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40-Hz steady state response in Alzheimer's disease and mild cognitive impairment

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Abstract

The 40-Hz steady state response (SSR) reflects early sensory processing and can be measured with electroencephalography (EEG). The current study compared the 40-Hz SSR in groups consisting of mild Alzheimer's disease patients (AD) ($n = 15$), subjects with mild cognitive impairment (MCI) ($n = 20$) and healthy elderly control subjects ($n = 20$). All participants were naïve for psychoactive drugs. Auditory click trains at a frequency of 40-Hz evoked the 40-Hz SSR. To evaluate test–retest reliability (TRR), subjects underwent a similar assessment 1 week after the first. The results showed a high TRR and a significant increase of 40-Hz SSR power in the AD group compared to MCI and controls. Furthermore a moderate correlation between 40-Hz SSR power and cognitive performance as measured by ADAS-cog was shown.

The results suggest that 40-Hz SSR might be an interesting candidate marker of disease progression.

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Keywords: Alzheimer's disease; MCI; EEG; 40-Hz; Steady state response; Cortical inhibition; Reliability; Neurophysiology

1. Introduction

Cortical neural activity is reflected in the electroencephalogram (EEG). Fast neural oscillations measured with EEG and magnetoencephalography (MEG) have been proposed to be an important mechanism in the integration and binding of neural networks in perceptual and cognitive processes (Herrmann et al., 2004; Joliot et al., 1994; Tallon-Baudry and Bertrand, 1999).

A basic method for measuring these fast oscillations is by evoking a 40-Hz steady state response (SSR). The 40-Hz SSR is elicited by auditory stimulation with “click trains” at 40-Hz.

These very short individual clicks each evoke an event-related response (ERP). The short inter-stimulus intervals in

the click trains do not allow the ERP's to return to baseline, resulting in a nearly sinusoidal SSR (Tallon-Baudry and Bertrand, 1999). As a result, the 40-Hz SSR can be considered as a superimposition of middle-latency responses (P50) to each individual click (Galambos et al., 1981). Early gamma band responses such as the 40-Hz SSR are involved in the sensory processes that precede perceptual or attentional processes (Karakas and Basar, 1998).

Impaired sensory processing is one of the hallmarks of Alzheimer's disease (AD).

A study using magnetoencephalography showed that the 40-Hz SSR in a drug naïve AD population is enhanced compared to that in healthy controls (Osipova et al., 2006). Osipova et al. related their findings to decreased cortical inhibition in AD. This explanation is substantiated by results from studies using a sensory gating or dual-click paradigm. This paradigm involves the presentation of two consecutive clicks, whereby the P50 amplitude to the second click should be lower. This paradigm is considered a measure for cortical inhibition. Several studies have shown that subjects with

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AD diverged from the paradigm and exhibited increased P50 amplitude to the second click in AD (Cancelli et al., 2006; Jessen et al., 2001). A study that examined healthy volunteers with a family history of AD also showed a similar divergence in the P50 amplitude (Boutros et al., 1995). This suggests that impaired cortical inhibition may be present very early in the course of the disease. With a view to detecting the disease at an early stage, it is important to identify whether the difference in the 40-Hz rhythm is already present in a well-defined MCI population.

The current study aims to examine whether differences, similar to the findings of Osipova et al. (2006) are revealed when EEG is used to study AD patients. Furthermore, it sets out to discover whether these differences are already present in subjects with MCI. The current study reports data from a psychoactive drug naïve population. This is an important methodological issue since several studies showed that pharmacological modulations have a profound effect on the power of the 40-Hz rhythm (Ahveninen et al., 1999, 2002).

To evaluate the robustness and reproducibility of the results, the test–retest reliability (TRR) of the 40-Hz SSR paradigm will be evaluated.

We hypothesized that the 40-Hz SSR is enhanced in patients with AD compared to subjects with MCI and healthy controls. Furthermore, it is to be expected that the SSR in the MCI group will be higher than in the control group, but lower than in the AD group.

2. Materials and methods

2.1. Subjects

The study included three different groups of subjects:

- (1) Fifteen psychoactive drug naïve patients with a diagnosis of probable AD according to the NINCDS-ADRDA criteria were included (McKhann et al., 1984).
- (2) Twenty psychoactive drug naïve patients with a diagnosis of MCI according to the Petersen criteria were included (Petersen et al., 2001). MCI subjects also received standard blood workup, neuro-imaging and neuropsychological testing. The diagnosis AD or MCI was made at a weekly consensus meeting of different specialists. The diagnostic assessment included the following: a detailed history-taking of the subjects; a psychiatric, neurological and physical examination; the Mini Mental State Examination (MMSE) (Folstein et al., 1975); CAMDEX part-B (CAMCOG) (Derix et al., 1991); an assessment using clinical rating scales (i.e. GDS) (Reisberg et al., 1982), the Hamilton Depression scale (Hamilton, 1960) and the Blessed Dementia Rating scale (Blessed et al., 1968); appropriate laboratory tests (i.e. haematology, glucose, biochemical analysis, vitamin B12 and thyroid stimulating hormone); a neuropsychological assessment including tests covering the

domains of memory, attention, executive functioning, language, praxis and intelligence and CT or MRI imaging as described elsewhere (Verhey et al., 1993).

- (3) Twenty healthy control subjects were recruited from the Maastricht Aging Study (MAAS), a longitudinal study of the determinants of healthy cognitive aging (van Boxtel et al., 1998). The control subjects were not using any psychoactive medications. Their medical history was screened by a medical health questionnaire. Main exclusion criteria were: a history of stroke, head trauma, and/or any other neurological or psychiatric disorders. Additional exclusion criteria were: severe cardiovascular disease, a Hachinski Ischemic Scale (HIS) (Hachinski et al., 1974; Rosen et al., 1980) higher than three or a history of substance abuse and/or other serious system diseases (e.g. malignancy, uncontrolled hypertension, neuropathy or seizure disorders).

All AD and MCI patients were recruited at the Memory Clinic of the Maastricht University Hospital and were judged competent to give consent by their treating physicians. This study was carried out in accordance with the declaration of Helsinki. All participants gave written informed consent prior to the study and in the case of the AD patients a family member also signed the consent form. The local Medical Ethics Committee of the Maastricht University Hospital approved the study.

2.2. Experimental procedure

All subjects took part in two identical recording sessions, temporally spaced apart by 1 week. All subjects were required to abstain from alcohol, nicotine and caffeine, from 08:00 pm, the evening prior to the test sessions. All subjects were tested between 09:00 am and 5:00 pm. On both occasions, the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) (Rosen et al., 1984; Verhey et al., 2004) was assessed prior to EEG acquisition. The Dutch version of the National Adult Reading Test (NART) (Schmand et al., 1998) was assessed to estimate pre-morbid intelligence. The 40-Hz steady state response was part of a larger study, which further included: induced gamma band measurement; contingent negative variation (CNV); checkerboard task; and an oddball paradigm. Headphones were used to present the auditory stimuli.

To evaluate the robustness of the results the test–retest reliability was evaluated. Therefore subjects visited our facilities twice for similar assessments with an interval of 1 week.

2.3. Stimulation

In the current study there were two conditions; auditory 40-Hz stimulation and resting state.

During EEG recording the subjects were presented with 1-ms clicks at a frequency of 40-Hz. Headphones presented 80 click trains of 450 ms binaurally. Subjects were instructed

to focus on a white crosshair in the centre of a black screen during the 40-Hz stimulation. During the resting state condition, subjects were instructed to keep their eyes open and focus on a white crosshair on a black screen for 90 s.

2.4. EEG acquisition

EEG was recorded on a commercially available EEG acquisition system (Nuamps®). Electrodes (AgCl) were positioned following the 10–20 system on a 32-channel electrode cap, using 19 electrodes (Medcat®). A low-pass filter of 100 Hz and a high-pass filter of 0.1 Hz were applied. The sample frequency was 512 Hz and analogue–digital conversion was 20 bit. Electrode impedance was kept below 5 k Ω . A reference electrode was placed on the right ear lobe. To control for possible vertical eye movements, an electro-oculogram (EOG) electrode was placed 1 cm under the midline of the right eye. A ground electrode was placed on the forehead, at Fpz position.

EEG's were recorded in a magnetically shielded and sound-attenuated room. During EEG recording subjects were instructed to focus on a white crosshair on a black screen. Subjects were able to see the screen through magnetically shielded glass. Neuroscan® 4.3 software was used for EEG recording and analyses.

2.5. 40-Hz SSR analysis

EEG analysis was performed off-line. Epochs were recorded in two conditions, during stimulation and during resting state, each with a length of 450 ms. Epochs containing eye movements, electromyographic activity (EMG), or head motion artefacts were omitted from analysis. Since EMG activity is in the same frequency spectrum as gamma band activity (Whitham et al., 2007), extra effort was taken to remove the EMG activity from the data. This procedure is described in more detail in van Deursen et al. (2008). As a result the 40-Hz SSR data reported here is completely free of EMG activity. Further pre-processing procedures included; band-pass filtering (35–45 Hz, 48 dB/oct) and baseline correction. The mean number of uncontaminated epochs that were included in the analysis was 58 (S.D. 13.9) for the AD group, 59 (S.D. 10.7) for the MCI group and 61 (S.D. 11.6) for the control group. The number of uncontaminated epochs did not differ between the groups ($F_{2,52} = .72$, $p = .49$). The uncontaminated epochs were transformed from the temporal domain to the frequency domain using fast-Fourier transformation (1 Hz resolution, 512 point block-size, Hanning window 35–45 Hz). The mean power at 40-Hz was calculated for each subject and each session.

2.6. Statistics

Significance levels associated with the differences in 40-Hz SSR power between the AD, MCI and control groups were calculated using ANOVA for repeated measures. Elec-

trode position was used as a within-subject variable. Since 40-Hz power was measured in two sessions the mean of these sessions was used in the ANOVA analysis. Post hoc Bonferroni correction for multiple comparisons was used. To evaluate the effect of stimulation compared to resting state, ANOVA for repeated measures was used with condition as a within-subject variable.

To examine TRR, a paired samples *t*-test was used to evaluate potential differences between the two sessions for the Fz, Cz and Pz electrode. Furthermore, Pearson's correlation coefficient between the sessions was calculated at Fz, Cz and Pz. These analyses were done for each patient group separately.

To examine the relation between 40-Hz power and cognitive performance as measured by ADAS-cog, Pearson's correlation coefficient between these variables was calculated.

3. Results

3.1. Subjects' demographics

Fifteen AD patients were included. They had a mean age of 75.2 (S.D. 6.9) and a mean MMSE of 20.8 (S.D. 2.7, range 17–26). Eleven of the AD patients were male.

Twenty MCI patients were included. They had a mean age of 70.6 (S.D. 7.2) and a mean MMSE of 26.3 (S.D. 1.6, range 23–29). Twelve of the MCI patients were male.

Twenty healthy control subjects were included. They had a mean age of 69.5 (S.D. 6.1) and a mean MMSE of 29.3 (S.D. 0.8, range 28–30). Twelve of the healthy control subjects were male. ANOVA analysis showed no statistical differences between the groups in age ($F_{2,52} = 2.2$, $p = .14$). However, when the age differences are studied in more detail with a *t*-test, there is a small difference between the AD and controls group ($t_{1,33} = 2.59$, $p = .0143$). Pre-morbid intelligence as estimated by NART, did not differ ($F_{2,52} = 1.7$, $p = .20$) between the groups.

3.2. Test–retest reliability

Table 1 presents the results of the TRR analysis.

The paired samples *t*-test between the sessions showed a significant difference in the AD group at Fz ($t_{15,1} = 2.42$; $p = .032$), and in the MCI group at Fz ($t_{19,1} = 3.37$; $p = .004$), Pz ($t_{19,1} = 3.44$; $p = .003$) and Cz ($t_{19,1} = 3.42$; $p = .003$). Despite the significant differences in the *t*-test the correlation coefficient was high in all groups and in all electrodes.

3.3. 40-Hz steady state response

The results of the 40-Hz power analysis during stimulation condition and resting state are presented in Fig. 1.

During stimulation condition ANOVA analysis showed that the 40-Hz SSR differed between the groups at T5 ($F_{52,2} = 3.46$; $p = .034$), T6 ($F_{52,2} = 7.20$; $p = .002$) and O2 ($F_{52,2} = 4.29$;

Table 1
Test–retest reliability of 40-Hz SSR during stimulation. The table presents the mean power in μV^2 of the electrodes per session (i.e. s1 = session and s2 = session 2).

40-Hz SSR	Alzheimer group				MCI group				Control group			
	Mean (μV^2) s1	Mean (μV^2) s2	Sig. <i>p</i>	Pearson's <i>R</i>	Mean (μV^2) s1	Mean (μV^2) s2	Sig. <i>p</i>	Pearson's <i>R</i>	Mean (μV^2) s1	Mean (μV^2) s2	Sig. <i>p</i>	Pearson's <i>R</i>
Fz	1.039	.728	.034	.82 (<i>p</i> = .001)	.820	.606	.004	.81 (<i>p</i> = .000)	.727	.762	.655	.83 (<i>p</i> = .000)
Cz	.936	.647	.056	.76 (<i>p</i> = .005)	.668	.507	.003	.73 (<i>p</i> = .001)	.620	.647	.713	.76 (<i>p</i> = .000)
Pz	.899	.595	.066	.73 (<i>p</i> = .008)	.596	.443	.003	.68 (<i>p</i> = .002)	.518	.537	.908	.54 (<i>p</i> = .016)

The *p* value represents the significance of the difference between the sessions. Pearson's *R* represents the correlation coefficient between the two sessions.

p = .019). Bonferroni post hoc analysis for multiple comparisons showed that the 40-Hz power was higher in the AD group compared to controls at T5, T6 and O2. There was a significant difference between AD and MCI only at T6. There were no significant differences between the MCI and control group during the stimulation condition.

To ensure that the differences are related to the task and are not due to aspects of the resting state, the effect of stimulation was examined using ANOVA for repeated measures. Results showed a significant increase in 40-Hz SSR power during stimulation condition compared to resting state condition at T5 ($F_{52,2}$: 32.00; *p* < .000), T6 ($F_{52,2}$: 30.61; *p* < .000) and O2 ($F_{52,2}$: 23.08; *p* < .000).

The 40-Hz power showed a moderate but significant correlation with cognitive performance as measured with ADAS-cog at T5 (*r* = .43, *p* = .019) and T6 (*r* = .38, *p* = .028). The correlation between 40-Hz power at O2 and ADAS-cog was low and not significant (*r* = .19, *p* = .064).

4. Discussion

The current study showed almost a universally high TRR and a significant difference in 40-Hz SSR power between the patient groups. The correlations between the sessions ranged from 0.68 to 0.83, which is high. Only the Pz electrode in the control group showed a moderate correlation (i.e. 0.54). These high correlations suggest that the 40-Hz SSR can reliably be assessed in a cognitively impaired population.

40-Hz SSR power was higher the AD group compared to MCI and control groups. Additionally, we also discovered a difference between the AD and MCI group. The difference between the AD and control group is in line with a previous MEG study by Osipova et al. (2006). A difference between AD and MCI with regard to 40-Hz SSR power has not been reported before this study. The absence of a difference between MCI and controls might be related to the heterogeneous nature of the MCI concept (Visser and Brodaty, 2006). MCI not only includes patients in the prodromal stage of AD, but also patients with other causes for cognitive impairment. Had we confined ourselves to amnesic MCI patients, who are more prone to progress to AD (Petersen, 2004), the difference between MCI and controls would probably have been larger. Previous EEG studies already showed that when focusing on alpha band power, there is a significant difference between progressive MCI patients and stable MCI patients (Huang et al., 2000; Luckhaus et al., 2008). Despite the absence of a significant difference between MCI and healthy controls, the 40-Hz SSR power in the MCI group is in between that the AD and the control group. The correlations between 40-Hz power and cognitive performance as measured by ADAS-cog varied between *r* = .19 and .43. However, a previous study showed that theta, alpha and beta band power has a higher correlation with ADAS-cog (i.e. *r* = .42–.53) (Brinkmeyer et al., 2004). Despite the lower cor-

Fig. 1. The mean + S.E.M. 40-Hz SSR power for each group in stimulation condition (left) and resting state condition (right). In stimulation condition 40-Hz SSR power was higher in the AD group compared to controls at T5, T6 and O2. At T6 there was a difference between AD and MCI. During stimulation condition 40-Hz SSR power was significantly higher than in resting state.

relation, the findings of the present study suggest that the 40-Hz SSR power increases as the severity of the disease increases. Whether 40-Hz SSR can be used to predict the progression of MCI to AD is at present not clear. The findings of this study suggest that this would be an interesting subject of future research.

In EEG studies of an elderly population differences in age can be a possible confounder of the results. Although the results show no significant differences between the groups with regard to age and pre-morbid intelligence, we performed a post hoc analysis to ensure that these parameters did not bias the results. Age and pre-morbid intelligence were entered as covariates in the GLM model and proved to have no effect on the group results. Another possible confounder in the 40-Hz SSR measurements is the contamination with EMG. In a previous study we showed that when an extra EMG reduction procedure is performed, gamma band (30–100 Hz) power is reduced (van Deursen et al., 2008). Therefore in the current study, the same procedure was included in the pre-processing steps, which removed this possible confounder from our data.

A methodologically strong aspect of the current study was that only psychoactive drug naïve patients were included. Most drugs used in AD affect the cholinergic nervous system. Since acetylcholine seems to be involved in the regulation of the 40-Hz SSR, these types of drugs will bias the results when medicated AD patients are included. The cholinergic involvement in the regulations of 40-Hz SSR has been suggested by a study that showed that scopolamine, which is a muscarine antagonist that is often used as a pharmacological model for AD, increased 40-Hz power in healthy young and elderly subjects (Ahveninen et al., 1999, 2002).

The location of the group differences indicates that the main difference was found in the auditory cortex, which is in agreement with a previous MEG study (Osipova et al., 2006). The auditory cortex has been proposed as the main generator of the 40-Hz rhythm (Gutschalk et al., 1999) although thalamocortical circuits also seem to play a role

(Ribary et al., 1991). The temporal cortex is one of the first areas to be affected by the neurodegenerative processes in AD (Braak and Braak, 1995). Therefore, the difference between the groups is most probably related to changes in the 40-Hz generators that are located in the temporal cortex.

Increased 40-Hz SSR power in the auditory cortex of AD patients has previously been associated with decreased inhibition of the superimposed middle-latency auditory peaks that are related to sensory processing (Osipova et al., 2006). Dual-click sensory gating paradigms showed that in AD the second P50 peak is increased compared to healthy controls, which suggests impaired cortical inhibition (Cancelli et al., 2006; Jessen et al., 2001). The current results confirm these previous findings.

Cortical disinhibition in AD can be associated with dysfunction of the neurotransmitters gamma-aminobutyric acid (GABA) and glutamate (Jacob et al., 2008). There is variable evidence for dysfunction of GABA and glutamate in AD (Francis, 2003; Garcia-Alloza et al., 2006; Lanctot et al., 2004; Lowe et al., 1988). GABA seems to play an important role in the regulation of the 40-Hz SSR, as administration of the GABA agonist temazepam attenuates the 40-Hz SSR (Jaaskelainen et al., 1999). The role of acetylcholine, GABA and glutamate in the regulation of the 40-Hz rhythm is however not clearly understood and will need more attention in future research.

In sum, the current study showed that the 40-Hz SSR power is higher in patients with AD compared to MCI subjects and healthy controls. The high TRR together with the correlation with cognitive performance suggest that the 40-Hz SSR can reliably be used to measure disease progression.

Conflict of interest

All authors state that there were no conflicts of interest involved in this study.

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