Review

Effects of pharmacological agents, sleep deprivation, hypoxia and transcranial magnetic stimulation on electroencephalographic rhythms in rodents: Towards translational challenge models for drug discovery in Alzheimer's disease

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HIGHLIGHTS

- Analysis of electroencephalographic (EEG) rhythms in animal models of deficit and drug-induced EEG normalisation provides a useful approach to drug discovery.
- Effects on EEG rhythms of challenges represented by administration of pharmacological agents, hypoxia, sleep deprivation and transcranial magnetic stimulation provide a knowledge platform for pre-clinical investigation in Alzheimer's disease.
- Expected changes of EEG rhythms due to experimental manipulations can promote preclinical innovative translational models fitting dynamics in humans.

ABSTRACT

Different kinds of challenge can alter spontaneous ongoing electroencephalographic (EEG) rhythms in animal models, thus providing paradigms to evaluate treatment effects in drug discovery. The effects of challenges represented by pharmacological agents, hypoxia, sleep deprivation and transcranial magnetic stimulation (TMS) on EEG rhythms are here reviewed to build a knowledge platform for innovative translational models for drug discovery in Alzheimer's disease (AD). It has been reported that antagonists of cholinergic neurotransmission cause synchronisation of spontaneous ongoing EEG rhythms in terms of enhanced power of EEG low frequencies and decreased power of EEG high frequencies. Acetylcholinesterase inhibitors and serotonergic drugs may restore a normal pattern of EEG desynchronisation. Sleep deprivation and hypoxia challenges have also been reported to elicit abnormal synchronisation of spontaneous ongoing EEG rhythms in rodents. The feasibility and reproducibility of TMS have been demonstrated in rodents but information on a consistent modulation of EEG after TMS manipulation is very limited. Transgenic mice over-expressing human amyloid precursor protein complementary DNAs (cDNAs) harbouring the 'Swedish' mutation and PS-1 cDNAs harbouring the A264E mutation, which recapitulate some of the pathological features of AD, exhibit alterations of spontaneous ongoing EEG

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rhythms at several low and high frequencies. This does not appear, however, to be a consequence of beta-amyloid deposition in the brain. The present review provides a critical evaluation of changes of spontaneous ongoing EEG rhythms due to the experimental manipulations described above, in order to stimulate the promote more adherent models fitting dynamics in humans.

Contents

1. Introduction

1.1. Searching novel markers and translational models for drug discovery in Alzheimer's disease (AD)

It is well known that Alzheimer's disease (AD) is a progressive, neurodegenerative disease of the elderly, characterised by memory loss as well as additional cognitive and behavioural abnormalities. Early AD is associated with pathological changes in the basal forebrain cholinergic system, thalamocortical system, associative parietal–temporal areas and the complex of inter-related brain regions formed by the entorhinal cortex, hippocampus and amygdala (Daulatzai, 2010). Cholinergic neurotransmission protects neurons from amyloid beta (Abeta) production and its toxicity, which are enhanced by cholinergic depletion (Mohamed et al., 2011; Schliebs and Arendt, 2011). Symptomatic therapies target the cholinergic and glutamatergic systems, but no approved therapy is currently available to slow down or halt the neurodegenerative process.

A key objective of AD research is to develop and validate procedures for effective early proof-of-concept studies to evaluate novel symptomatic and disease-modifying agents in humans. The European Innovative Medicines Initiative project, PharmaCog, (IMI Undertaking on Neurodegenerative disorders, 2008) has adopted a strategy of parallel preclinical and human research for this purpose. In particular, procedures transiently interfering with cortical activity and cognitive processes in healthy volunteers and normal animals, that is, challenge models, are evaluated in this project. Such deficit models overcome the inherent difficulty of detecting significant improvements in cognitive performance in normal subjects. Pharmacological challenges include systemic administration of cholinergic or glutamatergic antagonists such as scopolamine and ketamine, hypoxia, sleep deprivation (SD) and transcranial magnetic stimulation (TMS). Validation of these models in drug discovery requires that potential symptomatic drugs normalise deficits or pathological alteration induced by challenge models in key neurophysiological mechanisms and cognitive processes.

In this article, the literature on animal models is reviewed in order to weigh the relative value of resting state or spontaneous ongoing electroencephalographic (EEG) patterns as putative 'end' points for an understanding of neurodegenerative processes. The aim is also to review drug effects in relevant animal models. The interest in these markers stems from the fact that recording of EEG activity is relatively inexpensive and able to probe the brain key features of oscillatory nature (Berger, 1929; Nunez, 2000; Michel et al., 2004; Rossini et al., 2007; Rossini, 2009; Babiloni et al., 2009a). Furthermore, spontaneous ongoing EEG rhythms in the resting state seem to reflect, at least at group level, preclinical and clinical stages of AD in humans (Babiloni et al., 2004, 2006a). From a translational point of view, spontaneous ongoing EEG rhythms show some similarities in humans and rodents. For example, alertness in humans and rodents is associated with enhanced power of low-voltage fast frequencies in EEG rhythms (i.e., beta rhythms spanning about 14–30 Hz), whereas non-rapid eye movement (REM) sleep and drowsiness are characterised by the enhanced power of high-voltage slow frequencies in EEG rhythms (i.e., delta and theta rhythms spanning about 1–7 Hz; Marshall and Born, 2002; Vyazovskiy et al., 2005). Anxiety has been shown to increase the power of low-voltage high frequencies in the resting-state EEG rhythms in both humans and rodents (Sviderskaia et al., 2001; Oathes et al., 2008). Finally, there is converging evidence that cholinergic and monoaminergic drugs have similar effects on spontaneous ongoing EEG rhythms in humans and rodents (Dimpfel et al., 1992; Jongsma et al., 1998, 2000; Coenen and Van Luijtelaar, 2003; Dimpfel, 2005). In the following sections, basic concepts about EEG techniques and markers are introduced.

2. Electroencephalographic techniques for translational research on AD

In humans, spontaneous ongoing scalp EEG rhythms reflect extracellular ion flow due to excitatory and inhibitory postsynaptic potentials in large populations of cortical pyramidal neurons (Nunez, 2000). There is a consensus that scalp EEG voltages mainly correspond to the local field potentials generated in superficial cortical layers, as local field potentials deriving from deeper cortical

layers are attenuated by resistance of the head as a volume conductor. Specifically, the synaptic activity of pyramidal neurons located in cortical gyri, whose apical dendrites are oriented radially to the scalp surface, is reflected by neural ion currents and voltages of the superficial cortical layer (Nunez, 2000). During dendritic depolarisation of pyramidal neurons (i.e., post-synaptic excitatory potentials), neural ion currents are associated to (extracellular) negative local field potentials in the superficial cortical layers (Buzsáki and Chrobak, 1995; Llinás, 1988). This superficial cortical level of local field potentials provides the most important contribution to the generation of scalp EEG voltages recorded in humans or to the generation of epidural EEG voltage recorded in rodents. During depolarisation of pyramidal neurons at deeper soma level (i.e., post-synaptic excitatory potentials), neural ion currents are associated to local negative (extracellular) field potentials at the deep cortical level and to local positive (extracellular) field potentials at the superficial cortical level. In this framework, neural ion currents of pyramidal neurons located in the depth of cortical sulci propagate tangentially to the scalp surface, so that they contribute to a lesser extent to the generation of ongoing scalp EEG rhythms (Nunez and Srinivasan, 2006). Taking this into account, the recording of ongoing EEG rhythms probes the oscillatory nature of the integrative synaptic activity of cortical pyramidal neurons as triggered by cortical and subcortical inputs. This model opens an important perspective to the understanding of clinical neurophysiology of neurodegenerative processes in humans and animal models (Berger, 1929; Pfurtscheller and Lopes Da Silva, 1999; Steriade, 2006; Nunez, 2000; Michel et al., 2004; Rossini et al., 2007; Rossini, 2009; Babiloni et al., 2009a). In animal models, intracerebral recording of spontaneous ongoing EEG rhythms typically measures local field potentials generated in small populations of cortical pyramidal neurons and/or neurons of subcortical structures, depending on electrode positioning and features.

Temporal resolution of EEG activity is high, namely up to fractions of milliseconds. In contrast, its spatial resolution (centimetres) is much lower than that of positron emission tomography (PET) or functional magnetic resonance imaging (fMRI, millimetres). Indeed, EEG spatial resolution essentially depends on the number of EEG recording channels, as well as on the mathematical procedures used to model cortical sources of EEG activity and to take into account the properties of the head as a volume conductor (Nunez, 2000). However, this limited spatial resolution is not a problem for the recording of EEG activity in animals. For these applications, electrodes are typically placed over or into the brain, coupling high temporal resolution with very high spatial resolution (a few millimetres).

EEG recordings can also reveal temporal and spatial information about externally triggered event-related (i.e., event-related potentials, ERPs; Picton et al., 2000; Murray et al., 2008) or spontaneous ongoing EEG activity (Nuwer, 1988; Steriade, 2006). Measurement of ERPs requires averaging many short, ongoing EEG epochs that are phase- and time-locked to sensory, cognitive or motor events, in order to remove non-phase-locked EEG rhythms from ERPs. Event-related cortical activity can be quantified by measuring latencies and amplitudes of distinct ERP components in distinct short epochs. In contrast, spontaneous ongoing EEG rhythms are usually recorded over longer time periods to assess states of vigilance or consciousness, such as sleep and resting state wakefulness at eyes closed or open (in humans), or background brain oscillatory activity at lights on and off (in animals). The analysis of spontaneous ongoing EEG activity can reveal activity such as resting state rhythms, seizures or sleep spindles and typically implies the computation of EEG power density at electrode contact and/or of functional coupling of EEG rhythms recorded between electrode pairs (i.e., spectral coherence for linear interactions) in distinct frequency domains (Nunez, 2000).

The recording and analysis of spontaneous ongoing EEG activity in rodents are characterised by some intrinsic limitations that should be carefully taken into account for the planning of experiments and interpretation of results. Voltage is a differential physical measurement, so that EEG recordings from exploring cortical or hippocampal electrodes require a reference electrode, which has to be placed in an electrically inactive site. This may not be needed in some circumstances and the use of more than one reference electrode is a good practise to control this methodological aspect. There is a consensus that in rodents the cerebellum is a suitable location for the reference electrode location. Furthermore, cranial or nasal bone is a suitable location to place a ground electrode. Another methodological issue is the quality of the electrical contacts over time. Sometime after the implantation of subdural or intracerebral electrodes (i.e., days to weeks), the quality of the electrical contacts can deteriorate due to gliosis or other inflammatory processes. Placement of epidural electrodes typically ensures less spatial resolution than subdural or intracerebral EEG recordings, and allows a long-lasting voltage measurement of reasonable quality.

Spectral analysis of the ongoing EEG rhythms typically implies the computation of EEG power density at electrode contacts and/or the calculation of functional coupling of the EEG frequency bands between electrode pairs (i.e., spectral coherence for the estimation of the linear inter-relatedness of ongoing EEG rhythms at electrode pairs; Nunez, 2000). In this respect, it should be noted that the above-mentioned approaches to the analysis of ongoing EEG rhythms in rodents have methodological limitations, which should to be taken into account. The spectral analysis of ongoing EEG rhythms is unsuited for the study of effects of drugs on rapid temporal evolution of brain activity, as reliable estimate of spectral EEG variables requires EEG segments lasting several seconds. Furthermore, the typical procedures for EEG spectral analysis assume a substantially stable EEG activity over time (Fingelkurts et al., 2003, 2005). This may not be the case in some circumstances, especially when long EEG segments lasting several tens of seconds are selected for spectral analysis (Fell et al., 2000). Finally, the typical spectral analysis of ongoing EEG rhythms is performed by mathematical procedures assuming linear models of generation of EEG oscillations. This may not always apply, so that the preliminary control of the linearity of the EEG signals is a good methodological practise (Landa et al., 2000).

Spontaneous ongoing EEG markers in humans are virtually unaffected by processes and events not immediately pertaining to the task, skill and the subjects' social compliance. Recording of spontaneous ongoing EEG rhythms can be repeated in the same subject with minimal repetition effects on EEG markers, and thus suited for longitudinal studies, including assessment of disease progression. Importantly, spontaneous ongoing resting state EEG rhythms seem to reflect, at least at the group level, preclinical and clinical stages of AD in humans. In particular, the following results on resting state eyes-closed EEG rhythms have been reported in AD patients, in patients suffering from the preclinical condition called mild cognitive impairment (MCI) and in control subjects: (1) dominant alpha frequencies (8–10 Hz) of EEG rhythms are specifically abnormal in AD subjects when compared to normal, elderly subjects and patients suffering from cerebrovascular dementia (Babiloni et al., 2004); (2) delta (2–4 Hz) and alpha rhythms are related to attention and global cognitive status in both MCI and AD subjects (Babiloni et al., 2006a); (3) alterations in alpha (8–10 Hz) rhythms are more pronounced in MCI and AD subjects who are carriers for ApoE4 (a genetic risk factor for AD) than in non-ApoE4 carriers (Babiloni et al., 2006b); (4) haplotype B of cystatin (another genetic risk factor for AD) is related not only to alpha rhythms, but also to delta rhythms (2–4 Hz) in MCI and AD subjects (Babiloni et al., 2006c); (5) brain white matter atrophy and delta rhythms (1.5–4 Hz) show a correlation in MCI and AD subjects (Babiloni et al.,

2006d); long-term (1-year) cholinergic therapy slows down the decline of alpha rhythms only in AD and MCI subjects in whom vascular lesions in cholinergic pathways affects alpha rhythms (Babiloni et al., 2006e, 2009b); (6) non-linear functional coupling of EEG rhythms is abnormal in MCI and AD subjects (Babiloni et al., 2006f); (7) serum 'free' copper (a biomarker of AD) is correlated to an increase of pathological delta rhythms (Babiloni et al., 2007a); (8) in turn, pathological delta rhythms correlate to the amount of homocysteine, an amino acid with neurotoxic effects present in the serum (Babiloni et al., 2007b); (9) the power and directionality of functional coupling of EEG rhythms are abnormal in MCI and AD subjects as a function of the number of white-matter vascular lesions (Babiloni et al., 2009b, 2009c); (10) alpha rhythms are altered in subjects with subjective memory complaints (but no objective memory deficits) compared with MCI and normal elderly subjects (Babiloni et al., 2010); (11) combined power and linear functional coupling of EEG rhythms predicts conversion from MCI to AD after approximately 1 year (Rossini et al., 2006); and (12) hippocampal atrophy correlates to the decline of alpha rhythms in MCI and AD subjects (Babiloni et al., 2009d).

Taken together, these data suggest that resting eyes-closed EEG rhythms can provide reliable neurophysiological information on AD related to the severity of the neurodegenerative processes, as indicated by brain atrophy and biological markers of neurodegeneration.

3. Physiological generation of ongoing EEG rhythms

EEG activity characterised by slow-frequency oscillation and large-voltage amplitude can be observed in large slabs of neocortical tissue after an isolation procedure, suggesting that intrinsic cortical networks can sustain this type of slow, deactivated cortical oscillations (Timofeev et al., 2000). The presence of two distinct types of synchronised high-voltage, low-frequency rhythms has been suggested by the EEG recordings in cats and humans, namely one ensemble of slow-frequency rhythms in the typical delta range (about 1–4 Hz), and the other rhythms below 1 Hz (Steriade et al., 1993; Steriade, 1993; Achermann and Borbély, 1997). Desynchronised low-voltage, fast-frequency EEG rhythms are not present in the isolated cortex, thus indicating that subcortical input is necessary for the induction of these rhythms expressing EEG activation or arousal.

Cholinergic fibres that originate from the basal forebrain and target the cerebral cortex play a major role in the desynchronisation of spontaneous ongoing EEG rhythms, that is, the suppression of high-voltage, low-frequency rhythms in the EEG and the appearance of low-voltage, fast-frequency EEG rhythms (Steriade et al., 1993; Steriade, 1993). During slow, synchronised EEG rhythms, cortical pyramidal cells display low-frequency intracellular membrane oscillations and pronounced, long-lasting inhibitory after-hyperpolarisations following spike discharge (Buzsáki and Gage, 1989; Metherate et al., 1992). Extracellular currents associated with these slow, synchronised events are believed to summate in the extracellular fluid, resulting in the appearance of large-amplitude, low-frequency EEG activity. Acetylcholine blocks slow, intracellular membrane oscillations and the outward potassium current associated with inhibitory after-hyperpolarisations, thus blocking slow, synchronised EEG rhythms and facilitating a shift to a desynchronised pattern of EEG rhythms. This activity is mediated by cortical muscarinic receptors rather than nicotinic receptors (Buzsáki
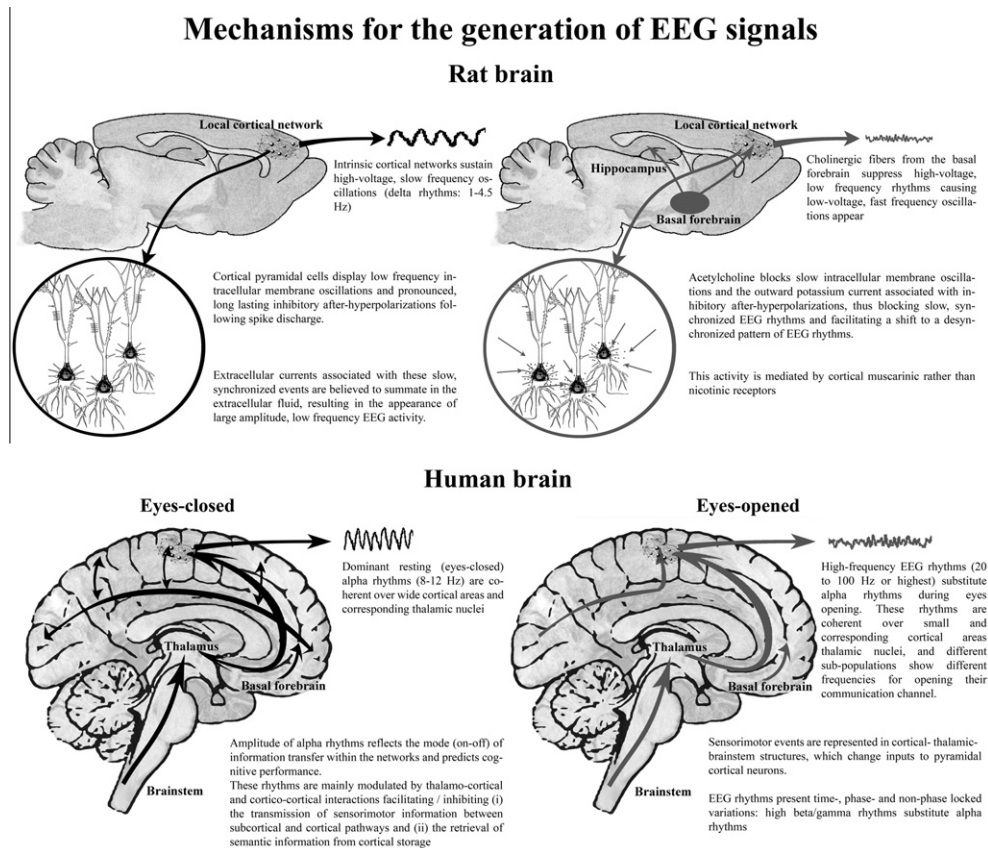
Fig. 1. Putative neurophysiological mechanisms for the generation of on-going electroencephalographic (EEG) rhythms in the human and in the rat brain. A sketch of the EEG rhythms is reported for the condition of eyes-closed and -open in human subjects and for the passive and active behavioural states in rats. The text in the figure suggests that acetylcholine promotes the desynchronisation of spontaneous on-going EEG rhythms by a direct, local effect on cortical neurons (see main text for more details).

and Gage, 1989; Metherate et al., 1992; Steriade et al., 1993; Steriade, 1993). Fig. 1 illustrates the main mechanisms underlying the physiological generation of ongoing EEG rhythms in rodents and humans.

The generation of sleep and wake spontaneous ongoing EEG rhythms in the cerebral cortex has long been debated. Some consensus has been reached on the following physiological model. During slow-wave sleep, corticofugal slow oscillations (<1 Hz) are effective in grouping thalamic-generated delta rhythms (1–4 Hz) and spindling activity (7–14 Hz; Steriade, 2003), with delta dominating EEG rhythms, and low amplitude of the alpha rhythm (about 8–12 Hz). In the case of endogenous or exogenous arousing stimuli, spindles, high and low components of the delta rhythms, are blocked by the inhibition of reticulothalamic (7–14 Hz), thalamocortical (1–4 Hz) and intracortical (<1 Hz) oscillators. These rhythms are replaced by fast oscillations (beta and gamma) induced by forebrain (nucleus basalis) cholinergic inputs to hippocampus and neocortex as well as by thalamocortical projections (Steriade et al., 1996; Steriade, 2003). In the wake resting state, alpha dominates the EEG rhythms and delta is low in amplitude (Steriade and Llinás, 1988; Pfurtscheller and Lopes da Silva, 1999). The relative amplitude of delta and alpha rhythms during sleep and awakening suggests a reciprocal inhibition between their generators.

Spontaneous ongoing human EEG rhythms reflect the continuous transitions between synchronisation (i.e., reduced arousal) and desynchronisation (i.e., increased arousal) of pyramidal cortical neurons at alpha rhythms together with the increased synchronisation of specialised task-relevant neural populations demonstrating beta/gamma rhythms spanning 14–40 Hz or higher frequencies (Pfurtscheller and Lopes da Silva, 1999). An important control on these transitions is exerted by the activity of cholinergic basal forebrain neurons projecting to the hippocampus, to a large neocortical expanse and to the thalamic reticular nucleus (Helkala et al., 1996; Holschneider et al., 1999; Mesulam et al., 2004). The activity of cholinergic neurons would explain not only the replacement of spindles and delta rhythms by fast EEG rhythms during wakefulness, but also the modulation of cortical neurons during the resting state (Dringenberg et al., 2000a,b, 2002). However, spontaneous ongoing EEG rhythms during wake depend not only on the cholinergic system but also on other neuromodulatory systems that act on the cerebral cortex directly or indirectly via the cholinergic system. Indeed, the basal forebrain cholinergic system itself is under the powerful modulatory control by fibres arising in the brainstem and diencephalon, including noradrenergic, dopaminergic, serotonergic, histaminergic and brainstem cholinergic inputs (Vertes, 1988; Jones and Cuello, 1989; Semba and Fibiger, 1989; Zaborszky, 1989).

Considerable evidence indicates that the release of acetylcholine in the neocortex plays a critical role in maintaining the desynchronisation of ongoing EEG rhythms, as characterised by low-voltage beta/gamma oscillations. Levels of acetylcholine in the cerebral cortex are increased during periods of low-voltage beta/gamma oscillations when compared to synchronised EEG patterns as characterised by large-amplitude, slow-frequency rhythms (Kanai and Szerb, 1965; Celesia and Jasper, 1966). Electrical stimulation of basal forebrain cholinergic neurons increases acetylcholine release at cortical targets (Mesulam et al., 1983; Semba and Fibiger, 1989) and concurrent desynchronisation of ongoing EEG rhythms (Belardetti et al., 1977; Casamenti et al., 1986; Metherate et al., 1992). Conversely, experimental lesions of the basal forebrain reduce the desynchronisation of EEG rhythms and induce a shift to large-amplitude, slow-frequency delta/theta rhythms; this effect correlates to loss of choline acetyltransferase, the acetylcholine synthetic enzyme and therefore a marker of cholinergic activity, in the cortex (Stewart et al., 1984; Buzsáki et al., 1988; Ray and Jackson, 1991). The same holds true for basal forebrain lesions similar to those observed in AD patients (Rodriguez et al., 1999a,b; Dierks et al., 1993, 2000; Huang et al., 2000; Babiloni et al., 2004, 2006b; Moretti et al., 2004; Mesulam et al., 2004). These lesions relatively spare brainstem cholinergic innervations of the thalamus (Mash et al., 1985; Geula and Mesulam, 1989, 1996; Tanaka et al., 2003; Mesulam et al., 2004).

4. Pharmacological modulation of ongoing EEG rhythms in animal models: the effects of cholinergic agonists and antagonists

Cholinergic therapies have been the mainstay of symptomatic therapeutic approaches in the treatment of AD for over 20 years. Acetylcholinesterase inhibitors sustain the availability of the natural transmitter by limiting its removal from the synapse. Alternatively, direct exogenous agonists or positive allosteric modulators of both nicotinic and muscarinic receptors still represent important therapeutic targets. For example, postsynaptic muscarinic M1 receptors are expressed in brain areas that play a key role in cognition, such as the hippocampus and prefrontal cortex. The M1 positive allosteric modulator BQCA has been reported to reverse cognitive impairment in a transgenic 'AD' mouse model of amyloid pathology (Shirey et al., 2009).

Effects of cholinergic agonists and antagonists on spontaneous ongoing EEG rhythms in animal models have greatly contributed to the understanding of the physiology of cortical arousal. A variety of direct and indirect cholinergic agonists induce desynchronisation of spontaneous ongoing EEG rhythms at beta/gamma frequencies, while muscarinic-receptor cholinergic antagonists reduce both the endogenous desynchronisation of ongoing EEG rhythms and the desynchronisation provoked by stimulation of cholinergic basal forebrain neurons (Funderburk and Case, 1951; Celesia and Jasper, 1966; Cuculic et al., 1968; Metherate et al., 1992). In anaesthetised animals, the desynchronisation of ongoing EEG rhythms is also blocked by direct, intracortical application of anti-muscarinic drugs (Metherate et al., 1992), suggesting that acetylcholine promotes the desynchronisation of spontaneous ongoing EEG rhythms by a direct, local effect on cortical neurons, rather than an indirect effect on subcortical neurons (see Fig. 1).

Acetylcholinesterase inhibitors such as physostigmine, tacrine, galantamine, rivastigmine or donepezil enhance the availability of acetylcholine in the synaptic cleft and hence empower cholinergic neuromodulation. These drugs affect spontaneous ongoing EEG rhythms as repeatedly documented in rodents (Dringenberg et al., 2000a,b, 2002; Dimpfel, 2005). Pre-treatment with reserpine (10 mg kg^{-1}) and scopolamine (1 mg kg^{-1}) has been shown to induce an abnormal synchronisation of resting state EEG rhythms characterised by high amplitude of low-frequency EEG oscillations. Tacrine (5–20 mg kg^{-1}) was then administered to restore the normal desynchronisation frequency pattern of spontaneous ongoing EEG rhythms (Dringenberg et al., 2000a,b, 2002). The effect of tacrine was shown to be dependent upon the dose of scopolamine used, causing suppression of high-voltage, slow-frequency EEG rhythms more effectively in rats treated with 1 mg kg^{-1} scopolamine than in those treated with a higher (5 mg kg^{-1}) dose (Dringenberg et al., 2002). Of particular relevance is the finding that EEG can be modulated by both direct and indirect acetylcholine receptor ligands (Dimpfel, 2005).

Pharmacological modulation of brain activity by the selective nicotinic agonist metanicotine, as well as the selective nicotinic antagonist methyllycaconitine, induces major changes in delta (1–4.5 Hz) and high-frequency alpha (9–12.5 Hz) rhythms (Dimpfel, 2005). In general, cholinergic activation by agonists decreases the power at these EEG rhythms, whereas inhibition of

Table 1
Pharmacological modulation of on-going EEG rhythms in animal models: the effects of cholinergic agonists and antagonists.

Study	Animal model	Experimental design	Findings
Shirey et al. (2009)	Tg2576 and WT mice	Evaluation of reversal learning in Tg and WT mice treated with BQCA or vehicle	M1 PAM BQCA reverse cognitive impairment in TG mice
Dringenberg et al. (2000a)	Male long evans rats	Analysis of EEG rhythms in scopolamine-treated rats after administration of deprenyl and tacrine	Deprenyl enhanced the effectiveness of tacrine in reversing EEG slowing after reserpine-scopolamine administration
Dringenberg et al. (2000b)	Male long evans rats	EEG were recorded in rats pre-treated with reserpine and scopolamine after administration of tacrine, imipramine, pargyline, and fluoxetine	The acetylcholinesterase inhibitor tacrine reversed the EEG slowing caused by scopolamine
Dringenberg et al. (2002)	Male long evans rats	EEG were recorded in rats pre-treated with reserpine and scopolamine after administration of tacrine, deprenyl, or quipazine	The acetylcholinesterase inhibitor tacrine reversed the EEG slowing caused by scopolamine, the monoamine oxidase inhibitor deprenyl and the serotonergic receptor agonist quipazine restored EEG activation, an effect that was largely unaffected by different scopolamine doses
Dimpfel (2005)	Fisher rats	EEG revealed the pharmacological modulation of brain activity by the selective nicotinic agonist metanicotine as well as the alpha 7 selective nicotinic antagonist methyllycaconitine	Blockade of the cholinergic system resulted in electrical power increases and activation in decreases

the cholinergic system results in increased EEG power. Nonspecific modulation of cholinergic activity by cholinesterase inhibitors such as physostigmine, tacrine and galantamine leads to changes in low-frequency alpha rhythms (7–9.5 Hz) in addition to the delta and high-frequency alpha rhythms (Dimpfel, 2005). These drugs produce a nearly identical pattern of changes on EEG rhythms. Theta (4.75–6.75 Hz) and low-frequency beta (12.75–18.5 Hz) rhythms change to a lesser degree. As for the effects of muscarinic antagonists, biperiden induces a large increase in delta and low-frequency alpha rhythms as well as a general decrease of high-frequency alpha rhythms in cortical and subcortical areas, whereas scopolamine induces an opposite effect (Dimpfel, 2005).

Table 1 summarises the main results of the studies on pharmacological modulation of EEG rhythms in animal models.

5. Pharmacological modulation of spontaneous ongoing EEG rhythms in animal models: interaction between cholinergic agents and other neuromodulatory agents

The interaction between cholinergic agents and other neuromodulatory (noradrenergic, dopaminergic, serotonergic and histaminergic) agents has contributed to the understanding of the physiology of spontaneous ongoing EEG rhythms and cortical arousal (Vertes, 1988; Jones and Cuello, 1989; Semba and Fibiger, 1989; Zaborszky, 1989). The available evidence suggests that these transmitters can indirectly modulate spontaneous ongoing cortical EEG rhythms by an action in the basal forebrain that affects basal forebrain–cortical connectivity. For example, direct infusions of noradrenaline into basal forebrain facilitates desynchronisation of spontaneous ongoing EEG rhythms with the appearance of beta and gamma oscillations (14–40 or higher Hz) and waking behaviour in rats (Cape and Jones, 1998). Electrical stimulation of the noradrenergic locus coeruleus elicits low-voltage beta/gamma cortical EEG rhythms after blockade by systemic anti-muscarinic cholinergic treatment. Such a finding clearly indicates that acetylcholine mediates this activating effect (Dringenberg and Vanderwolf, 1997). Similarly, infusions of histamine or histamine H1 receptor agonists into basal forebrain trigger an increased release of acetylcholine at cortical level and relative desynchronisation of ongoing EEG rhythms (Cecchi et al., 2001). Some effects of noradrenaline and histamine on spontaneous ongoing EEG rhythms and cortical excitability are, therefore, indirect, mediated by the basal forebrain cholinergic system. The fact that depletion of histamine, dopamine or noradrenaline does not result in loss of desynchronised low-voltage beta/gamma EEG rhythms (Whishaw

et al., 1978; Servos et al., 1994) suggests that these systems exert a modulatory role but are not essential for the maintenance of desynchronised spontaneous ongoing EEG rhythms and cortical arousal/activation (see Dringenberg and Vanderwolf, 1997).

As mentioned above, desynchronisation of spontaneous ongoing EEG rhythms induced by selective noradrenergic or dopaminergic stimulation (electrical or agonist-induced) is blocked by cholinergic muscarinic receptor antagonists (Vanderwolf et al., 1980; Berridge et al., 1996; Dringenberg and Vanderwolf, 1997), suggesting that the action of these transmitters on EEG desynchronisation is mediated by acetylcholine. In support of this assumption, direct infusion of noradrenaline or adrenergic agonists into the basal forebrain area elicits EEG desynchronisation (i.e., activation) in anaesthetised and freely moving rats (Berridge et al., 1996; Cape and Jones, 1998). In contrast, desynchronisation of ongoing EEG rhythms induced by serotonin agonists is not affected by large doses of muscarinic receptor antagonists (e.g., 5 and 50 mg kg^{-1} scopolamine and atropine, respectively; Vanderwolf et al., 1980, 1989). These findings suggest that the effects of serotoninergic transmitters on EEG desynchronisation are not mediated by acetylcholine.

Monoamine oxidase inhibitors have also been reported to modulate EEG activity in rodents (Dringenberg et al., 2000a,b, 2002). The monoamine oxidase inhibitor deprenyl (10–50 mg kg^{-1}) or pargyline (20 mg kg^{-1}) restores the desynchronisation of EEG rhythms (i.e., cortical activation) in rats pre-treated with reserpine (10 mg kg^{-1}) or scopolamine (1 mg kg^{-1}; Dringenberg et al., 2000a,b). This effect is largely independent of the dose of scopolamine administered (Dringenberg et al., 2000a). Deprenyl can restore desynchronised, low-voltage beta/gamma EEG rhythms in rats pre-treated with reserpine and scopolamine, and this effect is also independent of the dose of scopolamine (1 or 5 mg kg^{-1}). The insensitivity of the deprenyl-induced EEG effects to scopolamine suggests that these effects are not mediated by a cascade of dopamine and/or noradrenaline stimulation, indirectly eliciting an increase in the release of acetylcholine at the cortical level. Rather, deprenyl directly induces desynchronisation of ongoing EEG rhythms at the cortical level. In contrast, the acetylcholinesterase inhibitor tacrine restores low-voltage beta/gamma rhythms more effectively in rats given 1 mg kg^{-1} scopolamine than in rats given a 5-mg kg^{-1} dose (Dringenberg et al., 2002). Finally, cumulative administration of the 5-hydroxytryptamine (5-HT) receptor agonist quipazine (escalating dose 5 + 5 + 10 mg kg^{-1}, i.p.) also reverses synchronised high-voltage, slow EEG rhythms and restores normal EEG desynchronisation (i.e., activation) in rats given reserpine or scopolamine (Dringenberg et al., 2002). Similarly to

the effect of deprenyl, the effect of quipazine is not affected by the dose of scopolamine used (1 or 5 mg kg^{-1}), indicating that the effect is not mediated by the cholinergic system.

The co-administration of acetylcholinesterase and monoamine oxidase inhibitors desynchronises spontaneous ongoing EEG rhythms in rats when compared to the single use of either inhibitor (Dringenberg et al., 2000a,b). Blockade of cholinergic–monoaminergic neuromodulation abnormally synchronises ongoing EEG rhythms as revealed by high-amplitude slow rhythms. This effect is reversed by deprenyl (10–50 mg kg^{-1}) or tacrine (1–20 mg kg^{-1}) and co-administration of a subthreshold dose of deprenyl plus tacrine is markedly more effective (Dringenberg et al., 2000a). Neither tacrine (5 mg kg^{-1}) nor deprenyl (10 mg kg^{-1}) alone reduces water maze deficits due to cholinergic-monoaminergic hypofunction. In contrast, co-treatment (using the above doses) improves performance (Dringenberg et al., 2000a). Therefore, cholinergic–monoaminergic co-treatment may provide a useful pharmacological approach to restore physiological and cognitive deficits due to neurotransmitter deficiencies in AD.

An interesting study in rats (Dringenberg et Diavolitsis, 2002) also reported that the serotonin re-uptake inhibitor fluoxetine (10 and 20 mg kg^{-1}) restores the normal desynchronisation pattern of spontaneous ongoing EEG rhythms that had been abolished by combined treatment with reserpine (10 mg kg^{-1}) and scopolamine (1 mg kg^{-1}) in a frequency-dependent manner. Fluoxetine alone is ineffective in reversing all effects of abnormal synchronisation of spontaneous ongoing EEG rhythms (i.e., EEG slowing) produced by reserpine–scopolamine administration. However, fluoxetine can suppress EEG synchronisation in the alpha (8–12 Hz) band when administered with the 5-HT(1A) receptor antagonist WAY 100635 (0.5 mg kg^{-1}). Furthermore, fluoxetine, independently of WAY 100635, markedly potentiates the effectiveness of the inhibitor tacrine (5 mg kg^{-1}) on its ability to restore the normal desynchronisation of ongoing EEG rhythms between 4 and 30 Hz. These data indicate that 5-HT uptake inhibition and concurrent 5-HT(1A) receptor blockade produce a limited normalisation of the ongoing EEG rhythms altered by monoaminergic–cholinergic blockade. However, fluoxetine strongly potentiates the efficacy of tacrine in restoring the normal desynchronisation of spontaneous ongoing EEG rhythms.

Another interesting study reported that combined pharmacological stimulation of the cholinergic system and 5-HT sub-type 2 receptors can suppress cortical high-voltage spindles reflecting thalamocortical oscillations in aged rats (Jäkälä and Riekkinen, 1997). The cholinesterase inhibitors tetrahydro-aminoacridine (THA: 1.0 and 3.0 mg kg^{-1}), physostigmine (0.36 mg kg^{-1}), and the 5-HT2 receptor agonist 1 2,5-dimethoxy-4-iodoamphetamine (DOI; 0.3 and 1.0 mg kg^{-1} sc) can suppress high-voltage spindles in aged rats. A combination of sub-threshold doses of THA (0.3 mg kg^{-1} i.p.) and DOI (0.1 mg kg^{-1} sc) suppresses high-voltage

Table 2
Pharmacological modulation of spontaneous on-going EEG rhythms: interaction between cholinergic and other neuromodulatory agents.

Study	Animal model	Experimental design	Findings
Cape and Jones (1998)	Wistar rats	EEG were recorded to determine the effect of noradrenergic and serotonergic modulation of the cholinergic neurons	Noradrenaline facilitate gamma activity and elicite waking, serotonin diminish gamma activity and not significantly affect slow wave sleep
Dringenberg and Vanderwolf (1997)	Male long evans rats	Effects of administration of the anti-muscarinic agent scopolamine after 100-Hz electrical stimulation of the amygdaloid complex or dorsal raphen on EEG activity	Electrical stimulation of the noradrenergic locus coeruleus elicited low voltage beta/gamma EEG rhythms, which were blocked by systemic anti-muscarinic cholinergic treatment
Cecchi et al. (2001)	Wistar rats	Evaluation of the the effect of the perfusion of the nucleus basalis magnocellularis with histamine agonists and antagonists	The activation of histamine H1 (methylhistaprodifen) receptors in the nucleus basalis magnocellularis increases spontaneous release of acetylcholine from the cortex
Servos et al. (1994)	Rats	Evaluation of the the effect of intraperitoneal injection of a specific inhibitor of histidine decarboxylase in rats	Intraperitoneal injection of alpha-fluoromethylhistidine has no effect on either low voltage fast activity (LVFA) in the neocortex or on rhythmical slow activity (RSA) in the hippocampus
Vanderwolf et al. (1980)	Rats	Replacement of specific monoamines or injection of suitable agonists in reserpine pretreated rats	Beta-phenylethylamine was quite effective in restoring atropine-resistant LVFA, conversely several compounds alone or in various combinations failed
Berridge et al. (1996)	Sprague dawley rats	Effect of the infusions of β-agonist and β-antagonist in basal forebrain on EEG activity	A region of the basal forebrain, situated either within or immediately lateral to the medial septum, is a site at which norepinephrine acts to modulate forebrain EEG in the rat through actions at β-receptors
Vanderwolf et al. (1989)	Rats	Effect of multiple intrabrainstem injections of 5,7-dihydroxytryptamine in rats on forebrain levels of serotonin and 5-hydroxyindoleacetic acid and on EEG activity	This treatment strongly reduced or abolished atropine-resistant cerebral activation in most cases but did not reduce atropine-sensitive cerebral activation which appears to be dependent on ascending cholinergic projections from the basal forebrain to the cerebral cortex
Dringenberg et al. (2002)	Male long evans rats	Frequency-specific EEG effects of the 5-HT re-uptake inhibitor fluoxetine to restore EEG activation abolished by combined treatment with the monoamine depletor reserpine and the muscarinic antagonist scopolamine	Fluoxetine slowed EEG after cholinergic–monoaminergic blockade
Jäkälä and Riekkinen (1997)	Male han:wistar rats	Combined stimulation of the cholinergic system and 5-hydroxytryptamine (5-HT) subtype 2 receptors can suppress neocortical high-voltage spindles (HVSs) reflecting thalamocortical oscillations in aged rats	Cholinesterase inhibitors—tetrahydro-aminoacridine (THA) and physostigmine and a 5-HT2 receptor agonist (DOI) suppressed HVSs in aged rats. A combination of subthreshold doses of THA and DOI suppressed HVSs more effectively than either drug alone. Ketanserin reduced the efficacy of cholinesterase inhibitors
Rispoli et al. (2006)	Male wistar rats	Intraperitoneal administration of choline pivaloyl ester combined with tacrine or galantamine has been performed in aged rats and also in rats that have been subjected to experimental lesions of the nucleus basalis magnocellularis	The pharmacological cholinergic stimulation is able to desynchronize spontaneous on-going EEG rhythms, especially at lower frequency bands. Cholinergic drug combinations reversed the abnormal synchronization of on-going EEG rhythms

spindles more effectively than either drug alone. Furthermore, the 5-HT2 receptor agonist ketanserin (5.0 and 20.0 mg kg^{-1} sc) can reduce the efficacy of THA (1.0 and 3.0 mg kg^{-1} i.p.) and physostigmine (0.12 and 0.36 mg kg^{-1} i.p.) in decreasing high-voltage spindles. THA and ketanserin slightly decreased cortical activity of the rats, whereas physostigmine tended to increase it and DOI significantly increased it. Taken together, these results suggest that the effects of these drugs on cortical activity may be separated from their effects on generation of thalamocortical oscillations.

Combined pharmacological stimulation of the cholinergic system (i.e., i.p. administration of choline pivaloyl ester combined with tacrine or galantamine) has been performed in aged rats and also in rats subjected to basal forebrain lesions (Rispoli et al., 2006). The results demonstrated that the pharmacological cholinergic stimulation is able to desynchronise spontaneous ongoing EEG rhythms, especially at lower frequency bands (delta 0.25–3 and theta 4–7 Hz). Furthermore, cholinergic drug combinations reversed the abnormal synchronisation of ongoing EEG rhythms (high-voltage delta rhythms and HVS) in aged rats. Finally, the combined administration of the choline pivaloyl ester and tacrine improved behavioural performances (i.e., object discrimination, percentage T-maze alternation, passive avoidance and decreased escape latency in the Morris water maze) both after basal forebrain lesion and in aged rats.

Table 2 summarises the main results of studies on the interaction between cholinergic and other neuromodulatory agents.

6. Effects of SD on EEG rhythms in animal models

Three sets of data are briefly discussed in this section: (1) the physiological model of the generation of EEG rhythms during sleep stages, (2) the main caveats of the experiments on SD in animal models and (3) the main effects of drug treatments on sleep.

A widely accepted model of sleep regulation postulates that sleep is under the control of two fundamental processes, the circadian and homeostatic processes (Daan et al., 1984). The circadian process governs the timing of virtually all 24 h behavioural, physiological and molecular processes, including sleep and wakefulness (see, e.g., Rosenwasser and Turek, 2005). Advancing age can alter sleep patterns, reducing sleep length and high-voltage EEG slow-wave activity, or delta power (0.5–4 Hz), in non-rapid eye movement (NREM) sleep. Although the mechanism by which these alterations occur is unknown, age-related changes in normal circadian processes may play a role. For example, advanced age produces cellular and functional changes in the suprachiasmatic nucleus (SCN) and alters the amplitude and phase of circadian rhythms (e.g., Aujard et al., 2006; Bentivoglio et al., 2006). Reduced sleep has been found in young mice carrying a mutation of the *Clock* gene (Naylor et al., 2000). In aged rats, reductions in the maximal firing rate of SCN neurons have been noted; moreover, transplantation of foetal SCN tissue has been shown to restore circadian behaviour (Li and Satinoff, 1998).

The sleep homeostatic process regulates the propensity for sleep determined by the amount of prior wakefulness. EEG slow-wave activity in NREM sleep has been used as the main quantitative operational measurement of sleep homeostasis, and is commonly equated with sleep intensity or sleep depth (Steriade, 2005). *In vivo* studies have shown that in rodents acute (e.g., 6–24 h) total sleep deprivation (TSD) leads to an immediate compensatory increase in NREM delta power (Rechtschaffen et al., 1999). In addition, animals usually exhibit a positive rebound in NREM and REM sleep time during the recovery opportunity (Laposky et al., 2005).

The response to acute TSD has served as major paradigm for investigations into the physiological and molecular mechanisms

that underlie sleep homeostatic regulation. In contrast, rat studies by Rechtschaffen et al. (1999) have shown that the compensatory sleep response to acute TSD does not generalise to longer durations of sleep loss. For example, after 48–96 h of continuous TSD, rats exhibit a large REM rebound but fail to generate any positive rebound in EEG NREM delta power. Furthermore, NREM sleep time is actually decreased to below baseline levels, indicating that the animals do not regain what was lost in these two sleep parameters. These data provide evidence that the sleep homeostatic process may differ between acute and chronic TSD conditions.

Rats can tolerate prolonged (10–18 week) partial sleep restriction of a few hours per day (Licklider and Bunch, 1946). Rats deprived of sleep during the 12-h light phase for 5 consecutive days generate a similar homeostatic response (i.e., increased NREM delta power and sleep amount) during each of the 12-h dark-phase recovery opportunities. This suggests that animals fully compensate this mild SD on a daily basis (Lancel and Kerkhof, 1989).

A number of key SD parameters may impact sleep EEG rhythms, especially the length of SD and the procedures to maintain the animals awake. Rebound from 1 day of SD is sufficient to produce subsequent rebound of high-amplitude, slow-wave EEG activity in NREM sleep, usually accompanied by substantial REM sleep rebound (for a review, see Robert et al., 1999). In contrast, chronic SD produces long-lasting rebound of REM sleep with no rebound of high-amplitude NREM sleep. Furthermore, EEG studies of SD based on platform techniques (i.e., animals are placed on top of a small platform surrounded by water) have reported that both NREM and REM sleep are affected (Grahnstedt and Ursin, 1985; Maloney et al., 1999; Suchecki et al., 2000; Van Luijtelaar and Coenen, 1986). However, selective REM suppression has also been reported in the small platform groups, with no significant variation in NREM for either small or large platform groups (Porkka-Heiskanen et al., 1995). These differences could reflect the impact of social isolation versus the possibility for social interaction in the group platform SD approach. In support to this assumption, animals on large platforms in a single platform set-up showed slow-wave sleep reduction only in the first 24 h of SD (−29%), whereas their counterparts subjected to the multiple platforms (i.e., rats placed in a large tank containing a number of platforms) showed NREM reductions throughout the 4 days of SD (Machado et al., 2004).

In addition to the experimental protocols used for SD, the procedure used for EEG data analysis also needs to be carefully considered to interpret the effects of SD on brain mechanisms generating sleep EEG activity. Indeed, two phases can be distinguished within NREM sleep in rats: one is characterised by low- to medium-voltage EEG and the other by high-amplitude, slow-wave EEG activity (for a review, see Robert et al., 1999). It should be considered that the effects of SD may be especially evident only in terms of augmented high-amplitude slow waves (for review, see Rechtschaffen et al., 1999).

In human subjects, SD impairs performance in several verbal and non-verbal memory tasks (Smith and MacNeill, 1994; Walker et al., 2002a,b) and affects a variety of cognitive and attentional abilities (Linde and Bergstrom, 1992; Harrison and Horne, 1999; Doran et al., 2001; Belenky et al., 2003; Kendall et al., 2006; Oken et al., 2006; Drummond et al., 2006; Killgore et al., 2006, 2008; Bocca and Denise, 2006; Fimm et al., 2006; Santhi et al., 2007). From the point of view of EEG analysis, TSD has been reported to enhance the frontal predominance of delta rhythms (2–4 Hz) only in the left hemisphere (Achermann et al., 2001; Kattler et al., 1994); this effect may be driven by the functional asymmetry between the dominant and non-dominant hemisphere (Achermann et al., 2001; Kattler et al., 1994). During TSD, theta rhythms (4–7 Hz) increased in relation to subjective sleepiness and fatigue (Dumont et al., 1999; Cajochen et al., 1995). Furthermore, the

alpha rhythms (8–12 Hz) during TSD showed different responses between eyes-open and -closed conditions in the resting state. Under eye-open conditions, alpha rhythms increase over time throughout SD (Cajochen et al., 1995; Torsvall and Åkerstedt, 1987; Corsi-Cabrera et al., 1996; Stampi et al., 1995). In contrast, in the eyes-closed resting state alpha rhythms decrease, with increased sleepiness level following nocturnal SD (Daurat et al., 1996). Extended SD for 40 h enhances the modulation of theta and alpha rhythms during mental tasks (Corsi-Cabrera et al., 1996). During TSD, exposure to bright light (more than 2500 lux) under a rest condition has been reported to be sufficient to delay the increase in theta and alpha rhythms and subjective sleepiness (Kräuchi et al., 1997; Daurat et al., 1996).

Table 3 summarises the effects of SD on ongoing EEG markers in human subjects.

In relation to the testing of the restorative effects of drugs used in AD, including donepezil and memantine, on SD in animal models, it should be recalled that cholinergic activity plays a crucial role in sleep-dependent memory consolidation. Furthermore, the acetylcholinesterase inhibitor donepezil has been found to increase sleep-related procedural memory consolidation in healthy aged subjects as well as spectral parameters of sleep typically linked to plasticity-related processes during sleep, that is, sigma and delta rhythms (Hornung et al., 2009). Specifically, donepezil led to an increase in sigma rhythms (about 12–15 Hz) during stage 2 NREM sleep and delta activity during slow-wave sleep, suggesting that an acetylcholinesterase inhibitor facilitates processes of sleep-dependent memory consolidation in aged subjects. These data complement previous preliminary evidence showing positive effects of donepezil in the treatment of narcolepsy (Niederhofer, 2006). Chronic administration of donepezil was, however, unable to restore the ageing-related decrease in REM sleep in rats (Zizzari et al., 2006).

Memantine is licenced for the treatment of moderate-to-severe AD, and acts as a non-competitive antagonist on N-methyl-D-aspartic acid (NMDA) receptors. Memantine has remarkable effects on sleep. In rats, memantine significantly increases sleep latency and total time of wake, and decreases total NREM and REM sleep time (Ishida and Kamei, 2009). Memantine can prevent excessive sleepiness in sleep-deprived rats (Deurveilher et al., 2009; Lima et al., 2008). Moreover, the wakefulness-promoting activity of memantine seems to be more potent than that of methylphenidate (Ishida and Kamei, 2009). It is therefore not surprising that agitation, restlessness and hyperexcitability have been reported as adverse effects during memantine therapy of moderate-to-severe AD patients (Guay, 2003). In rats, memantine can increase sleep latency and total time of wakefulness during the sleep period. Of note, this effect may be promoted by D1 but not D2 dopamine receptors as it may be modulated by SCH23390 but not raclopride (Ishida et al., 2010). Memantine may induce dopamine release in the prefrontal cortex eliciting consequently arousal and increases in the animal's locomotor activity (Spanagel et al., 1994; Hanania and Zahniser, 2002). It is important to note that memantine produces in rodents, behavioural effects and cognitive deficits similar to other NMDA receptor antagonists such as ketamine (Gilmour et al., 2009; Dix et al., 2010).

The synergistic administration of donepezil and memantine has been profiled on sleep EEG rhythms in rats (Ishida and Kamei, 2009; Ishida et al., 2009, 2010). This combination of AD therapeutic approaches increases sleep latency and total waking time, and decreases total non-REM sleep time. Furthermore, donepezil and memantine antagonise the decrease in sleep latency induced by morphine. Administration of either drug alone produces lower effects on each measure suggesting synergy between the mechanisms. Memantine decreases total REM sleep time and NREM stage 1, whereas it increases NREM sleep stage 3. Galantamine treatment results in no significant influence on EEG sleep pattern (Ishida and Kamei, 2009).

Table 4 summarises the effects of SD on ongoing EEG markers in rats.

7. Effects of hypoxia on EEG rhythms recorded in animal models

Hypoxia is caused by a reduction in blood supply due to a variety of pathophysiological or traumatic insults to the brain. It is

Table 3
Effects of sleep deprivation challenge on EEG rhythms in humans.

Study	Experimental design	Findings
Achermann et al. (2001)	Eight healthy, young, right-handed subjects were recorded during baseline sleep and recovery sleep after 40 h of SD	Sleep deprivation affected power spectra in all derivations. However, hemispheric asymmetries were observed in the delta range. Sleep deprivation enhanced the anterior predominance of delta activity in the left hemisphere but not in the right one
Dumont et al. (1999)	EEG of 14 normal subjects were recorded every 2 h during 38 h of SD	Adjacent narrow frequency bands with similar temporal trends were grouped into frequency clusters. Clusters I (2.00–7.75 Hz) and III (11.00–14.75 Hz) exhibited similar time courses which may reflect both the duration of time awake and a circadian modulation. Cluster II (8.00–10.75 Hz) was characterised by a time course similar to the circadian modulation of core body temperature. Cluster V (18.00–24.75 Hz) was correlated with subjective sleepiness and may reflect the increasing effort made by subjects to perform the task as sleep deprivation lengthened
Cajochen et al. (1995)	EEG power density and self-rated fatigue were assessed in nine healthy women during 40 h SD	EEG power density in the 6.25- to 9.0-Hz frequency range progressively increased across the recordings, suggesting an endogenous homeostatic component in the regulation of the theta/alpha frequencies under constant conditions. Subjective fatigue ratings and the theta/alpha power density correlated significantly
Torsvall and Åkerstedt (1987)	EEG, EOG and ECG were recorded on portable recorders on 11 train drivers during 1 night and 1 day journey	The results showed that rated sleepiness increased sharply during the night journey. A similar pattern was seen for spectral power density in the alpha band, SEM and, to a lesser extent, also for power in the theta and delta bands. he intra-individual correlations were very high between rated sleepiness and, alpha and theta power density
Corsi-Cabrera et al. (1996)	EEG, oral temperature (OT), and reaction time (RT) in a visual vigilance task was recorded in nine young adult male subjected to 40 h of SD	Absolute power (AP) was calculated for 4–20 Hz (full band) and for theta, alpha 1, alpha 2, and beta 1. SD induced an increase in RT and AP of the full band at C3 and C4, of all bands at C3, of theta at T3, and of beta 1 at T4. RT and EEG power showed a linear increase with accumulating hours of wakefulness. The increment in RT also correlated with the increase in EEG power

Table 4
Effects of sleep deprivation challenge on EEG rhythms in rats.

Study	Experimental design	Findings
Laposky et al. (2005)	Animals, after surgery, underwent EEG baseline recording, then were sleep deprived for 6 h	Ob/ob mice displayed an attenuated diurnal rhythm of sleep-wake stages, NREM delta power, and locomotor activity
Lancel and Kerkhof (1989)	The study examined the differences between sleep duration and EEG when sleep was restricted to the rest- or activity-phase for 5 successive days, achieved by repeated sleep deprivation in the dark (DSD) or light-period (LSD)	In the first hours after sleep deprivation the delta activity during NREM-sleep was enhanced in LSD and to a lesser extent in DSD. This effect diminished over the consecutive days in both experiments. The EEG energy gained during sleep and its accumulation pattern on each day in DSD and LSD were strikingly similar, thereby reflecting a homeostatic process
Grahnstedt and Ursin (1985)	Rats were sleep deprived by the platform method to look for differential effects on light and deep slow wave sleep depending on platform size, Sleep was recorded during a baseline light period, continuously during 48 h of SD and during the first lights on recovery period	Light slow wave sleep (SWS-1) was comparable to baseline while deep slow wave sleep (SWS-2) was still significantly reduced. In the small platform group both SWS-2 and REM sleep was considerably reduced on day 2
Suchecki et al. (2000)	Animals implanted with bipolar electrodes in the cortex, hippocampus and neck muscle, were exposed to the modified multiple platform method (MMPM), in which cage-mate rats were placed onto narrow platforms (NP), onto wide platforms (WP) or onto a grid for 90 h	Results of sleep rebound, the data indicated that placement of animals onto narrow platforms in the MMPM was an effective PS deprivation method and the grid should be considered as an adequate environmental control
Van Luijtelaar and Coenen (1986)	Three different techniques were used to study the effects of 72 h deprivation of paradoxical sleep on percentages total sleep, light slow wave sleep, deep slow wave sleep and paradoxical sleep during deprivation and recovery periods in rats. The paradoxical sleep deprivation methods used were the classical platform, the pendulum and the multiple platform techniques	The recovery is characterised by an immediate rebound of paradoxical sleep, completed within 2 days, as well as rapid re-normalisation of sleep percentages. A small rebound of deep slow wave sleep was recorded at the end of the dark period during the first three recovery days
Porkka-Heiskanen et al. (1995)	Animals were deprived of REM sleep with the platform method deprivation lasted 8, 24, or 72 h on small (REMSD) or large (control) platforms.	Polygraphy showed that small-platform treatment caused effective and selective REMSD, no significant variation in NREM for either small or large platform groups
Machado et al. (2004)	Sleep EEG was continuously recorded during baseline, during 96 h of sleep deprivation and during 4 days of recovery, the modified multiple platform technique for SD was used	Both multiple- and single-platform techniques completely abolished paradoxical sleep during the deprivation period, but also resulted in significant decreases in slow wave sleep (−31% and −37%, respectively)
Deurveilher et al. (2009)	Animals were ovariectomized and implanted subcutaneously with Silastic capsules containing oil vehicle, 17 beta-estradiol and/or progesterone. After 2 weeks, sleep/wake states were recorded during a 24-h baseline period, 6 h of total sleep deprivation induced by gentle handling during the light phase, and an 18-h recovery period	Following sleep deprivation, all rats showed rebound increases in NREMS and REMS, but the relative increase in REMS was larger in females receiving hormones, especially high estradiol. In contrast, the normal increase in NREMS EEG delta power during recovery was attenuated by all hormone treatments
Ishida et al. (2010)	The effect of memantine on excessive sleepiness after 6 h sleep deprivation was studied in comparison with that of methylphenidate was studied rats with chronically implanted electrodes into the cortex and dorsal neck muscle	Memantine and methylphenidate caused a significant increase of sleep latency compared with the control group. Furthermore, a significant increase in total awake time and significant decreases in total NREM sleep and REM sleep times were observed by administration of memantine and methylphenidate compared with control in sleep deprivation rats

hypothesised to induce glucose hypometabolism in the hippocampus and other key brain areas subserving cognitive functions including memory. During sleep, repeated hypoxic events may affect respiratory cholinergic mechanism, respiratory regulation, upper airway patency and cerebral oxygenation (Peers et al., 2009; Scragg et al., 2005; Daulatzai, 2010). Diurnally, hypo-oxygenation of the brain might be also due to chronic cerebrovascular and vasomotor deficits provoked by a poor cholinergic tone. These alterations may cause amyloid-beta deposition extracellularly and neurofibrillary cytopathology within cholinergic and other neurons (Peers et al., 2009; Scragg et al., 2005; Daulatzai, 2010). For this reason, hypoxia is a challenge model of interest for studies on preclinical models in AD.

During hypoxia in rats, a decrease of total power of spontaneous ongoing EEG rhythms has been reported (Jensen et al., 1991; Yang et al., 1994; Zagrean et al., 1995; Budzinska and Ilasz, 2007). However, other findings have described a decrease of theta power only (Rabinovici et al., 2000). In contrast, delta power is reported to increase (Akopian et al., 1982; Budzinska and Ilasz, 2007). The respiratory response to hypoxia is accompanied by gradual decrement of the total power of EEG (Budzinska and Ilasz, 2007). Relative EEG power increased in the delta frequency range and decreased in the remaining frequency ranges (Budzinska and Ilasz, 2007). During hypoxic bradypnoea or apnoea, the total power of EEG strongly diminished or ceased (Budzinska and Ilasz, 2007). Each episode of hypoxia caused similar cortical effects. However, in

comparison with the baseline level, the total power of EEG decreased gradually, while the power of the delta frequency range increased in subsequent hypoxic episodes (Budzinska and Ilasz, 2007). Following the last hypoxic exposure, ongoing EEG rhythms recovered within 40–60 min. Furthermore, gamma oscillations (30–100 Hz) were rapidly blocked by hypoxia, and prolonged hypoxia reduced the capability to generate such modulation of ongoing EEG rhythms.

Complex functional connectivity among brain regions is not essential for the effects of hypoxia on EEG rhythms to be evident. In a rat ventral hippocampal slice preparation, kainate-induced gamma oscillations reversibly declined 40 s after the onset of 3 min of hypoxia (Fano et al., 2007). Repetition of such hypoxic periods led to accumulative impairment of gamma activities. In contrast, 6 min of hypoxia led to a transient anoxic depolarisation, after which gamma oscillations remained almost completely blocked (Fano et al., 2007).

8. Effects of TMS on EEG rhythms recorded in animal models

TMS enables the quantification of motor system excitability and transient 'virtual' functional lesions of cortical networks subserving cognitive functions including attention and episodic memory. Although this approach is routinely used in humans, its application to laboratory animal species is rare and little is known about the

characteristics of animal TMS. Of note, TMS is non-invasive and produces predominantly interneuronal stimulation at low intensity, enabling its use in evaluating various models of brain injury and motor recovery (Luft et al., 2001). Spinal cord injury (Magnuson et al., 1999) and anaesthesia (Ebert and Ziemann, 1999) have been assessed using TMS in the rat.

Animal studies have elucidated TMS mechanisms (Wang et al., 1996) and demonstrated its safety (Russell et al., 1994; Post et al., 1999). Furthermore, the feasibility and reproducibility of TMS in the rat have also been assessed (Luft et al., 2001). It has also been shown that lateralised TMS leading to asymmetric brachioradialis activation is feasible with conventional TMS equipment in anaesthetised rats (Rotenberg et al., 2010). Furthermore, TMS, like electroconvulsive therapy, evokes in rats effects suggestive of anti-depressive action but with fewer undesirable side effects (Zyss et al., 2000). It has been reported that TMS stimulation induces in rats a reduction in bursts duration of spike-wave discharge. This effect was most pronounced 30 min from the moment of cessation of stimulation, when a decrease of 31.4% was noted in comparison with a sham-stimulated control group (Godlevsky et al., 2006).

In contrast to the effects of the other challenge models described, the effects of TMS on EEG rhythms have been described in detail in humans (Paus et al., 2001; Brignani et al., 2008; Fuggetta et al., 2008; Capotosto et al., 2009) but are still almost unexplored in animals. Only one study has reported the development of an EEG recording system for multimodal application of TMS and EEG. This system comprises electrodes and amplifiers compatible with TMS (single and rapid-rate) in animal studies (Ives et al., 2006). Specifically, this study developed a new subdermal wire electrode ideal for animal biopotential signal recording. This equipment avoids the possibility that the magnetic properties of electrodes could affect the TMS pulse. Indeed, this would cause movement or influence the distribution of the applied magnetic field. This methodological advancement should encourage further studies of TMS and EEG recordings in laboratory animals (Ives et al., 2006).

9. Cortical spontaneous ongoing EEG rhythms in transgenic animal models of AD

Many laboratories have produced transgenic mice that recapitulate certain features of AD pathology, for example, mice which over-express the amyloid precursor protein (APP), which is associated with familial forms of AD (Howlett and Richardson, 2009). Histopathological assessment shows that APP transgenic mice demonstrate an accumulation of Abeta in plaques from an early age; these plaques are invariably surrounded by activated inflammatory cells such as astrocytes and microglia, as is common in the AD brain.

Transgenic mice over-expressing human APP cDNAs harbouring the 'Swedish' mutation and PS-1 cDNAs harbouring the A264E mutation recapitulate some of the neuropathological features of AD. Indeed, these mice exhibit elevated levels of the highly fibrillogenic amyloid beta1-42 peptide (Abeta42) and develop amyloid plaques in their brains around the age of 9 months. Wang et al. (2002) tested whether ongoing EEG rhythms of these transgenic mice differ from those of wild-type littermates, and whether the alteration in EEG activity progresses with the accumulation of Abeta. Their findings concluded that APP/PS1 mice are characterised by reduced cortical ongoing theta rhythms and enhanced beta and gamma rhythms, but these changes are not age-dependent and therefore independent of amyloid load in the brain. APP single-mutant mice were characterised by similar EEG alterations in theta, beta and gamma bands as APP/PS1 double-mutant mice, while PS1 single-mutant mice did not differ from wild-type littermates.

In parallel to these EEG results, the amount of insoluble Abeta40 and Abeta42 levels robustly increased in APP/PS1 double-mutant mice and insoluble Abeta40 moderately increased also in APP single-mutant mice. Soluble Abeta42 was found in all APP mutant mice but also in lower concentrations in PS1 single-mutant mice. Plaques are deposited in 13-month-old APP/PS1 double-mutant mice but not in 8-month-old double-mutant or 13-month-old single-mutant mice. These results suggest that the alteration of ongoing EEG rhythms in APP/PS1 double-mutant and APP single-mutant mice is related to their APP genotype rather than to deposition of beta-amyloid in the brain *per se*.

Effects of Abeta on mechanisms of synchronisation/desynchronisation of the cortical neuronal network described above have been associated with susceptibility of transgenic rodent models of AD (Palop and Mucke, 2009). Indeed, AD is associated not only with cognitive decline but also with an increased incidence of seizures. Seizure activity in AD has been widely interpreted as a secondary process resulting from advanced stages of neurodegeneration, perhaps in combination with other ageing-related factors. However, recent findings in animal models of AD have challenged this concept, raising the possibility that aberrant excitatory neuronal activity represents a primary upstream mechanism that may contribute to cognitive deficits in these models (Palop and Mucke, 2009). Indeed, hAPPJ20 mice have intermittent, unprovoked EEG seizures involving diverse regions of the neocortex and hippocampus not accompanied by tonic or clonic motor activity. This suggests that high levels of Abeta are sufficient to elicit epileptiform EEG activity *in vivo* in the absence of behavioural symptoms of neurodegeneration. Consistent with this, aberrant network synchronisation may be considered as a primary effect of high Abeta levels rather than a secondary consequence of extensive neurodegeneration. This hypothesis is supported by findings showing EEG epileptiform activity in transgenic models of AD such as hAPPJ9/FYN, Tg2576 and hAPP/PS1 mice (Tanila et al., 2008; Chin et al., 2007). Some of the epileptic effects in these mice may be due to reactive astrocytes. Indeed, in an epileptogenic cortical lesion in mice, neighbouring astrocytes showed overlap of their processes with loss of astrocytic domains (Oberheim et al., 2008). These findings suggest that reorganisation of astrocytes may, in concert with dendritic spine changes and new synapse formation, provide a structural basis for recurrent excitation generating EEG seizures in animal models and humans.

This issue is of high relevance as ApoE4 carriers without dementia (i.e., the most important independent genetic risk factor of AD) showed signs of epileptiform activity and sharp waves on EEG after hyperventilation, although their EEG was normal under resting conditions (Ponomareva et al., 2003). Similar changes have been found in subjects with high risk of developing familial AD, such as first-order relatives of patients with early-onset AD (Ponomareva et al., 2003). Presence of ApoE4 also exacerbates epilepsy and promotes memory impairment in patients with long-standing, intractable, temporal lobe epilepsy (Busch et al., 2007). These data indicate that the major genetic risk factor for developing AD (i.e., ApoE4) is associated with increased network excitability in individuals without dementia. Such type of network dysfunction may play an early role in the establishment of pathogenic cascades leading to AD. Consequently, studies of ongoing EEG markers may be of high importance in the translational evaluation of abnormal cortical arousal in transgenic mice and AD subjects.

A further intriguing question is whether the effects of Abeta on spontaneous ongoing EEG rhythms, cognition and behavioural abnormalities associated with AD (i.e., anxiety, agitation and psychosis) can be mitigated by cholinergic therapy. The selective and potent alpha7 nicotinic acetylcholine receptor agonist ABT-107 was evaluated in rats and tau/APP transgenic AD mice

(Bitner et al., 2010). Rats concurrently infused with ABT-107 and donepezil at steady-state levels consistent with clinical exposure showed improved short-term recognition memory. Compared with nicotine, ABT-107 did not produce behavioural sensitisation in rats or exhibit psychomotor stimulant activity in mice. In addition, continuous infusion of ABT-107 reduced spinal tau hyperphosphorylation in tau/APP transgenic AD mice. ABT-107 administered acutely at 0.1, 1 and 10 µmol kg^{-1} i.p. did not alter high-voltage, slow-wave EEG activity at 1–4-Hz oscillations, typically measured to characterise the effects of active compounds on EEG arousal and behavioural drowsiness. Due to the limitation of EEG data analysis to slow waves, a clear picture of the effects of the pharmacological manipulations in transgenic AD mice and their wild-type counterparts remains to be obtained.

10. Conclusions

We here reviewed the literature on spontaneous, ongoing, resting-state EEG rhythms as potential biomarkers for preclinical research in AD. Antagonists of cholinergic neurotransmission can synchronise spontaneous ongoing EEG rhythms in terms of enhanced power of EEG low frequencies and decreased power of EEG high frequencies. Acetylcholinesterase inhibitors and serotonergic drugs can restore a normal pattern of EEG desynchronisation. SD and hypoxia challenges also produce abnormal synchronisation of spontaneous ongoing EEG rhythms in rodents. The feasibility and reproducibility of TMS challenge were demonstrated in rodents but information of EEG after TMS manipulation is very limited. In transgenic mice over-expressing human APPswe and PS1-A264E mutant cDNAs, spontaneous ongoing EEG rhythms are altered at several low and high frequencies, but not as a function of the deposition of Abeta in the brain.

The present review provides indication of the expected changes of spontaneous ongoing EEG rhythms in response to the described experimental manipulations, as well as the possible effects of pharmacological agents for the symptomatic treatment of AD. The large amount of data critically evaluated in the present review provides a knowledge platform of high interest for the development of translational protocols for drug testing in AD research. In this context, we propose that in rodents the most informative preclinical EEG markers for translational purposes are ongoing delta (slow-wave, 1–4 Hz) and theta (4–7 Hz) rhythms. Scopolamine increases delta rhythms, whereas acetylcholinesterase inhibitors normalise them. On the other hand, SD seems to be the most tested and reliable non-pharmacological challenge in preclinical EEG research. The clinical neurophysiological counterpart of these preclinical data could be represented by the use of the resting state delta/alpha ratio and SD in healthy volunteers at the early stages of the evaluation of new symptomatic drugs for improving cognitive processes in AD. It is expected that in healthy volunteers these EEG markers are altered by SD and are 'protected' by chronic administration of acetylcholinesterase inhibitors. This model including spectral EEG markers and a non-pharmacological challenge may represent a useful reference for the selection of new symptomatic drugs coming from preclinical research on AD. We are going to test this hypothesis in the framework of the IMI project, PharmaCog.

In conclusion, spectral EEG markers (e.g., slow-wave power density) and non-pharmacological challenges (e.g., SD) may contribute to improve the early stages of evaluation of new symptomatic drugs in both preclinical and clinical research on AD.

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