning paradigms can be subdivided into contextual fear conditioning (i.e. the animal presents the fear-conditioned response when exposed to the same context in which it was trained) and cued fear conditioning (i.e. the animal presents the fear-conditioned response when exposed to a discrete stimulus, e.g. a tone). It has been shown that contextual fear conditioning relies on the

**Table 3** Cholinergic influence on non-declarative memory in humans and animals

| Affected receptor | Compound | Species | Task/paradigm | Effects | References |
|---|---|---|---|---|---|
| Muscarinic | Scopolamine | Human | Conceptual priming | No effect | Bishop and Curran 1998 |
| Muscarinic | Scopolamine | Human | Mirror-reading task | No effect | Kopelman and Corn 1988 |
| Muscarinic | Scopolamine | Human | Serial reaction time task | No effect | Nissen et al. 1987; Bishop et al. 1996 |
| Muscarinic | Scopolamine | Human | Backward reading, pursuit rotor task | No effect | Bishop et al. 1996 |
| M1 | *AF150(S)* | Rat | Passive avoidance learning | + | Brandeis et al. 1995 |
| M1 | Dicyclomine | Rat | Passive avoidance learning | − | Fornari et al. 2000 |
| M1 | Dicyclomine | Rat | Contextual/cued fear conditioning | −/No effect | Fornari et al. 2000 |
| M2 | Knockout | Mouse | Passive avoidance learning | − | Tzavara et al. 2003 |
| α4β2* | *ABT-418* | Rat | Passive avoidance learning | + | Decker et al. 1994b |
| α4β2* | *RJR-2403* | Rat | Passive avoidance learning | + | Lippiello et al. 1996 |
| β2* | Knockout | Mouse | Passive avoidance learning | − | Picciotto et al. 1995 |
| β2* | Knockout | Mouse | Contextual and cued fear conditioning | (−) | Caldarone et al. 2000 |
| α7 | *GTS-21* | Rat | Active avoidance learning | + | Arendash et al. 1995 |
| α7 | *GTS-21* | Rabbit | Eyeblink conditioning | + | Woodruff-Pak et al. 1994; Woodruff-Pak 2003 |

− impaired performance, + improved performance; compounds in Italics have agonistic effects

integrity of both hippocampus and amygdala while cued fear conditioning is hippocampus-independent and mainly relies on the integrity of the amygdala (Phillips and LeDoux 1992). The M1 antagonist dicyclomine impaired contextual fear conditioning, but not tone fear conditioning in rats, thus suggesting that the M1 receptor is relevant for hippocampus-dependent aversively motivated tasks (e.g. contextual fear conditioning, passive avoidance), but not for hippocampus-independent tasks (Fornari et al. 2000).

Nicotinic receptors have also been implicated with emotional learning. For instance, passive avoidance performance has been linked to the α4β2* subtype (Decker et al. 1994b; Lippiello et al. 1996). Further support, especially for the β2 subunit, comes from a study in β2 knockout mice which showed no facilitation on a passive avoidance task upon nicotine administration (Picciotto et al. 1995). Knockout mice missing the β2 component were also impaired in contextual and cued fear conditioning. However, this finding applied only to aged (9–20 months), male animals, but not to young (2–4 months) or female animals (Caldarone et al. 2000). Active avoidance learning, in contrast, seems to rely more on the α7 nAChR (Arendash et al. 1995).

The role of cholinergic receptors in classical conditioning has been investigated by means of the eye blink response in rabbits. Eye blink conditioning is a form of classical conditioning that consists of pairing an auditory or visual stimulus (the conditioned stimulus) with an unconditioned stimulus that elicits an eye blink naturally (e.g. a puff of air). After many of these pairings, the conditioned stimulus alone will elicit an eye blink (the so-called conditioned response). The α7 nAChR seems to be involved in this kind of learning since GTS-21 was found to increase acquisition (Woodruff-Pak et al. 1994) and reverse mecamylamine-induced deficits (Woodruff-Pak 2003).

In sum, both muscarinic and nicotinic receptor subtypes are involved in certain forms of non-declarative learning in rodents, particularly (but not exclusively) in hippocampus-dependent tasks. While the α4β2* nAChR has been linked repeatedly to passive avoidance learning, the α7 subunit appears to be of particular importance for classical conditioning.

## Attention

### *Studies in humans*

Different attentional processes can be distinguished, e.g. selective attention, divided attention or sustained attention. The latter is often assessed in humans by means of the continuous performance task (CPT).

The non-selective muscarinic antagonist scopolamine has been shown repeatedly to impair performance on sustained attention tasks (Duka et al. 1996; Ellis et al. 2006; Koller et al. 2003; Terry and Buccafusco 2003; see Table 4 for details). Scopolamine also caused impairment on a span of apprehension test but only under certain conditions (Koller et al. 2003): Only the higher dose of 0.6 mg scopolamine, but not the smaller dose of 0.3 mg led to a performance decrement. Moreover, performance on the more difficult version of the test, which required the subject to recognise eight instead of only three characters at the same time, was unchanged under scopolamine.

Nicotinic receptor involvement for sustained attention tasks has been suggested as well (Jones et al. 1992; Lawrence et al. 2002; White and Levin 1999). In regard to specific receptor subtypes, the α7 subtype seems to be somehow involved in attentional processes (Kitagawa et al. 2003).

### *Studies in animals*

Attention, or rather sustained attention, is often tested with the 5-CSRT (five-choice serial reaction time) task in animals. Both muscarinic and nicotinic receptors appear to be involved (Grottick and Higgins 2000; Spinelli et al. 2006).

Interestingly, Day et al. (2007) observed in rats that nicotine improved accuracy and lowered the number of omissions on this task only when the rats' baseline performance was below 90%. If they performed better at baseline and achieved more than 90%, then nicotine actually tended to worsen their accuracy. This could be an indication for the presumed inverted-U function between vigilance/arousal and performance. Animals with a near-perfect baseline performance that are hypothesised to have gained their optimal arousal level already before the task begins, would not show a performance increase upon nicotine administration. Rather, the animals would tend to become hyperaroused when administered nicotine and thus, would show a performance decline.

Studies investigating several specific nicotinic agonists and antagonists suggest that the α4β2* subtype is involved more strongly than the α7 subtype (Grottick and Higgins 2000; Hahn et al. 2003; see Table 4 for details). However, α7-knockout mice have been found to be impaired on the 5-CSRT task as well (Hoyle et al. 2006; Young et al. 2004). In addition, the α2β4* receptor subtype seems to be involved (Terry et al. 2002).

The performance on signal detection tasks is also mediated by cholinergic mechansims (McQuail and Burk 2006; Rezvani et al. 2002). In a signal detection task where rats had to press the according lever depending on whether or not a signal had been given, scopolamine impaired the accuracy of the signal detection without affecting the detection of non-signals. The nAChR antagonist mecamyl-

**Table 4** Cholinergic influence on attention in humans and animals

| Affected receptor | Compound | Species | Task / paradigm | Effects | References |
|---|---|---|---|---|---|
| Muscarinic | scopolamine | Human | digit vigilance task | − | Ellis et al. 2006 |
| Muscarinic | scopolamine | Human | Continuous Performance Test | − | Koller et al. 2003 |
| Muscarinic | scopolamine | Human | visual vigilance, continous attention task, rapid information processing task | − | Duka et al. 1996 |
| Muscarinic | scopolamine | Human | span of apprehension test | (−) | Koller et al. 2003 |
| nicotinic | *nicotine* | Human (smokers, Alzheimer's disease) | RVIP (rapid visual information processing) task | + | Lawrence et al. 2002; Jones et al. 1992 |
| nicotinic | *nicotine* | Human (Alzheimer's disease) | Continuous Performance Test | + | White and Levin 1999 |
| α7 | *GTS-21* | Human | digit vigilance task | + | Kitagawa et al. 2003 |
| Muscarinic | scopolamine | Marmoset | 5-CSRT task | − | Spinelli et al. 2006 |
| Muscarinic | scopolamine | Rat | two lever signal detection task | − | McQuail and Burk 2006 |
| nicotinic | mecamylamine | Rat | 5-CSRT task | − | Grottick and Higgins 2000 |
| nicotinic | mecamylamine | Rat | two lever signal detection task | − | McQuail and Burk 2006 |
| nicotinic | *nicotine* | Marmoset | 5-CSRT task | + | Spinelli et al. 2006 |
| nicotinic | *nicotine* | Rat | 5-CSRT task | +/− (depending on baseline performance) | Day et al. 2007 |
| nicotinic | *nicotine* | Rat | operant visual signal detection | + | Rezvani et al. 2002 |
| α4β2* | *ABT-418* | Rat | 5-CSRT task | + | Hahn et al. 2003 |
| α4β2* | *SIB1765F* | Rat | 5-CSRT task | + | Grottick and Higgins 2000 |
| α7 | *AR-R17779* | Rat | 5-CSRT task | No effect | Grottick and Higgins 2000; Hahn et al. 2003 |
| α7 | MLA | Rat | 5-CSRT task | No effect | Grottick and Higgins 2000 |
| α7 | Knockout | Mouse | 5-CSRT task | − | Hoyle et al. 2006; Young et al. 2004 |
| α2β4* | *SIB-1553A* | Rat | 5-CSRT task | + | Terry et al. 2002 |

Compounds in italics have agonistic effects

*5-CSRT* five-choice serial reaction time, *MLA* methyllycaconitine, − impaired performance, + improved performance

amine, in turn, left accuracy unaffected but led to an increase in omissions. When scopolamine and mecamylamine were co-administered (in subthreshold doses that were not effective when administered alone), the number of omissions increased, the number of detected signals decreased and the non-signal detection was unaffected. These findings argue for a contribution of both mAChR and nAChR in this two lever attention task (McQuail and Burk 2006).

In sum, nicotinic receptors appear to be more relevant for attentional functions, particularly sustained attention, than muscarinic receptors, with stronger evidence pointing to the involvement of the α4β2* subtype.

To summarise the abovementioned findings, it can be concluded that the muscarinic receptors play an important role for memory functions, but, to a smaller extent, have also been linked to attentional processes. Their effect on conditioning tasks seems to be negligible though. Rather, conditional learning is mediated by nAChR. Furthermore, the nicotinic α7 receptor subtype appears to be predominantly involved in working memory, whereas the α4β2* subtype seems to be crucial for tests of attention.

## Cholinergic influence on emotion

As mentioned before, emotional states are also believed to be influenced by cholinergic receptor manipulations and, in turn, are thought to exert an influence on arousal and EEG vigilance, as well as cognition. Exemplary for the influence of cholinergic substances on the affective state, a brief overview on the findings concerning depression and anxiety shall be given in the following.

### Depression

#### *Studies in humans*

The muscarinic antagonist scopolamine has been reported to have antidepressant-like effects in patients suffering from unipolar depression (Drevets and Furey 2010; Furey and Drevets 2006). However, the main body of evidence for a cholinergic involvement in the regulation of mood comes from studies investigating nicotinic (and not muscarinic) receptor involvement. A number of clinical observations suggest that smoking, or rather the nicotine contained in tobacco, can regulate mood. For instance, the rate of smoking has been reported to be much higher in depressed subjects than in the general population (Breslau 1995; Glassman et al. 1990). Moreover, smoking cessation can aggravate symptoms of depression (Glassman et al. 1990), while antidepressants were found to have a beneficial effect on smoking cessation and nicotine withdrawal symptoms in a subgroup of smokers (Hitsman et al. 1999). On the other hand, the application of a transdermal nicotine patch has been found to reduce symptoms of depression in non-smokers (Salin-Pascual et al. 1995).

Further evidence for the involvement of the cholinergic system in the regulation of mood comes from studies suggesting that the acetylcholinesterase inhibitor donepezil may have mood and behavioural normalising effects on depressive symptoms in affective disorders (see Burt 2000).

In contrast, it has been reported that the acetylcholinesterase inhibitor physostigmine has antimanic effects, but may exacerbate depressive symptoms in some subjects (Janowsky et al. 1972, 1986). This ostensible contradiction may be resolved, however, when bearing in mind that the chronic administration of nicotine (as delivered through a patch) can desensitise nAChRs due to over-activation, what might result in functional antagonism (Mineur et al. 2007; Reitstetter et al. 1999). Therefore, it appears as if the blockade rather than activation of nAChRs might have antidepressant effects, a hypothesis that gains support from studies describing a decrease of depressive symptoms after administration of the unspecific nicotinic receptor antagonist mecamylamine (George et al. 2008; Shytle et al. 2002).

#### *Studies in animals*

Tests that are commonly used as animal models for antidepressant-like effects are the forced swim test and the tail suspension test. In the forced swim test, the animal (typically, a rat or mouse) is placed into a cylinder filled with water, from which it cannot escape. The measure of interest (which is believed to model the animal's hopelessness/depression) is the duration for which the animal remains immobile during the trial. In the tail suspension test, the duration of immobility as a reaction to the inescapable stress of being suspended by the tail is measured.

Antidepressant-like effects of nicotinic antagonists, especially mecamylamine, have been observed in animal models of depression (Caldarone et al. 2004; Mineur et al. 2007; Rabenstein et al. 2006). These effects seem to be dependent on both the α7 and β2 subunits since knockout mice lacking these nAChR subunits were insensitive to the effects of mecamylamine (Rabenstein et al. 2006). Furthermore, nAChR blockade by both the α4β2* antagonist DHβE and the α7-selective antagonist MLA had antidepressant-like effects (Andreasen et al. 2009). Nicotinic receptor agonists also show antidepressant-like effects in mice, e.g. cytisine (Mineur et al. 2007), sazetidine-A (Turner et al. 2010) or varenicline (Rollema et al. 2009a, b). These findings are consistent with the notion that reducing the nicotinic receptor activity either by antagonists or partial agonists that can partially desensitise the receptor is connected to antidepressant-like properties.

Nicotine potently activates nicotinic receptors, but chronic nicotine administration leads to continued desensitisation of nAChRs (e.g. Quick and Lester 2002). This might be the reason for nicotine's antidepressant-like effects that have been reported, for instance, in genetic depressive rats of the Flinders Sensitive Line (Tizabi et al. 1999). For a recent review of the literature on nicotinic acetylcholine receptors and depression, see Philip et al. (2010).

In sum, cholinergic mechanisms appear to have a modulating influence in the regulation of mood. In particular, previous research argues for a connection of depression and nicotinic receptors. There is evidence for an involvement of both α4β2* and α7 receptor subtypes.

## Anxiety

### *Studies in humans*

The cholinergic system has also been connected to anxiety. Anxiogenic effects after administration of the muscarinic antagonist scopolamine have been reported in healthy volunteers (Curran et al. 1991) and in patients with geriatric depression (Newhouse et al. 1988).

A more extensive body of literature exists on the involvement of the nicotinic cholinergic mechanisms in the regulation of anxiety. Nicotine appears to have both anxiolytic and anxiogenic effects. On the one hand, smokers report lower levels of state anxiety following consumption of nicotine (Gilbert et al. 1989; Pomerleau et al. 1984). Moreover, the number of cigarettes smoked has been reported to increase on stressful occasions, suggesting an anxiolytic effect (Todd 2004). On the other hand, it has been argued that smoking might play a causative role in the development of anxiety disorders, particularly panic disorder (Johnson et al. 2000; McCabe et al. 2004; Zvolensky et al. 2003). This is in agreement with the observation of decreased anxiety from the first week of abstinence after smoking cessation (West and Hajek 1997) and a study reporting increased anxiety in non-smokers after intravenous administration of nicotine (Newhouse et al. 1990).

### *Studies in animals*

Anxiety models used in rodents comprise several different tests, e.g. the shock–probe burying test, social interaction test, open field tasks, the elevated plus maze, the mirrored chamber as well as the fear-potentiated startle response (Picciotto et al. 2002; Rodgers 1997). Active and passive avoidance tasks have also been used as anxiety models (Brush 2003; Fernandez-Teruel et al. 1991), thus forming an intercept point between cognition and emotion.

Anxiogenic effects of scopolamine were reported in mice after intrahippocampal infusions of scopolamine (Smythe et al. 1998) and after systemic administration (Rodgers and Cole 1995; Smythe et al. 1996). Muscarinic receptor blockade through the M1-specific muscarinic antagonist pirenzepine, but not the M2-specific antagonist gallamine, caused an increase of anxiety-like behaviour in rats tested in the social interaction test (File et al. 1998a).

In contrast, facilitation of cholinergic activity via intrahippocampal administration of the acetylcholinesterase inhibitor physostigmine has anxiolytic effects in the plus maze and shock–probe tests (Degroot et al. 2001). These effects (i.e. increased open-arm exploration, decreased burying behaviour) can be observed after administration of physostigmine to either dorsal or ventral hippocampus. However, only infusions in the ventral, but not dorsal hippocampus increased the number of contacts rats made with the shock–probe (Degroot and Treit 2002). The authors suggested that although cholinergic stimulation in both dorsal and ventral hippocampus modulates anxiety, only the ventral hippocampus seems to be involved in the passive avoidance of painful stimuli. Nicotine—as in studies investigating human subjects—has been found to have both anxiogenic and anxiolytic effects. It has been suggested that these effects are dose-dependent: low doses of nicotine are believed to have anxiolytic effects, whereas higher doses act anxiogenic (e.g. Brioni et al. 1993; Cao et al. 1993; File et al. 1998b; Ouagazzal et al. 1999; Tucci et al. 2003). Moreover, the effects of nicotine appear to depend on the paradigm tested and the affected neurobiological substrates. Nicotine administration directly into the dorsal hippocampus and lateral septum had anxiogenic effects in the social interaction test (believed to model generalised anxiety disorder), but administration of nicotine into the dorsal hippocampus produced anxiolytic effects in trial 2 of the elevated plus maze (a model of specific phobia). On trial 1 (which models components of panic disorder), nicotine was ineffective when administered to the dorsal hippocampus, whereas it produced anxiogenic effects after lateral septal administration (File et al. 2000). For the elevated plus maze task, Gulick and Gould (2010) have found no effects of nicotine infusion into either dorsal or ventral hippocampus. However, nicotine infusion in the dorsal hippocampus reversed anxiolytic effects induced by administration of ethanol, whereas nicotine infusion in the ventral hippocampus enhanced ethanol-associated anxiolysis. In the social interaction test, the unspecific nicotinic antagonist mecamylamine has been found to have anxiogenic effects when administered into the dorsal hippocampus (File et al. 1998a), but anxiolytic effects when administered at low doses to the lateral septum (Ouagazzal et al. 1999).

The opposing actions of nicotine on anxiety might also be modulated by different nicotinic receptor subtypes. It has been reported that the α4β2* agonist ABT-418 has

anxiolytic effects, which can be blocked by mecamylamine (Brioni et al. 1994; Decker et al. 1994a). Further support for an anxiety modulating role of the α4 subunit comes from studies showing increased anxiety-like behaviour in knockout mice lacking this subunit (Ross et al. 2000) and knock-in mice with a leucine-to-serine mutation in the α4 receptor resulting in a hypersensitive channel (Labarca et al. 2001). Knockout mice lacking the β3 or β4 subunits showed decreased levels of anxiety-like behaviour (Booker et al. 2007; Cui et al. 2003; Salas et al. 2003), as did α7 knockout mice (Paylor et al. 1998). The selective antagonist MLA had an anxiolytic effect in the social interaction test (Tucci et al. 2003), further supporting the involvement of the α7 subtype in the modulation of anxiety.

## Discussion

The results of the studies reviewed here show that cholinergic mechanisms modulate cognition, emotion and brain electrical activity as measured by EEG.

In regards to the relationship between cognition and vigilance, the question arises whether the cognitive changes observed might be a result of the changes in the subjects' wakefulness and vigilance states as indicated by the EEG rather than cognition and vigilance just being independent consequences of cholinergic interference. Positive correlations between cognitive and memory performance and EEG alpha and theta oscillations have been demonstrated in previous studies, e.g. by Klimesch (1999) and van der Hiele et al. (2007). The latter group also showed that EEG markers were able to predict future cognitive performance in elderly subjects (van der Hiele et al. 2008). Similarly, O'Connell et al. (2009) showed that their subjects' lapses of sustained attention in a continuous temporal expectancy task could be registered in the EEG already up to 20 s before the error occurred.

The present article shows that cholinergic agonists and antagonists have an effect on both cognitive measures and the EEG. Scopolamine, which was found to impair several cognitive measures, has been shown to increase delta and theta activity, characteristics of low vigilance states. Nicotine, in turn, which enhances cognitive performance leads to a decrease of delta and theta activity, but increases alpha activity, the characteristic of the higher vigilance states.

Another indication for the presumption that cognitive results should only be interpreted against the background of the broader concept of vigilance stems from studies investigating the effects of sleep deprivation on cognitive measures. After sleep deprivation, the regulation of vigilance becomes unstable (e.g. Ulrich 1994). Taking this into account, it is not surprising that sleep deprivation has deteriorating effects on different cognitive measures ranging from memory and learning processes to attentional tasks and executive functions, e.g. fluency and go/nogo tasks (e.g. Chuah et al. 2006; Peigneux et al. 2001; Turner et al. 2007; Van Dongen et al. 2003). In a recent review article, Edgar et al. (2009) discuss the relationship between wakefulness/vigilance and cognition. They demonstrate a clear overlap not only in the assessment of both concepts but also in the neurobiological correlates underlying them. Another group of authors investigated the relationship between sleep/wake patterns and cognition in Alzheimer's disease patients (Moe et al. 1995). By means of regression analyses, they could show that sleep/wake variables were highly correlated with cognitive and functional measures and that they could explain significant variance.

Adding the concept of vigilance as another factor that is influenced by cholinergic receptor manipulation helps us to integrate a few cognitive results that—at first glance—might seem contradictory. If cognition was solely dependent on the cholinergic manipulation, we should receive accordant results no matter whether we investigate the receptor-subtype specificity of a particular cognitive task by administrating a receptor agonist (in which case performance is mostly enhanced) or antagonist (which leads mostly to a performance decrease). Sometimes, however, we only get a result for the agonist administration but not for the antagonist. These inconsistencies can be explained by the parallel effect of cholinergic receptor manipulation on a subject's vigilance. For instance, scopolamine has predominantly negative effects on cognition. Therefore, one would assume that scopolamine is connected with lower vigilance levels, while nicotine with its cognition-enhancing effects should come along with higher vigilance. The described EEG effects confirm these assumptions: scopolamine leads to an increase in lower frequencies that are connected with lower vigilance stages and nicotine causes an increase in alpha activity, the characteristic of the higher vigilance stages (the A stages). More generally, cholinergic antagonists are connected with a slowing of the EEG while cholinergic agonists are connected with higher frequencies, mainly in the alpha band. Knowing that the higher vigilance states (the A stages) are characterised mainly by alpha activity and the lower vigilance states (B stages) by theta and delta activity, it seems plausible that cholinergic agonists help to maintain a higher vigilance level (cf. the A stages) while cholinergic antagonists might cause a drop to lower vigilance levels (the B stages, cf. Fig. 1). Also keeping in mind that there is an optimal arousal level for cognitive performance, it makes sense to find correlative relationships between cognitive performance and cholinergic parameters more easily in the case of cholinergic agonist administration than after cholinergic antagonist administration, which might lead to a vigilance decline.

Van Dort et al. (2009) suggested that the cholinergic influence on arousal is mediated by adenosine receptors on cholinergic neurons in the basal forebrain. Studying the effects of $A_1$ and $A_{2A}$ receptor agonists and antagonists in mice, they concluded that an activation of the $A_1$ receptor leads to a decrease in ACh release, which in turn results in diminished behavioural arousal and an increase in EEG delta power. On the other hand, activation of the $A_{2A}$ receptor causes ACh release within the pontine reticular formation and thus a decrease in EEG delta power and an increase in arousal. Therefore, stimulation of $A_{2A}$ receptors acts arousing via intensified ACh release, while stimulation of $A_1$ receptors has sleep-promoting effects due to decreased ACh release. These findings support the idea that cortical cholinergic neurons are involved in vigilance and sleep–wake regulation. In fact, it has been suggested that the basal forebrain cholinergic system might represent a final common pathway for sleep and arousal modulating effects of multiple neurochemical systems. Selective lesions of this system were found to result in reduced high frequency EEG power (especially in the gamma band) and thus may be indicative of decreased cortical activation (Berntson et al. 2002).

Not only EEG measures have been linked to cognitive performance, but cognition has also been found to be affected in patients with affective spectrum disorders like for example, depression (e.g. Austin et al. 2001; Gallassi et al. 2001), bipolar disorder (e.g. Bearden et al. 2001) or ADHD (e.g. Castellanos et al. 2006). Interestingly though, the vigilance regulation patterns in these patient groups have been described as either particularly hyperstable or unstable, respectively (Bschor et al. 2001; Hegerl et al. 2008a, b, 2010; Small et al. 1999; Ulrich and Furstenberg 1999).

In any case, the unobjectionable separation from cognitive and affective effects of cholinergic receptor agonists/antagonists seems difficult. Cholinergic and anti-cholinergic drugs like nicotine or scopolamine, for instance, have not only an influence on cognitive measures, but are also effective in modulating depression and anxiety. This supports the view that cognition, vigilance and affect are all influenced by the cholinergic system while there are also interactions between each of these concepts.

The studies reviewed here also accentuate the need for further investigations of the influence of cholinergic receptor subtype availability on cognitive measures, e.g. by means of positron emission tomography (PET). PET gives us the opportunity to visualise and quantify nicotinic cholinergic receptors in vivo while studies in which agonists or antagonists are administered allow only a conclusion about behavioural changes after receptor manipulation. Therefore, PET can help to detect the underlying neurobiological structures implicated in the cholinergic modulation of certain cognitive functions in human subjects. Behavioural studies which investigate the effects of cholinergic substances can only then be of use to determine specific brain regions that might be relevant for the modulatory effects of ACh receptors on cognition, when the administration of nicotinic or muscarinic agonists or antagonists occurs directly into a particular brain structure of interest, which is naturally only possible in animal studies. As yet, studies have targeted mainly the ventral and dorsal hippocampus in rats (Arthur and Levin 2002; Bancroft and Levin 2000; Bettany and Levin 2001; Felix and Levin 1997; Levin et al. 2002; Nott and Levin 2006; Ohno et al. 1993, 1994). Singular studies have also looked at the basolateral amygdala (Addy et al. 2003), the prelimbic area of the prefrontal cortex (Granon et al. 1995), the frontal cortex (Chan et al. 2007) and structures connected to the dopaminergic system such as the ventral tegmental area and substantia nigra (Levin et al. 1994) or the nucleus accumbens (Kim and Levin 1996). Note, however, that for the latter structure, no discernible effect of cholinergic receptor manipulation on cognitive measures has been found.

An additional advantage of an in vivo quantification of nAChRs via PET is that changes in cholinergic receptor availability across different conditions can be investigated, e.g. differences between nicotine-deprived and nicotine-rich states in smokers or changes over the course of a disease characterised by cholinergic disturbance like Alzheimer's disease. 2-[F18]-F-A-85380 PET has already been used to study the availability of the nicotinic $\alpha4\beta2^*$ receptor subtype, amongst others in Alzheimer's disease patients (Sabri et al. 2008). For these patients, a relationship between cholinergic transmission and cognitive deficits has long been known, both through post-mortem (Perry et al. 1978) and PET studies (Herholz et al. 2008; Kuhl et al. 1999; Nordberg et al. 1997; Sabri et al. 2008). This knowledge is also reflected in the use of acetylcholinesterase inhibitors in the treatment of dementia. However, due to the possible interactions between cognition and vigilance, future PET research should perhaps not be restricted to the relationship between cholinergic availability and cognition but could be extended in such a way that it includes a measure of vigilance, preferably through simultaneous EEG. Such a simultaneous approach has been used, for instance, in Alzheimer's disease patients studied with 2-[F18]fluoro-2-deoxy-D-glucose PET (Günther et al. 2009).

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