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Cholinergic modulation of event-related oscillations (ERO)

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Abstract

The cholinergic system in the brain modulates patterns of activity involved in general arousal, attention processing, memory and consciousness. In the present study we determined the effects of selective cholinergic lesions of the medial septum area (MS) or nucleus basalis magnocellularis (NBM) on amplitude and phase characteristics of event related oscillations (EROs). A time–frequency based representation was used to determine ERO energy, phase synchronization across trials, recorded within a structure (phase lock index, PLI), and phase synchronization across trials, recorded between brain structures (phase difference lock index, PDLI), in the frontal cortex (Fctx), dorsal hippocampus (DHPC) and central amygdala (Amyg). Lesions in MS produced: (1) decreases in ERO energy in delta, theta, alpha, beta and gamma frequencies in Amyg, (2) reductions in gamma ERO energy and PLI in Fctx, (3) decreases in PDLI between the Fctx–Amyg in the theta, alpha, beta and gamma frequencies, and (4) decreases in PDLI between the DHPC–Amyg and Fctx–DHPC in the theta frequency bands. Lesions in NBM resulted in: (1) increased ERO energy in delta and theta frequency bands in Fctx, (2) reduced gamma ERO energy in Fctx and Amyg, (3) reductions in PLI in the theta, beta and gamma frequency ranges in Fctx, (4) reductions in gamma PLI in DHPC and (5) reduced beta PLI in Amyg. These studies suggest that the MS cholinergic system can alter phase synchronization between brain areas whereas the NBM cholinergic system modifies phase synchronization/phase resetting within a brain area.

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Contributors

All authors have given intellectual contributions to the study and the paper and have approved the final manuscript. Manuel Sanchez-Alavez, Patricia Robledo and Cindy L. Ehlers and Jim Havstad were responsible for the study design and prepared the manuscript. Derek Wills was responsible for collecting and coding the data. Jim Havstad was responsible for developing all software for ERO analyses.

Conflict of interest

Dr. Ehlers work has been funded by the NIH. She has received compensation as a consultant from Neurocrine Biosciences and Raptor Pharmaceutical Corp. in capacities not related to the subject of the report. Dr. Manuel Sanchez-Alavez, Dr. Patricia Robledo Dr. Jim Havstad and Derek Wills declare no potential conflicts of interest.

Keywords

Event-related potential; Electroencephalogram; Cholinergic system; Event related oscillation; Phase lock index; Phase difference lock index

1. Introduction

The cholinergic system in the brain modulates the pattern of activity involved in general arousal, attentional processing, motivation, memory formation and consciousness (Bauer et al., 2012; Butt and Hodge, 1995; Deiana et al., 2011; Everitt and Robbins, 1997; Muir et al., 1993; Wenk, 1997; Woolf, 1996, 2006; Yener et al., 2013). Central cholinergic pathways regulate global functions that rely upon the cerebral cortex and subcortical regions (Woolf, 1991, 1996). Two groups of cholinergic neurons in the basal forebrain play a substantial role in this process, the medial septal group (medial septal nucleus and vertical diagonal band) and the nucleus basalis group (nucleus basalis, substantia innominata and horizontal diagonal band) (Wenk, 1997; Wenk et al., 1994b; Woolf, 1991; Woolf et al., 1986).

Studies investigating the role of cholinergic neurons from the basal forebrain in animals have demonstrated that excitotoxic lesions can produce behavioral impairments (see Baxter and Bucci (2013) for review). Highly selective 192 IgG-saporin lesions to the medial septum and vertical limb of the diagonal band or bilaterally into the nucleus basalis magnocellularis and substantia innominata have been found to produce mild impairments in performance of a memory task in rats (Baxter et al., 2013). Cholinergic hypofunction has also been related to a number of cognitive disorders in humans including: the progressing memory deficits associated with aging, Alzheimer's disease (AD), Parkinson's disease, Down-syndrome, progressive supranuclear palsy, Jakob-Creutzfeld disease, Korsakoff's syndrome and traumatic brain injury (for review see Niewiadomska et al. (2009), Schliebs and Arendt (2011), Woolf (2006) and Woolf and Butcher, (2011)). Activity of the enzyme choline acetyl transferase (ChAT) is typically used as a marker for the loss of cholinergic neurons (Wenk et al., 1994a, 1994b). Although it has been suggested in AD that post-mortem assays of ChAT might not be representative of the extracellular levels of Ach and cholinergic neural activity, there have been significant validation of the functional loss of cholinergic neural activity using several bio-markers such as structural/amyloid imaging, cerebrospinal fluid measurements, and glucose positron emission tomography (Frings et al., 2013; Wirth et al., 2013). However, there is still a need for a functional biomarker that would reflect the changes in brain dynamics that might be associated with cholinergic hypofunction. Recently spontaneous electroencephalography (EEG), sensory-evoked oscillations, and event-related oscillations (EROs) have emerged as potential functional biomarkers for neuropsychiatric diseases in disorders such as: attention deficit hyperactivity disorder, Alzheimer's disease, bipolar disorder, schizophrenia (for review see Basar et al. (2013) and Yener and Basar (2013a)), and alcoholism (Andrew and Fein, 2010; Criado and Ehlers, 2009, 2010a, 2010b; Ehlers et al., 2010, 2012; Kovacevic et al., 2012; Rangaswamy and Porjesz, 2008). Thus these electrophysiological measures may also be capable of indexing hypofunction of the cholinergic system.

The generation of cortical event-related potentials (ERPs) in the rat has been previously demonstrated to involve cholinergic innervation (Pirch et al., 1986). We have also previously shown that lesions of the nucleus basalis magnocellularis (NBM) induce changes in several components of ERPs elicited by an auditory discrimination task, especially the amplitude of N1 and P2 components recorded in the frontal cortex and amygdala respectively (Ehlers et al., 1998; Robledo et al., 1998). The present study extended our initial analyses of neurophysiological endophenotypes observed in measures of ERPs after NBM lesions in rats, to the evaluation of event-related oscillations.

The stimuli that evoke ERPs components influence oscillatory changes within the dynamics of ongoing EEG rhythms (Basar-Eroglu et al., 1991; Demiralp and Ademoglu, 2001; Ehlers et al., 2012; Karakas et al., 2000a, 2000b; Schurmann and Basar, 2001; Yordanova et al., 2002), and this synchronization or enhancement of ongoing EEG oscillations by a time locked cognitive and/or sensory process is termed event-related oscillations (Basar et al., 2000; Begleiter and Porjesz, 2006; Roach and Mathalon, 2008). EROs are typically estimated by a decomposition of the EEG signal into phase and magnitude information for a range of frequencies and then changes in those frequencies are characterized with respect to their energy (amplitude) and phase relationships over a millisecond time scale with respect to task events (Ehlers et al., 1994). EROs have been demonstrated to be sensitive measures of both normal (Basar et al., 1999; Gevins, 1998) and abnormal cognitive functioning (Begleiter and Porjesz, 2006; Criado and Ehlers, 2009, 2010b; Ehlers et al., 2012; Porjesz and Begleiter, 2003).

The purpose of the present study was to examine whether selective cholinergic lesions of the medial septum area (MS) or the nucleus basalis magnocellularis (NBM) influence the amplitude and phase characteristics of ERO oscillatory activity in the delta, theta, alpha, beta and gamma frequency bands in the frontal cortex, DHPC and central amygdala elicited passively with an acoustic oddball paradigm in adult rats.

2. Results

2.1. MS-lesion induces lower ChAT activity in dorsal hippocampus and NBM-lesion induces lower ChAT activity in frontal cortex

Choline acetyltransferase (ChAT) activity (nmoles Ach/hr/mg prot) was measured in the frontal cortex and dorsal hippocampus from sham operated, MS-lesion and NBM-lesion rats. Results of those determinations were analyzed using a two way Analysis of Variance (ANOVA) that revealed a significant main effect of group (sham, MS-lesion and NBM-lesion) ($F=4.33$, $p=0.01$), region (frontal cortex, dorsal hippocampus) ($F=18.71$, $p<0.001$), and a group $\times$ region interaction ($F=4.59$, $p=0.01$). Post-hoc analyses revealed significant differences (Tukey LSD $p<0.05$) between sham and lesion groups, but there were no significant differences observed between MS-sham and NBM-sham groups. Therefore, for all subsequent analyses, MS sham and NB sham groups were collapsed into a common sham group.

Compared to the sham group, the MS-lesion was not found to produce significant changes in frontal cortex ChAT activity ($8.69\pm5.66\%$; $p=0.878$, sham 47.84 ± 2.89 vs. MS-lesion

43.68±2.7 nmoles Ach/h/mg prot) whereas it did induce a significant reduction in DHPC ChAT activity (29.4±5.72%; $p<0.001$, sham 59.29±3.43 vs. MS-lesion 41.87±3.39 nmoles Ach/h/mg prot). Compared to the sham group, the NBM-lesion was found to significantly reduce cortical ChAT activity (27.08±4.31%; $p=0.002$, sham 47.84±2.89 vs. NBM lesion 34.88±2.06 nmoles Ach/h/mg prot) but did not produce a significant change in DHPC ChAT activity (7.85±3.68%; $p=0.641$, sham 59.29±3.43 vs. NBM-lesion 54.64±2.17 nmoles Ach/h/mg prot). These results indicate that compared to the sham group the MS-lesion induced a significant reduction in hippocampal ChAT activity (Tukey post-hoc, $p<0.01$) whereas, the NBM-lesion induced a significant reduction in frontal cortex ChAT activity (Tukey post-hoc, $p<0.01$).

2.2. Rare (infrequent) tones have higher PLI than standard (frequent) tones

A two-way ANOVA was used to determine if the values for phase locking index (PLI) for the three electrode locations in the rat (Frontal cortex (FCTX), dorsal hippocampus (DHPC), amygdala (AMYG)) were higher following the rare (infrequent) tone as compared to the standard (frequent) tone within the ROI frequencies and time intervals under sham, MS-lesion and NBM-lesion conditions. When collapsing all bands across frontal cortex, DHPC and amygdala (Fig. 1a) there was a significant main effects of tone ($F=105.68$, $p<0.0001$), lesion ($F=8.81$, $p=0.0004$), although tone $\times$ lesion interaction was not significant ($F=1.26$, $p=0.28$). Post-hoc pairwise comparisons (Fig. 1a) showed higher PLI in response to rare tones (infrequent tone) compared to standard tones (frequent tone) (Tukey post-hoc, $p<0.01$). Thus, to reduce multiple comparisons EROs to the rare tones were used for all subsequent analyses.

2.3. MS-lesion induced changes in ERO energy associated to phase synchronization between frontal cortex and amygdala and between dorsal hippocampus and amygdala

A two way ANOVA with ERO energy as a dependent variable, and brain region (hippocampus, frontal cortex, amygdala) and lesion (sham, NBM lesion, MS lesion) as independent variables, revealed significant main effects of brain region ($F=22$, $p<0.0001$) and lesion ($F=4.84$, $p=0.0096$), on ERO energy, although the brain region $\times$ lesion interaction was not significant ($F=1.18$, $p=0.32$). Grand averages of the color equivalent of energy values for the entire group of subjects ($n=42$) including sham operated, MS-lesion and NBM-lesion rats are presented in Fig. 2. Compared to sham operated rats, lesions in MS and NBM decreased ERO energy in frontal cortex in the gamma frequency band in the 0–300 ms time interval (Fig. 3a), but did not cause a significant effect in DHPC in any of the frequency bands and time intervals (Fig. 3b). However the most significant effects were observed in the amygdala in all frequency bands (see Fig. 3c). Compared to sham operated rats, MS lesions significantly reduced ERO energy in the delta frequencies in the 200–500 ms time interval ($F=3.03$, $df=2,39$, $p=0.05$, post-hoc $p<0.01$), in theta frequencies in the 10–400 ms time interval ($F=6.09$, $df=2,39$, $p<0.005$, post-hoc $p<0.01$), in theta frequencies in the 400–800 ms time interval ($F=7.42$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$), and in alpha ($F=5.31$, $df=2,39$, $p<0.01$, post-hoc $p<0.05$), beta ($F=3.85$, $df=2,39$, $p<0.03$, post-hoc $p<0.05$) and gamma frequency bands ($F=16.39$, $df=2,39$, $p<0.001$, post-hoc $p<0.01$) in the 0–300 ms time interval, and, alpha ($F=6.75$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$), beta

($F=6.77$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$) and gamma frequency bands ($F=6.14$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$) in the 300–800 ms time interval.

Compared to sham operated rats, lesions in NBM significantly increased ERO energy in frontal cortex in the delta frequencies in the 200–500 ms time interval ($F=7.12$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$), in theta frequencies in the 10–400 ms time interval ($F=6.56$, $df=2,39$, $p<0.01$, post-hoc $p<0.05$) and significantly reduced ERO energy in the gamma frequency band ($F=13.19$, $df=2,39$, $p<0.001$, post-hoc $p<0.01$) in the 0–300 ms time interval. ERO energy in frontal cortex in the alpha frequency band was significantly increased in the NBM lesion group when it was compared to MS lesion group but not in comparison to the sham operated controls ($F=4.9$, $df=2,39$, $p<0.05$, post-hoc $p<0.05$, see Fig. 3a) in the 0–300 ms and 300–800ms ($F=3.41$, $df=2,39$, $p<0.05$, post-hoc $p<0.05$) time interval and in theta frequencies in the 400–800 ms time interval ($F=6.04$, $df=2,39$, $p<0.001$, post-hoc $p<0.01$). The NBM lesion was not found to produce significant effects in the DHPC in any of the frequency bands (see Fig. 3b). The effect of NBM lesions on ERO energy in amygdala was restricted only to the gamma frequency band ($F=16.39$, $df=2,39$, $p<0.001$, post-hoc $p<0.01$, Fig. 3c) in the 0–300 ms time interval.

Two-way ANOVA with ERO phase difference locking index (PDLI) as the dependent variable, and brain region and lesion as independent variables, revealed a significant main effect of lesion ($F=7.01$, $p=0.0013$) but not brain region ($F=1.69$, $p=0.189$) or brain region $\times$ lesion interaction ($F=0.69$, $p=0.6$). Compared to sham operated rats, lesions in MS significantly reduced PDLI in the electrode pair Fctx–DHPC in the theta frequencies at 400–800 ms time interval ($F=3.56$, $df=2,39$, $p<0.05$, post-hoc $p<0.05$, Fig. 4a). Reductions in PDLI in the electrode pair Fctx–Amyg were also seen in the theta frequencies at the 10–400 ms time interval ($F=9.64$, $df=2,39$, $p<0.001$, post-hoc $p<0.01$), and the 400–800 ms time interval ($F=11.79$, $df=2,39$, $p<0.001$, post-hoc $p<0.05$), and in the alpha ($F=3.61$, $df=2,39$, $p<0.05$, post-hoc $p<0.05$), beta ($F=7.21$, $df=2,39$, $p=0.002$, post-hoc $p<0.01$) and gamma ($F=7.69$, $df=2,39$, $p=0.001$, post-hoc $p<0.05$) frequency bands in the 0–300 ms time interval (Fig. 4b). Analysis on the 300–800 ms interval for PDLI revealed that in the electrode pair Fctx–Amyg a reduction in alpha ($F=10.29$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$) and beta ($F=8.64$, $df=2,39$, $p=0.01$, post-hoc $p<0.01$) frequencies were found. The PDLI for the electrode pair DHPC–Amyg shows a significant reduction in the theta ($F=5.25$, $df=2,39$, $p=0.009$, post-hoc $p<0.05$) frequency band at 10–400 ms time interval (see Fig. 4c).

Compared to sham operated rats, lesions in the NBM did not cause significant changes in any of the electrode pairs; Fctx–DHPC, Fctx–Amyg, DHPC–Amyg (Fig. 4a–c).

2.4. NBM-lesions induce reductions in phase synchronization in frontal cortex, dorsal hippocampus and amygdala

Two-way ANOVA, with ERO phase locking index (PLI) as the dependent variable, and brain region and lesion as independent variables, revealed significant effects of brain region ($F=3.63$, $p<0.03$) and lesion ($F=8.97$, $p=0.0002$) but no brain region $\times$ lesion interactions ($F=1.45$, $p=0.222$). Grand averages of the PLI values for the entire group of subjects ($n=42$) for sham operated, MS lesion, and NBM lesioned rats are presented in Fig. 5. Compared to sham operated rats, lesions in MS or NBM were associated with a reduction in evoked

gamma PLI in the Fctx ($F=5.37$, $df=2,39$, $p<0.01$, post-hoc $p<0.05$, see Fig. 6a) in the 0–300 ms time interval. NBM lesion produced a significant reduction in theta in the 10–400 ms time interval ($F=4.03$, $df=2,39$, $p<0.03$, post-hoc $p<0.05$) and in beta ($F=7.15$, $df=2,39$, $p<0.01$, post-hoc $p<0.01$) PLI in frontal cortex in the 0–300 ms time interval (Fig. 6a). In addition, NBM lesions induced a reduction in gamma phase locking ($F=3.9$, $df=2,39$, $p<0.03$; post-hoc $p<0.05$) in DHPC, as well as a reduction in beta phase locking ($F=6.74$, $df=2,39$, $p<0.01$; post-hoc $p<0.01$) in the 0–300 ms time interval in amygdala (Fig. 6b and c).

3. Discussion

The purpose of the present study was to investigate oscillatory activity in the delta, theta, alpha, beta and gamma frequency bands in the frontal cortex, DHPC and central amygdala of adult rats after selective cholinergic lesions of the medial septum or nucleus basalis magnocellularis. Network oscillations provide a mechanism to functionally link ensembles of neurons from discrete and regulatory pathways into complex interplay during information processing and represent neurophysiological correlates of human information processing and cognitive function (Basar et al., 1999, 2001c; Karakas et al., 2000b). ERO energy and phase locking of frequency specific, neuro-oscillatory activity within and between neural assemblies may underlie the processes whereby the brain organizes and communicates information (Barutcu et al., 2013; Basar et al., 1999; Roach and Mathalon, 2008; Sauseng et al., 2007), and represents a methodology whereby neuronal synchrony and/or phase resetting can be quantified and compared among experimental conditions in both man and animals providing thereby a translatable measure with which to explore the neural basis of behavior (Basar and Guntekin, 2008; Sazonov et al., 2009; Thatcher, 2012).

Using a simple auditory task we found that the infrequently presented (rare) stimulus produced a robust and highly significant increase in phase locking of EROs. The most likely explanation of this finding is that it represents a change in neural state associated with attending to a more novel, possibly environmentally relevant noise. Our findings are consistent with a previous study that evaluated phase locking of EROs using a complex motor-learning task (Sauseng et al., 2007). In that task, long-range theta phase coherence was stronger in the novel condition compared to learned sequences, independent of task-difficulty. Based on these data it has been suggested that the processing of sensory information, such as those used in our simple auditory task, is primarily guided by automatic “bottom up” processes that do not require active mental processing (Klimesch et al., 2007).

3.1. MS-lesion induced changes in ERO energy associated to phase synchronization between brain areas

Medial septal lesions were associated with reductions in ERO energy in the delta, theta, alpha, beta and gamma bands in the amygdala and the gamma band energy in the frontal cortex. In contrast to the NBM lesions, MS lesions produced decreases in evoked gamma phase locking index only in the frontal cortex. However, lesions in the medial septum, while not producing decreases in synchronization within brain areas as shown by PLI, did decrease phase synchronization between brain areas as shown by PDLI. MS lesions induced a reduction in synchronization between Fctx and Amyg in theta, alpha, beta and gamma frequency bands, reduction in synchronization between Fctx and DHPC in theta frequency

bands, and between DHPC and Amyg in theta frequency band. However, it is not clear whether the principal action of MS lesions is a reduction in Amyg oscillatory energy within the Amyg, or phase synchronization between brain regions, since it is theoretically possible that reductions in power within the Amyg may reduce the strength of the structure to entrain other brain areas.

Since the MS is critically involved in the rhythm generation of theta frequency output to cortical targets (Petsche et al., 1962), the reduction of synchronization seen between brain regions following loss of cholinergic tone still suggests a possible modulation of MS cholinergic system in synchronization between brain regions, and this observation is supported by pharmacological studies in humans and animal models. For instance, aging or administration of cholinergic M1 antagonists have been shown to reduce interregional phase synchronization between premotor/prefrontal cortex and the medial temporal lobe in humans using functional MRI and EEG (Wink et al., 2006). Comparable reports of cholinergic modulation of EEG coherence (Kikuchi et al., 2000), age-related change in hippocampal connectivity measured using fMRI (Grady et al., 2003) and evidence for age- and Alzheimer-related changes in hippocampal connectivity (Greicius et al., 2004) support the cholinergic involvement in interregional phase synchronization.

3.2. NBM-lesion induced changes in ERO energy are associated with phase synchronization within a brain area

This study demonstrated that NBM lesions increase ERO energy in the delta and theta frequency bands in Fctx and reduce gamma ERO energy in Fctx and Amyg. NBM provides the major source of cholinergic projections to the cortex (Amaral and Kurz, 1985; Bigl et al., 1982; Harati et al., 2008; Mesulam, 1995, 2004, 2013), the olfactory bulbs, and the amygdala (Wenk, 1997; Woolf, 1991). The reduction observed in ChAT activity in frontal cortex after lesioning NBM may account for the redistribution of ERO energy: increasing ERO energy in low frequencies (delta, theta and alpha bands) and decreasing ERO energy in high frequencies (such as gamma band). Although we did not measure ChAT activity in the amygdala other studies have shown that AMPA lesion into the MS/NBM induced up to 20% reduction compared to control (Waite et al., 1994), and the deficit of cholinergic projection from NBM could be involved in the decrease in ERO energy in gamma band in amygdala.

These studies may also be of theoretical interest in understanding several disorders that are associated with cholinergic hypofunction or loss. One important component of the pathophysiology of AD is degeneration of the cholinergic system (Perry et al., 1978; Sabbagh and Cummings, 2011) where an overall 55% loss of cortical cholinergic fibers has been reported in the basal forebrain in humans (Geula and Mesulam, 1995, 1996). Spontaneous activity in the EEG of AD patients reveals a topographically changed pattern of oscillations characterized by decrease of fast and increase of slow frequencies (Yener and Basar, 2010, 2013b; Yener et al., 2012). ERO studies in humans also show decreased responses in fronto-central regions of the brain in delta and theta frequencies (Yener and Basar, 2013b). While EEG synchronization between different brain regions, in mild AD subjects, appears to be mostly intact, event-related synchronization between brain regions is decreased in alpha, theta, and delta frequency ranges. Alpha synchronization also seems to

be sensitive to cholinergic treatment in AD (Yener and Basar, 2013b). Thus human studies suggest that ERO may be a good index of both cholinergic loss and cognitive deficit in AD.

Several authors have suggested that oscillations in specific frequency ranges may underlie specific mental functions. Some studies have demonstrated that cholinergic neuromodulation contributes to gamma oscillation production in vivo and in vitro (Bauer et al., 2012; Buhl et al., 1998; Hentschke et al., 2007; Liljenstrom and Hasselmo, 1995; Pafundo et al., 2013; Tiesinga et al., 2001). Synchronized gamma band (30–80 Hz) oscillations may be an index of ACh signaling during cognitive tasks, since gamma band power increases in relation to working memory load (Roux et al., 2012) and abnormal gamma oscillations are associated with cognitive deficits (Sun et al., 2012; Uhlhaas and Singer, 2006; Uhlhaas et al., 2011). For instance, event-related alpha oscillations have been attributed to attentional resources, semantic memory, and stimulus processing (Basar et al., 1997; Klimesch et al., 1994, 2004) whereas, beta and gamma oscillations have been associated with sensory integrative processes (Basar, 2013; Basar et al., 2001b; Schurmann et al., 1997). Oscillations in the delta and theta frequency ranges have been associated with signal detection, decision-making, conscious awareness, recognition memory and episodic retrieval (Basar et al., 2001a, 2013; Gevins et al., 1998; Klimesch et al., 2005). It has been suggested that high frequency oscillations (above 30 Hz) reflect synchronization of neuronal ensembles that are interacting over short distances in response to primarily sensory processes (Bressler and Freeman, 1980; Ohl et al., 2003) whereas, lower frequency oscillations (1–4 Hz) are generated by synchronization of ensembles interacting at longer distances during higher cognitive processing (Kopell et al., 2000; Lubar, 1997).

There is evidence for a functional dissociation between medial septum and nucleus basalis cholinergic systems in aspects of cognitive function (Lehmann et al., 2003). In general, NBM lesions have shown to impair performance on a variety of tasks involving sustained attention and discrimination (Dunnett, 1991; Harati et al., 2008; Lehmann et al., 2003; Motohashi et al., 1986; Nieto-Escamez et al., 2002; Risbrough et al., 2002; Santucci and Haroutunian, 1989). Lesions of medial septum impair learning and memory and generation of hippocampal theta rhythm (Brito and Brito, 1990; Colom et al., 1991; Easton et al., 2011; Harati et al., 2008; Martin et al., 2008). The cholinergic innervation of the hippocampus plays a key role in spatial reference memory processes involved in place navigation (Hagan et al., 1988) and rats with lesions of cholinergic medial septum are impaired in a task that requires the association of places with contexts (Easton et al., 2011). Combined lesions in the medial septum/diagonal band and nucleus basalis magno-cellularis (NBM) in rats induces spatial memory impairment (Waite et al., 1994) which is qualitatively similar to nucleus basalis lesions alone involving decreasing of the attentional load (Lehmann et al., 2003).

In this study selective cholinergic lesions produced changes in energy, PLI and PDLI depending on the area of the lesion (see Table 1). Whether the electrophysiological results obtained were due exclusively to the loss of cholinergic tone or whether they reflect a compensation or adaption of other brain systems to the loss of cholinergic tone is not clear at the time. Independent of the exact mechanisms of the effects observed, we have demonstrated that loss of cholinergic modulation can influence the output of brain

oscillations in this rat model. These findings could theoretically contribute to the understanding of the role of cholinergic function in a number of cognitive disorders including: Alzheimer diseases, Parkinson diseases, other cognitive disorders including Down-syndrome, progressive supranuclear palsy, Jakob–Creutzfeld disease, Korsakoff's syndrome and traumatic brain injury and alcoholism.

4. Conclusions

These studies suggest that MS lesions to cholinergic neurons are associated with phase synchronization across stimulus trials between brain areas whereas NBM lesions to cholinergic neurons contribute to phase synchronization/phase resetting across stimulus trials within a brain area.

5. Experimental procedures

5.1. Animal subjects

Forty-two (42) rats weighing 250–410 g were used. All rats had ad libitum access to food and water. A detailed description of the environmental conditions of rats can be found in previous reports (Ehlers et al., 1998; Robledo et al., 1998). The work described herein adheres to the guidelines stipulated in the NIH *Guide for the Care and Use of Laboratory Animals* (NIH publication No. 80-23, revised 1996) and was reviewed and approved by The Scripps Research Institute's Institutional Animal Care and Use Committee.

5.2. Surgical and electrophysiological recording procedures

Surgical and electrophysiological recording procedures performed in this study have been previously described (Ehlers et al., 1994; Robledo et al., 1998). Briefly, rats were divided into three groups (sham-operated controls, MS-lesion and NBM-lesion groups). Rats were deeply anesthetized with Nembutal (50 mg/kg, intraperitoneally) and surgically implanted with bilateral cannula above the nucleus basalis magnocellularis (NBM: AP −0.8; ML ±2.5; DV −4.3 mm) or medial septal nucleus (MS: AP 0.6; ML 0.0; DV −4.3 mm) together with stainless steel single-wire recording electrodes in the frontal cortical area (AP: −3.0 mm, ML: ±3.0 mm, DV: −3.0 mm), DHPC (AP: −4.2 mm, ML: ±3.0 mm, DV: −3.0 mm) and amygdala (AP: 1.0 mm, ML: ±5.3 mm, DV: −8.5 mm). Additional screw electrodes were placed in the skull overlying the frontal (AP: 3.0 mm, ML: ±3.0 mm, FR1) and parietal (AP: −3.0 mm, ML: ±4.0 mm, PAR3) cortices using the Paxinos and Watson atlas (1986). A midline screw “reference” electrode was placed 3 mm posterior to lambda in the skull overlying the cerebellum. Electrode connections were made to a multi-pin amphenol connector and the assembly was anchored to the skull with dental acrylic and anchor screws. EEG signals were recorded, using a unipolar montage, with a band pass of 0.5–70 Hz with a 60-Hz notch filter in. ERPs were elicited by auditory stimuli that were presented through a small speaker centered approximately 20 cm above the rat's head. ERPs were elicited passively with an acoustic “oddball” paradigm as described previously (Ehlers and Chaplin, 1992; Ehlers et al., 1994) and consisted of 200 individual tone presentations. The tones were generated by a programmable multiple-tone generator. Two tone types were presented: standard tones (1000 Hz square wave, duration 20 ms, 71 dB, 83.5% probability) and rare tones (2000 Hz square wave, duration 20 ms, 71 dB, 16.5% probability). Individual trials

were 1000 ms in duration (100 ms pre-stimulus+900 ms post-stimulus) and were separated by variable intervals ranging from 500 to 1000 ms. Rare tones were interspersed with standards such that no two rare tones occurred successively. The EEG amplifier input range corresponding to the full range of the 12-bit analog-to-digital converter was about $\pm 250 \mu\text{V}$. Periodic calibration results were used to scale the digitized EEG to microvolts. An artifact rejection program was utilized to eliminate individual trials in which the EEG exceeded $+400 \mu\text{V}$. Potential artifacts identified by computer software were excluded only after visual analysis of raw EEG. Trials containing excessive movement artifact were eliminated prior to averaging ($<5\%$ of the trials). ERPs trials were digitized at a rate of 256 Hz.

5.3. ERO energy and PLI analyses

Data from single trials generated by the stimuli were entered into the time frequency analyses algorithm. The S-transform (ST), a generalization of the Gabor transform (Gabor, 1946), was used (see Stockwell et al., 1996).

$$S\left[jT, \frac{n}{NT}\right] = \sum_{m=0}^{N-1} H\left[\frac{m+n}{NT}\right] e^{-\frac{2\pi^2 m^2}{n^2}} e^{\frac{i2\pi m j}{N}} \quad n \neq 0$$

The S transform mathematically resembles the continuous wavelet transform but it uses Gaussian windows which do not meet a requirement of wavelet analysis, and it includes a “phase correction” that is not part of wavelet analysis. The actual use of the S-transform was simplified by performing first a forward Fourier transform of the time series. Then, for each frequency of the Fourier transform, summing the results of multiplication by a set of Fourier transforms of Gaussian windows of varying width. Finally, for each of these sums, taking the inverse Fourier transform. The equation for calculation of the S-transform of discrete time series $h(kT)$ at time jT and frequency n/NT is where T is the sample period of the discrete time series, j is the sample index, N is the number of samples in the time series, n is the frequency index, and $H[\]$ is the Fourier spectrum of the discrete time series. The S-transform results in a time–frequency representation of the data. The exact code we used is a C language, S-transform subroutine available from the NIMH MEG Core Facility web site (<http://kurage.nimh.nih.gov/meglab/>). This code is specifically for use with real time series, so it sets the input imaginary values, required by the S-transform, to zero, and it always uses the Hilbert transform so that each of the complex output time series is an analytic signal.

To reduce anomalies in the S-transform output at the beginning and the end of the output time series, we used a Hanning window over the initial and final 100 ms of the input time series. The output of the transform for each stimuli and electrode site was calculated by averaging the individual trials containing the time–frequency energy distributions. To quantify S-transform magnitudes, a region of interest (ROI) was identified by specifying the band of frequencies and the time interval contained in the rectangular ROI. The time–frequency points saved from each S transformation are from 100 ms before to 900 ms after the onset of the stimulus, and from 1 Hz to 50 Hz at intervals of 0.5 Hz. Energy is the square of the magnitude of the S-transform output in a time frequency region of interest. The S-transform output for a time/frequency ROI, for a specific EEG lead, is proportional to the

input voltage of the lead over the time/frequency interval. The S-transform magnitude squared for a time/frequency interval is therefore proportional to volts squared. These analyses are similar to what has been previously described (Jones (2004)).

An S transformation at time t and frequency f has real and imaginary parts:

$$S(t, f) = \text{Re } S(t, f) + i \text{Im } S(t, f)$$

where i is the square root of -1 . The cosine and sine of the phase angle at this time–frequency point are

$$\begin{aligned}\cos \varphi(t, f) &= \text{Re } S(t, f) / |S(t, f)| \\ \sin \varphi(t, f) &= \text{Im } S(t, f) / |S(t, f)|\end{aligned}$$

where the vertical bar pair indicates magnitude, here and below.

ERP trials are averaged by summing separately the real and imaginary parts of the S transform outputs, and dividing each by the sum over trials of the magnitudes of S transform outputs. The sums over trials of the real and imaginary parts of the S transform outputs are the sides of a right triangle and the sum of magnitudes is the hypotenuse. From this, the angles of the triangle of the sums are calculated:

$$\begin{aligned}\langle \cos \varphi(t, f) \rangle &= \sum \text{Re } S_n(t, f) / \sum |S_n(t, f)| \\ \langle \sin \varphi(t, f) \rangle &= \sum \text{Im } S_n(t, f) / \sum |S_n(t, f)|\end{aligned}$$

where an angle bracket pair indicates mean value from S transforms, and a vertical bar pair indicates magnitude, here and below.

PLI is a measure of synchrony of phase angle over trials, as a function of frequency and of time relative to the start of the stimulus for each trial. The range of PLI is from zero to 1.0, with high values at a time and frequency indicating little variation, among trials, of phase angle at that time and frequency. PLI is defined as follows:

$$\text{PLI}(t, f) = |\langle \cos \varphi(t, f) + i \sin \varphi(t, f) \rangle|$$

where the angle bracket pair indicates mean value over eligible trials, here and below. Eligibility depends on the stimulus type and absence of significant artifact. This definition is mathematically equivalent to the definition in Schack and Klimesch (2002).

PDLI is a measure of constancy over trials of the difference in phase angle between two channels, as a function of frequency and of time relative to the start of the stimulus for each trial. The range of PDLI is from zero to 1.0, with high values at a time and frequency indicating little variation, among trials, of phase angle difference between channels of the pair, at that time and frequency. PDLI is defined for frequency f at time t as

$$\text{PDLI}(t, f) = |\langle \cos(\varphi_A(t, f) - \varphi_B(t, f)) \rangle + i \langle \sin(\varphi_A(t, f) - \varphi_B(t, f)) \rangle|$$

where φ_A and φ_B are phase angles of channels A and B, respectively. This definition of PDLI is equivalent to a definition of PLV, phase lock value, in Brunner et al. (2005). By means of some standard trigonometric identities the equation above is equivalent to the following, which, as for PLI, does not require that the phase angles be calculated:

$$\text{PDLI}(t, f) = |\langle \cos \varphi_A(t, f) \cos \varphi_B(t, f) + \sin \varphi_A(t, f) \sin \varphi_B(t, f) \rangle + i \langle \sin \varphi_A(t, f) \cos \varphi_B(t, f) - \cos \varphi_A(t, f) \sin \varphi_B(t, f) \rangle|$$

Rectangular regions of interest (ROIs) were defined within the time–frequency analysis plane by specifying, for each ROI, a band of frequencies and a time interval relative to the stimulus onset time. Time 0 in these definitions is the onset of the stimulus. The 9 ROIs were: ROI1 (delta band, 1–4 Hz, 200–500 ms), ROI2 (theta band, 4–7 Hz, 10–400 ms), ROI3 (theta band, 4–7 Hz, 400–800 ms), ROI4 (alpha band, 7–13 Hz, 0–300 ms), ROI5 (alpha band, 7–13 Hz, 300–800 ms), ROI6 (beta band, 13–30 Hz, 0–300 ms), ROI7 (beta band, 13–30 Hz, 300–800 ms), ROI8 (gamma band, 30–50 Hz, 0–300 ms), and ROI9 (gamma band, 30–50 Hz, 300–800 ms) (see Fig. 1b). These regions were chosen a priori to co-inside with the major EEG frequencies and the latency windows of the N1 and P3 components in the rat. Using mean values over trials, the maximum values were calculated for each ROI, for each electrode location or, for PDLI, for a pair of electrode locations (FZ–PZ) for energy (E), PLI amplitude, and PDLI amplitude.

5.4. Statistical analyses

Statistical analyses were performed by using One-Way Analysis of Variance and Two-Way Analysis of Variance on line (www.vassarstats.net). Values are mean $\pm$ standard error of the mean (SEM). Analyses were performed on data generated from trials in response to the infrequently presented (rare) tone collected from sham-operated, MS-lesion and NBM-lesion rats. Energy, PLI and PDLI for the 9 ROIs. Group (sham-operated, NBM-lesion and MS-lesion rats) was assessed as a between subject variable. Lesion effects were determined using a two way ANOVA (lesion $\times$ brain region) (sham-operated, NBM-lesion and MS-lesion rats), brain region (frontal cortex, DHPC, amygdala) and lesion $\times$ brain region interaction was computed. Post-hoc analyses (Tukey LSD $p < 0.05$) between sham and lesioned groups was determined. One-way ANOVA was used to assess lesion site differences. For these analyses, P -value was set at $p < 0.05$ to determine the levels of statistical significance. ANOVA with Tukey post-hoc analyses were utilized to statistically evaluate ChAT activity.

5.5. Lesion and perfusion

Lesion and perfusions were conducted as previously described (Robledo et al., 1998). Under Nembutal anesthesia (1 ml/kg) rats were infused through previously implanted guide cannula with 0.5 μ l per side 0.01 M AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Cambridge Research Biochemicals, UK) (Muir et al., 1994) into the NBM (3 mm below cannula at DV = -7.3), the MS (3 mm below cannula at DV = -7.3), and the

controls were infused with vehicle (0.2 M PB). ERPs trials were conducted 10 days following the sham/lesion surgery. At the end of the study rats were euthanized and their brains were extracted rapidly and dissected on wet ice. The frontal and parietal cortices and hippocampus were removed and choline acetyltransferase (ChAT) activity was measured. In brief, extracted tissue was sonicated in 400 µl of 50 nM phosphate buffer (pH 7.4). ChAT activity was measured by the incorporation of 14C-acetyl coenzyme A into 14C-Ach. The assay is based on the transfer of the radiolabeled acetyl moiety from acetyl CoA to choline, and separation of radiolabeled 14C-acetyl CoA from the radiolabeled product, 14C-Ach (Fonnum, 1969).

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Abbreviations

Ach	Acetylcholine
AD	Alzheimer's disease
AMYG	Amygdala
ANOVA	Analysis of Variance
ChAT	Choline acetyltransferase
DHPC	Dorsal Hippocampus
EEG	Electroencephalogram
ERO	Event-related oscillations
ERP	Event-related potentials
FCTX	Frontal Cortex
MS	Medial Septum
NBM	nucleus basalis magnocellularis
PDLI	phase difference lock index
PLI	phase locking index
ROI	region of interest

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Fig. 1.

(a) Grand mean values for the phase locking index (PLI) of event-related oscillations in sham operated, MS- and NBM-lesion rats. ANOVA revealed that the rare (infrequent) tone (gray bars), as compared to the standard (frequent) tone (black bars) produce significant increase in phase locking in ROI. (b) schematic representations of ROI: ROI1 (delta band, 1–4 Hz, 200–500 ms), ROI2 (theta band, 4–7 Hz, 10–400 ms), ROI3 (theta band, 4–7 Hz, 400–800 ms), ROI4 (alpha band, 7–13 Hz, 0–300 ms), ROI5 (alpha band, 7–13 Hz, 300–800 ms), ROI6 (beta band, 13–30 Hz, 0–300 ms), ROI7 (beta band 13–30 Hz, 300–800 ms), ROI8 (gamma band, 30–50 Hz, 0–300 ms), and ROI9 (gamma band, 30–50 Hz, 300–800 ms). Post-hoc Tukey pairwise comparisons indicate the following: frequent tone vs. rare tone (* $p < 0.05$) in sham operated group; frequent tone vs. rare tone (** $p < 0.01$) in septal lesion (MS-les) and NBM lesion (NBM-les) groups. Pairwise comparisons using frequent tone indicate significant reduction in the NBM lesion group (# $p < 0.05$, sham vs. NBM lesion).

Fig. 2.

Grand averages of event related oscillations energy color equivalent for sham-operated, MS-lesion (MS les) and NBM-lesion (NBM les). Each graph depicts a time–frequency representation of ERO energy values in the delta, theta, alpha, beta and gamma bands following the rare tone in Frontal cortex, dorsal hippocampus (DHPC) and Amygdala electrode locations. In each graph frequency (Hz) is presented on the Y-axis, time regions of interest on the X-axis (ms) and ERO energy is presented as color equivalents of energy as indicated in the color bar at the bottom of each graph. NBM-lesion produced increases in color equivalents in frontal cortex (color equivalents in sham and MS les was adjusted to NBM les scale for visual purposes) and MS-lesion produced decreases in color equivalents in amygdala (color equivalents in NBM les and MS les was adjusted sham scale for visual purposes).

Fig. 3.

MS-lesion reduces ERO energy in amygdala and NBM-lesion increases ERO energy in Frontal cortex. Grand mean values for the event-related oscillations energy equivalents in sham operated (black bars), MS-lesion (white bars) and NBM-lesion (gray bars) rats for the rare tone in ROI1 (delta band, 1–4 Hz, 200–500 ms), ROI2 (theta band, 4–7 Hz, 10–400 ms), ROI3 (theta band, 4–7 Hz, 400–800 ms), ROI4 (alpha band, 7–13 Hz, 0–300 ms), ROI5 (alpha band, 7–13 Hz, 300–800 ms), ROI6 (beta band, 13–30 Hz, 0–300 ms), ROI7 (beta band, 13–30 Hz, 300–800 ms), ROI8 (gamma band, 30–50 Hz, 0–300 ms), and ROI9 (gamma band, 30–50 Hz, 300–800 ms). Energy was calculated in: (a) the frontal cortex (Fctx), (b) dorsal hippocampus (DHPC), and (c) amygdala (Amyg). Compared to sham lesions, lesions in MS decreased ERO energy in frontal cortex only in the gamma frequency band (ROI8, see (a)) and reduced the ERO energy in the theta (ROI2, ROI3), alpha (ROI4, ROI5), beta (ROI6, ROI7), and gamma (ROI8, ROI9), frequency bands in amygdala (see (c)). Compared to sham lesions, lesions in NBM significantly increased ERO energy in frontal cortex in the delta (ROI1), and theta (ROI2) frequency bands and significantly reduced ERO energy in the gamma (ROI8) frequency band (see (a)); in addition, lesions in NBM induced a reduction in ERO energy in the gamma (ROI8) frequencies in the amygdala (see (c)). ERO energy in the alpha frequency band was significantly increased when the NBM lesion group was compared to MS lesion group but not to the sham operated controls (see (a)). Post-hoc Tukey pairwise comparisons indicate the following: sham vs. MS-les

(* $p < 0.05$), sham vs. MS-les and NBM-les (** $p < 0.05$), MS-les vs. sham and NBM-les
(⁺ $p < 0.05$), NBM-les vs. sham and MS-les ([#] $p < 0.05$) and NBM-les vs. MS-les ([@] $p < 0.05$).

Fig. 4.

MS lesion reduces phase synchronization between Frontal cortex-amygdala and between dorsal hippocampus-amygdala. Grand mean values for the phase difference lock index (PDLI) of event-related oscillations (EROs) in sham operated (black bars), MS-lesion (white bars) and NBM-lesion (gray bars) rats for the rare tone in ROI1 (delta band, 1–4 Hz, 200–500 ms), ROI2 (theta band, 4–7 Hz, 10–400 ms), ROI3 (theta band, 4–7 Hz, 400–800 ms), ROI4 (alpha band, 7–13 Hz, 0–300 ms), ROI5 (alpha band, 7–13 Hz, 300–800 ms), ROI6 (beta band, 13–30 Hz, 0–300 ms), ROI7 (beta band, 13–30 Hz, 300–800 ms), ROI8 (gamma band, 30–50 Hz, 0–300 ms), and ROI9 (gamma band, 30–50 Hz, 300–800 ms). In the upper graph (a), phase difference was calculated between frontal cortex (Fctx) and dorsal hippocampus (DHPC); in the middle graph (b), phase difference was calculated between Fctx and amygdala (Amyg); and in the bottom graph (c), phase difference was calculated between DHPC and Amyg. MS lesions reduced phase synchronization between frontal cortex and DHPC (Fctx–DHPC) in the theta (ROI3) frequency bands. In addition, MS lesions reduced phase synchronization between frontal cortex and amygdala (Fctx–Amyg) in theta (ROI2 and ROI3), alpha (ROI4 and ROI5), beta (ROI6 and ROI7) and gamma (ROI8) frequency bands and reduced phase synchronization between dorsal hippocampus–amygdala (DHPC–Amyg) in theta (ROI2) frequency band. Post-hoc Tukey pairwise comparisons

indicate the following: sham vs. MS-les or MS-less vs. NBM ($^*p<0.05$), and MS-les vs. sham and NBM-les ($^+p<0.05$).

Fig. 5.

Grand averages of phase locking index values of event related oscillations for sham-operated, MS-lesion and NBM-lesion rats. Each graph depicts a time–frequency representation of PLI values in the delta, theta, alpha, beta and gamma bands following the rare tone in Frontal cortex, dorsal hippocampus (DHPC) and Amygdala electrode locations. In each graph frequency (Hz) is presented on the Y-axis, time regions of interest on the X-axis (ms) and PLI is presented as color equivalents as indicated in the bar at the bottom of each graph. NBM lesion shows reduction in color equivalents of phase locking at all three electrode sites.

Fig. 6.

Effects of NBM-lesions on phase synchronization in frontal cortex, dorsal hippocampus or amygdala. Grand mean values for the phase locking index (PLI) of event-related oscillations in sham operated (black bars), MS-lesion (white bars) and NBM-lesion (gray bars) rats for the rare tone in ROI1 (delta band, 1–4 Hz, 200–500 ms), ROI2 (theta band, 4–7 Hz, 10–400 ms), ROI3 (theta band, 4–7 Hz, 400–800 ms), ROI4 (alpha band, 7–13 Hz, 0–300 ms), ROI5 (alpha band, 7–13 Hz, 300–800 ms), ROI6 (beta band, 13–30 Hz, 0–300 ms), ROI7 (beta band, 13–30 Hz, 300–800 ms), ROI8 (gamma band, 30–50 Hz, 0–300 ms), and ROI9 (gamma band, 30–50 Hz, 300–800 ms). Phase locking index was calculated in: (a) the frontal cortex (Fctx), (b) dorsal hippocampus (DHPC), and (c) amygdala (Amyg). Compared to sham operated rats, MS-lesions (MS les) induced a significant reduction in gamma PLI in Fctx. Compared to sham operated rats NBM-lesion (NBM les) induced a significant reduction in gamma phase locking in Fctx and DHPC and a significant reduction in beta phase locking in Fctx and Amyg and theta phase locking in Fctx. Post-hoc Tukey pairwise comparisons indicate the following: sham vs. NBM-les (* $p < 0.05$) and sham vs. MS-les and NBM-les (** $p < 0.05$).

Table 1
Effects of MS or NBM lesions on energy, phase-locking index (PLI), and phase difference lock index (PDLI).

MS lesion		NBM lesion																	
Frequency band	δ	θ	α	β	γ	δ	θ	α	β	γ	δ	θ	α	β	γ	δ	θ	α	β
Time window (ms)	200–500	10–400	0–300	0–300	0–300	200–500	10–400	0–300	0–300	0–300	200–500	10–400	0–300	0–300	0–300	0–300	0–300	0–300	0–300
Region of interest	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	9
Energy																			
Fctx																			↓
DHPC																			
Amyg																			
PLI																			
Fctx																			↓
DHPC																			↓
Amyg																			
PDLI																			
Fctx–DHPC																			
Fctx–Amyg																			
DHPC–Amyg																			

Effects of medial septal (MS) or nucleus basalis magnocellularis (NBM) lesions on measures of event-related oscillations (EROs) (Energy; PLI, phase locking index; PDLI, phase difference lock index) in 9 time frequency regions of interest for three brain areas: frontal cortex (Fctx), dorsal hippocampus (DHPC), and amygdala (Amyg). Arrows indicate direction of change in the lesion group as compared to the sham lesion group.