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Research article

Non-invasive electroencephalographical (EEG) recording system in awake monkeys

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ABSTRACT

Background: Human clinical studies reported that several electroencephalographical (EEG) parameters can be used as biomarkers of psychiatric disorders. EEGs recorded from non-human primates (monkeys) is useful for understanding of human pathologies of psychiatric disorders and development of new therapeutic agents.
New methods: In this study, we expand a previous non-invasive head holding system with face masks for awake monkeys to be applied to scalp EEG recording. The new design of a head holding system allows to attach scalp EEG electrodes on the positions comparable to human electrode placement and to present auditory stimuli.
Results: With this system, we could record auditory evoked potentials (AEPs) in auditory sensory gating and oddball paradigms, which are often used as biomarkers of psychiatric disorders in animal models and human patients. The recorded AEPs were comparable to previous human clinical data.
Comparison with existing methods: Compared with previous non-invasive head holding systems, top, side (cheek and ears), and rear of the head can be open for attachment of EEG electrodes and auditory stimulation in the present system.
Conclusions: The results suggest that the present system is useful in EEG recording from awake monkeys. Furthermore, this system can be applied to eye-tracking and chronic intra-cerebral recording experiments.

1. Introduction

Electroencephalograms (EEGs) have been used as one of diagnostic criteria for various psychiatric disorders such as schizophrenia, bipolar disorder, attention deficit/hyperactivity disorder (ADHD) and Alzheimer's disease (O'Donnell et al., 2004, 2013; Roach and Mathalon, 2008; Javitt et al., 1998; Yordanova et al., 2001; Koenig et al., 2005). Although similar EEG findings to those in human patients were reported in various psychiatric animal models in rodents (Gandal et al., 2010; Dringenberg, 2000; Dugovic et al., 2000), non-human primates (monkeys) should be useful to develop psychotropic agents since the structure and connectivity of the monkey brain are highly similar to the human brain (Petrides and Pandya, 2002; Neubert et al., 2014). However, most previous studies in monkeys recorded EEGs invasively using implanted electrodes (e.g. Gervais et al., 2016; Woodman et al., 2007; Javitt et al., 1992; Pineda and Nava, 1993), or using an invasive head-holding system, i.e., a head post implanted into the cranium to stabilize the head position (Gil-da-Costa et al., 2013). Considering animal ethics especially in monkeys (Mitchell et al., 2018), non-invasive methods are recommended in non-human primate EEG studies. To non-invasively record scalp EEGs, it is necessary to fix the subject's head to prevent movement related-artifacts. Previous studies reported non-invasive head holding systems using thermoplastic face masks or side head mold for monkey eye-tracking and chronic intra-cerebral recording (Machado and Nelson, 2011; De Luna et al., 2014; Amemori et al., 2015; Drucker et al., 2015). However, these previous systems are not suitable for EEG recording or auditory stimulation since top, side (cheek and ears) or rear of the head, where electrodes are attached or auditory stimuli are delivered, are partly covered by a mask, mold or a plate in a monkey chair (Amemori et al., 2015; Drucker et al., 2015). In this study, we expand these previous

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head-holding systems to be applied to non-invasive EEG recording so that top, side and rear of the head can be open for attachment of electrodes and auditory stimulation. To validate the present EEG recording system, two kinds of auditory evoked potentials (AEPs) that are frequently assessed in human clinical studies were recorded.

Auditory sensory gating is a phenomenon in which the brain shows reduced responses to repeated auditory stimuli, which is usually assessed by inhibition of AEPs in response to a second auditory stimulus compared with AEPs in response to a first auditory stimulus presented shortly in advance. Gating failure is thought to lead to a flooding of sensory stimulation (Venables, 1964). An auditory sensory gating deficit has been reported in schizophrenic patients and animals injected with phencyclidine (PCP) or amphetamine including monkeys with implanted electrodes (Jin et al., 1997; Brockhaus-Dumke et al., 2008; Adler et al., 1986; Huang et al., 2016). Rodents and monkeys injected with PCP, methamphetamine or ketamine were often used in animal studies of the schizophrenia because those drugs are known for inducing schizophrenic-like symptoms in animals (Becker et al., 2003; Nabeshima et al., 2006; Nakamura et al., 2016).

Second, auditory mismatch negativity (MMN) is a component of the AEPs to a deviant infrequent (odd) stimulus in the repetitive background of the standard stimulus; MMN is the negative component of AEPs obtained by subtracting AEPs to the standard stimuli from those to the deviant stimuli. The MMN is thought to reflect brain cognitive functions, in which attention is switched to focus on odd stimuli in an unattended stimulus stream (Näätänen et al., 2007). Cognitive deficit is one of the core symptoms of schizophrenia (Bowie and Harvey, 2006; Fioravanti et al., 2012), and deficit of MMN has been reported in schizophrenic patients and in animal models of schizophrenia including monkeys (Javitt et al., 1996, 1998; Shelley et al., 1991; Ehrlichman et al., 2008, 2009; Gil-da-Costa et al., 2013).

Thus, these AEPs have been widely used to assess cognitive deficits in human patients and animal models of psychiatric disorders, and should be useful in basic researches for understanding of pathologies of psychiatric disorders as well as pre-clinical translational researches (Arango et al., 2003; Hong et al., 2004; O'Donnell et al., 2013; Todd et al., 2013).

2. Material and methods

2.1. Subjects

A total of four adults (aged 3–4 years) male rhesus monkeys (*Macaca mulatta*, averaged body weight 4.4 ± 0.4kg) were used. All of the four animals were used in the auditory sensory gating experiment and two of them were additionally used in the auditory oddball experiment with a small pitch difference (see below). One of the two monkeys used in the auditory oddball experiment with a small pitch difference was further used in the auditory oddball experiment with a large stimulus pitch difference (see below). The subjects were housed in individual home cages on 12hr on/12hr off lighting schedule with food and water available ad libitum. The size of the home cage used in the present study was consistent with the criteria of the cage size for monkeys in the National Institute of Health guide for the care and use laboratory animals 8th edition. Supplemental fruits and vegetables were given after each day's testing session. To check the subject's health, their weight was routinely monitored, and their physical size and feces were monitored every day by animal care staffs and experimenters under the supervision of veterinarians. Environmental enrichment, in the form of toys, was provided daily, and all efforts were made to maximize the well-being of the animals. The subjects were treated in strict compliance with the United States Public Health Service Policy on Humane Care and Use of Laboratory Animals, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, Guidelines for the Care and Use of Laboratory Animals of the University of Toyama, and the Institutional Animal Care and Use Committee of Astellas Pharma Inc. This study was approved by the Committee for Animal Experiments and Ethics at the University of Toyama (Permit Number: A2016med-8) and Institutional Animal Care and Use Committee of Astellas Pharma Inc. (Permit Number: C-T12053, C-T12128, C-T13229, C-T14140, C-T15210, C-T15533, C-T17016, C-T18027).

2.2. Experimental setup

To hold the subject's head during EEG recording, a net-like facial mask made of thermoplastic (Shell seet, Esform, Matsumoto, Japan), which is used for patient immobilization for radiotherapy, was molded to fit the face of each subject. The perimeter of the net-like thermoplastic plate (160 × 140 × 2 mm) was strengthened using a polyacetal plate, which was later attached to a metal frame fixed on a monkey chair (O'HARA & CO., LTD., Tokyo, Japan) during EEG recording. To mold a facial mask, a subject sat in a monkey chair under light anesthesia (ketamine, 10 mg/kg, i.m.) while the experimenter supported the body and head to prevent tightening of the neck. A thermoplastic plate was softened by hot water, and was pressed against a face of a subject. A space for nose was formed to allow subjects to breathe easily during EEG recordings. Then, the subject was put back into a home cage, and the thermoplastic plate was further modified. The upper region of the mask was modified using boiled water to open a space for electrode placement on the head. In addition, small pieces of softened thermoplastics (approximately 30 × 50 × 2 mm) were attached to the jaw and forehead parts of the mask to strengthen it (see Supplementary Figure S1B in Results), since these two parts were prone to the greatest force from the head. Thus, the mask consisted of a single-layer part made of an original mesh plate around the eye regions, and a reinforced part without mesh holes covering the jaw and forehead (Figure 1A).

After the mask molding and modification, all subjects were trained for two weeks to habituate to the mask. A monkey was seated in a monkey chair, and then face mask with the metal frame was attached on the monkey chair. The anterior part of the head was held by the mask, and the posterior part of the head (i.e., the occipital bone below the inion) was held by around U-shaped acrylic plate (Figure 1A). This head holding system could hold the head stably without obvious visible head movements (see Results). For auditory stimulation, two speakers were always placed in the same position relative to the chair: 50 cm away from both sides of the chair (Figure 1B).

2.3. Auditory stimuli

Stimuli were generated by MT-ST-S (Melontechnos, Kanagawa, Japan). In the auditory sensory gating experiment, the 200 paired clicks (S1 and S2, 80 dB) separated by short interval (300 ms) were presented with an 8-s inter-stimulus interval. In the auditory odd ball experiment, two sets of auditory stimuli (75 dB; 50 ms duration with 5 ms rise/fall; 600 ms inter-stimulus interval) consisting of standard (frequent) and deviant (infrequent) tones with different frequencies [330 (standard) vs. 349 (deviant) Hz for 390 ms; 1500 (standard) vs. 500 (deviant) Hz for 325 ms] were presented. Standard and deviant stimuli were pseudo-randomly presented 80 % (330 Hz, 480 times; 1500 Hz, 400 times) and 20 % (349 Hz, 120 times; 500 Hz, 100 times) of the number of presentations (no two deviants right after one another).

2.4. EEG recordings

The subject's head was shaved using a depilatory cream in advance. The subject sat in the monkey chair and the head was fixed. EEG electrodes were placed on the subject's head according to the International 10–20 system (Figure 2, left panel). A total of eleven active electrodes (F3, FZ, F4, C3, CZ, C4, P3, PZ, P4, A1, A2) and a passive electrode for ground (G) were placed on the scalp (Figure 2). EEG signals were amplified and recorded using a Polymate II AP216R2 system with active electrodes (Miyuki Giken Co., Ltd., Tokyo, Japan). All EEG channels were referred to the linked ear lobes, and the impedance was kept below 30

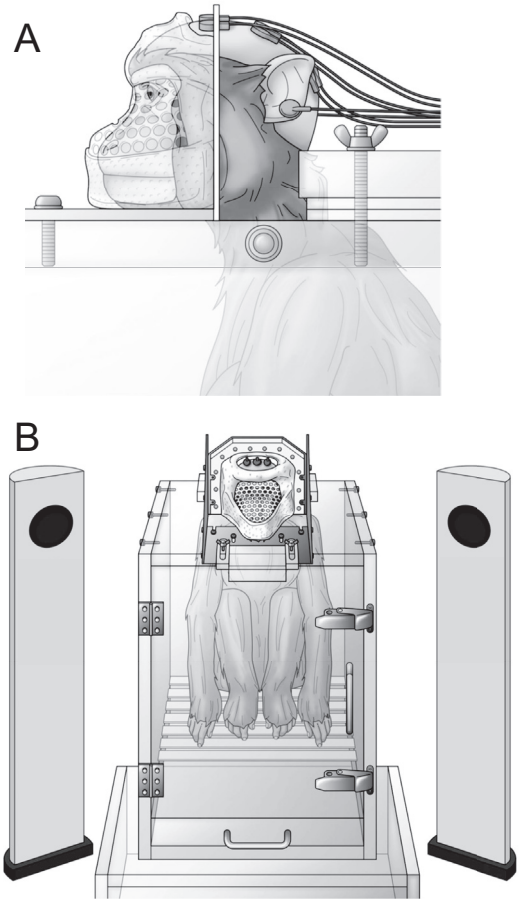

Figure 1. Illustrations of the non-invasive EEG recording system for monkeys. (A) Schematic diagram showing relative positional relationships among a face mask, monkey head, and acrylic plate on a monkey chair. (B) A perspective illustration of the whole EEG recording system for AEPs. Bilateral semi-cylindrical columns indicate speakers for auditory stimulation.

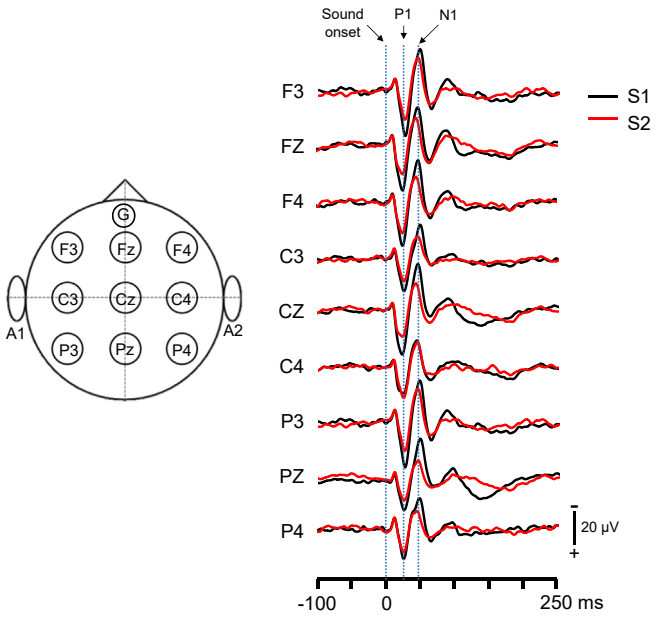

Figure 2. Examples of typical AEPs recorded from 9 electrodes elicited by S1 (black) and S2 (red) in a single subject in the auditory sensory gating task. P1 and N1 waves were smaller in S2 than S1. The left panel in the figure indicates placement of EEG electrodes. The right panel indicates AEPs recorded from the EEG electrodes shown in the left panel. G, ground electrode.

kΩ. Ear lobes were fixed by a surgical tape to prevent artifacts due to ear lobe movements. The EEG data were digitized at a sample rate of 1 kHz and stored on a CF memory card. Tones were delivered from the speakers placed near the monkey chair. Tone intensity was calibrated at the location of the ears of the monkeys. In the present study, to avoid effects of motor processes such as motor preparation (readiness potentials), the monkeys sat on the chair with no behavioral requirements during auditory stimulation in the auditory sensory gating and MMN experiments as in human studies (e.g., Gomes et al., 2000; Grunwald et al., 2003). Visual inspection from the mesh plates indicated that the monkeys' eyes were open during EEG recording, suggesting that the monkeys were in an awake condition during the experiment.

EEG data were band-pass-filtered between 5 to 80 Hz using a butterworth digital filter (12dB/oct slope) and segmented into 1200 ms epochs of a stimulus including 600 ms pre- and post-stimulus intervals. Epochs in each channel were discarded to remove movement-related artifacts if peak magnitudes of the epochs exceeded mean peak amplitudes of all epochs ± 2SD: average 7.2 ± 0.5 in 200 epochs (auditory sensory gating), 18.5 ± 1.4 in 480 epochs (standard 330 Hz), 4.7 ± 0.4 in 120 epochs (deviant 349Hz), 19.7 ± 2.2 in 400 epochs (standard 1500Hz), 6.7 ± 0.6 in 100 epochs (deviant 500Hz) were removed in each channel. Topographic voltage-distribution maps were produced by the toolbox of EEGLAB (Schwartz Center for Computational Neuroscience; Delorme and Makeig, 2004).

2.5. Data analysis

Quantitative data were expressed as means ± SEM. Data in the auditory gating were analyzed by bootstrap test. In this analysis, the mean peak values (P1, maximum value between 0 and 30 ms after the tone onset; N1, minimum value between 40 and 70 ms after the tone onset) of each S1 and S2 were restored and extracted by computer, building 2500 mean differences between S1 and S2 by using JMP pro 14 (SAS institute Inc., USA). The statistical significance level was set at $p < 0.05$.

3. Results

3.1. Head holding system

Supplementary Figure S1 shows photos of an original mesh plate before thermo-forming (A) and an example face mask after thermo-forming with attachments of small plates to the forehead and jaw regions (B). By thermo-forming, face masks fitted with individual monkey faces were made. To non-invasively record scalp EEGs, it is important to hold the subject's head stably to prevent head movement-related artifacts. To prevent rotation of the head, a part of the mask covering the jaw was reinforced. To prevent turning the head up and down, the forehead part of the mask was reinforced, and the U-shaped acrylic plate was set below the occipital protuberance. Taken together, the system held the subject's head by jaw, forehead, and occipital protuberance (Figure 1). It is noted that both sides of the head including the ears are open for precise auditory stimulation (see Discussion). All of the four monkeys could adapt to this head holding system without indicating stressful behaviors such as facial aggressions and vocalizations after training. Eye movement of monkeys could be observed by visual inspection through the mesh holes around the eye region. Occasional visual inspection indicated that the monkeys could follow human movements around the monkey by eye movements, and extensive eye movements and eye closure were not observed with the face mask. Although the head was held not as rigidly as a head holding system using a head-post, this system could hold the monkey head stably without obvious visible head movements.

3.2. Auditory sensory gating

AEPs were recorded stably from 9 electrodes (Figure 2), with relatively small number of averaging times as small as 100 times (Supplementary Fig. S2A). Positive potentials (P1) were observed around 24 ms after stimulus onset while negative potentials (N1) were observed around 50 ms after stimulus onset. In the examples shown in Figure 2, AEPs elicited by S2 (red) had smaller amplitudes than those elicited by S1 (black) on most electrodes except C4. In all of the four subjects, peaks of P1 were reliably observed in 20–24 ms latencies, and peaks of N1 and N1/N2 complex were observed in 50–82 ms latencies at Cz (Figure S2B). Topographical maps at peak latencies of P1 in the individual 4 monkeys indicated that P1 elicited by both S1 and S2 were observed with high amplitudes around Fz and Cz (Figure 3A(i)). Topographical maps at peak latencies of N1 indicated that N1 elicited by both S1 and S2 were also observed with high amplitudes around Fz and Cz (Figure 3B(i)). The topographical maps of the subtraction AEPs (S1–S2: AEPs elicited by S1 minus those elicited by S2) at peak latencies indicated that amplitude reduction of P1 and N1 by stimulus repetition was stronger in Cz (Figure 3A(i) and B(i), respectively).

Mean peak potentials of P1 and N1/N2 complex elicited by S1 and S2 is shown in Figure 3A(ii) and B(ii), respectively. Their mean peak difference was tested using a bootstrap resampling procedure. The mean peak potentials of P1 were significantly lower in the second (S2) than first (S1) stimuli [S1, 31.9 ± 4.2, mean ± SEM, μV; S2, 16.8 ± 1.3μV] (bootstrap test, $p < 0.0001$) (Figure 3A(ii)). The mean peak potentials of N1/N2 complex were significantly higher in the second (S2) than first (S1) stimuli (i.e., lower amplitudes in S2 than S1) (S1, -31.0 ± 5.0 μV; S2,

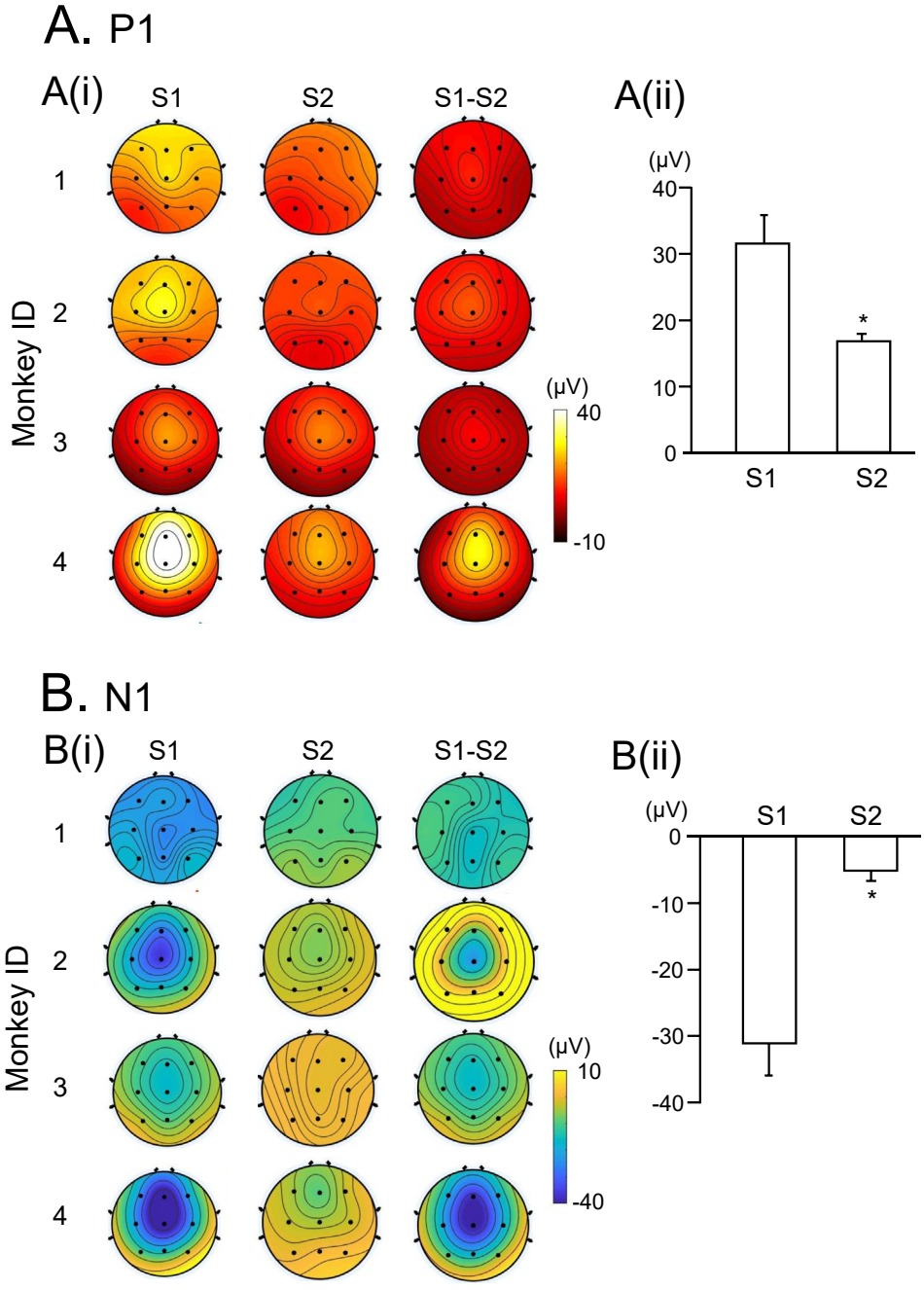

Figure 3. AEP components of auditory sensory gating. (A) Topographical maps of P1 of the four subjects (1–4) in response to S1 and S2 (A(i)) and comparison of mean amplitudes at Cz between S1 and S2 (A(ii)). (B) Topographical maps of N1 of the four subjects (1–4) in response to S1 and S2 (B(i)) and comparison of mean amplitudes at Cz between S1 and S2 (B(ii)). *Significant difference by bootstrap test. Error bars represent SEMs.

-5.1 ± 1.5 μV; bootstrap test, $p < 0.0001$) (Figure 3B(ii)). These data indicated that peak amplitudes of both P1 and N1/N2 complex of the AEPs were reduced in S2 compared with S1.

3.3. MMN

A previous study suggests that MMN reflects stimulus-specific adaptation rather than deviance detection in the auditory cortex in monkeys, and other brain areas such as the frontal cortex might be involved in deviance detection (Fishman and Steinschneider, 2012). Since the frontal cortex was more sensitive to small deviance (Opitz et al., 2002; Doeller et al., 2003), the standard and deviant stimuli with small pitch difference were also introduced in the present study (see Discussion for details). Thus, two kinds of stimulus sets were used (first stimulus set: standard 330 Hz and deviant 349 Hz; second stimulus set: standard 1500 Hz and deviant 500 Hz) to confirm that MMN could be observed even if the tone pitch differences were small. Only one monkey (Monkey 1) was tested with the second stimulus set.

Figure 4A indicates example AEPs in response to the first stimulus set [330 (standard) vs. 349 (deviant) Hz]; N1 elicited by the deviant stimulus (red) was observed with larger amplitude than that elicited by the standard stimulus (black) at Fz. Figure 4B shows the topographical maps of the AEPs at N1 peak latencies, in which negative potentials in response to the deviant stimulus were observed around the Cz and Fz in the monkey 1 and Fz in the monkey 2. Figure 4C shows the AEP amplitudes at Fz at N1 latencies elicited by the deviant and standard stimuli in the two monkeys. N1 elicited by the deviant stimulus (red) was observed with larger amplitudes than that elicited by the standard stimulus (black) at Fz in the two monkeys.

Figure 4D indicates AEPs at F3 and Fz in response to the second stimulus set [1500 (standard) vs. 500 (deviant) Hz] in Monkey 1. A positive potential (P1) was observed around 30 ms after stimulus onset while a negative potential (N1) was observed around 50 ms after stimulus onset. The difference AEPs (AEP elicited by the deviant stimulus minus AEP elicited by the standard stimulus) indicate clear MMN around 50 ms, consistent with the results in the first stimulus set as well as previous studies using scalp EEG recording with head post holding and epidural and intra-cerebral EEG recording (Javitt et al., 1992; Fishman and Steinschneider, 2012; Gil-da-Costa et al., 2013). Figure 4E show topographic maps at N1 peak latencies in the second stimulus set (standard 1500 Hz, deviant 500 Hz) in Monkey 1. Negative potentials were also observed around the frontal area in this subject.

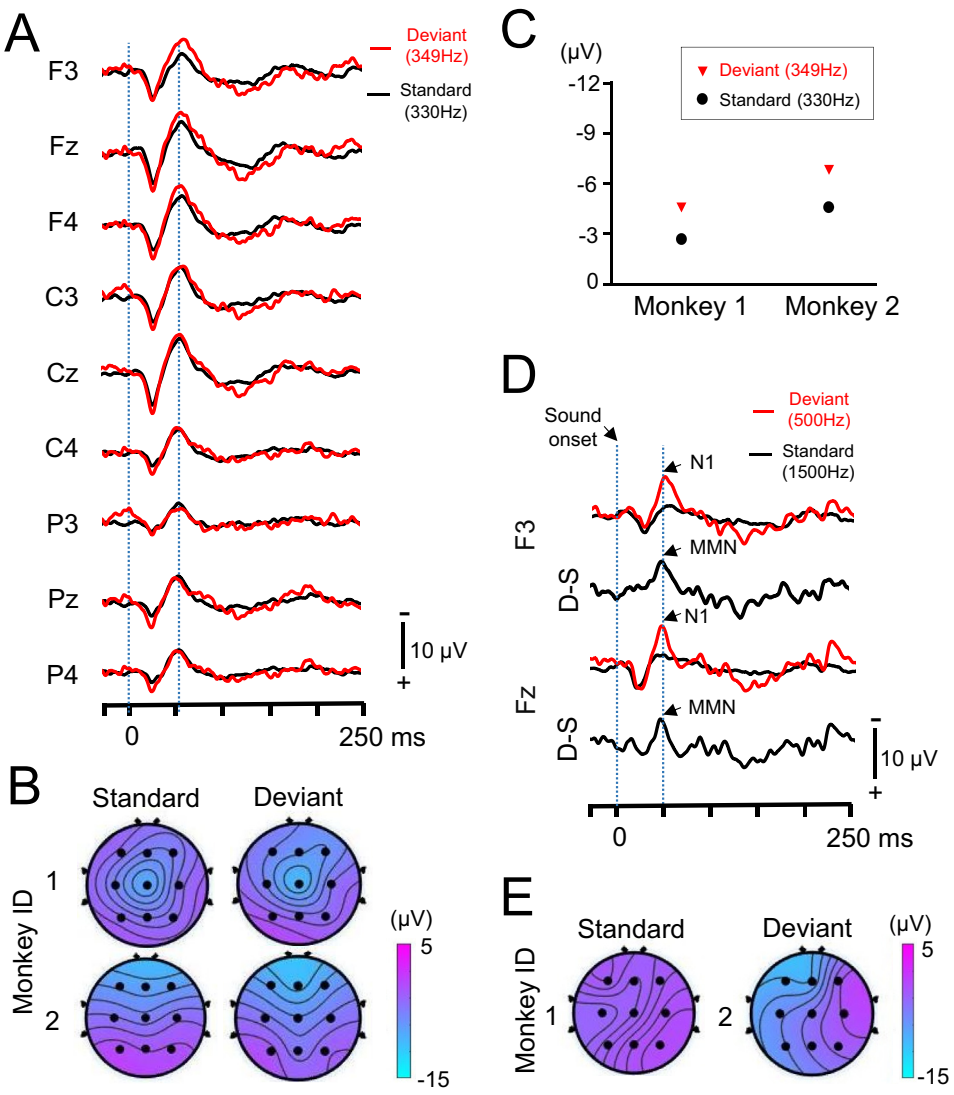

Figure 4. AEPs recorded in the auditory oddball paradigm. (A) Typical recordings from 9 electrodes of AEPs elicited by 330-Hz standard (black) and 349-Hz deviant (red) stimuli from Monkey 1. (B) Topographical maps of AEPs at N1 latencies in the two subjects (Monkeys 1, 2). (C) Comparison of N1 peak amplitudes in the two subjects elicited by 330-Hz standard (black circles) and 349-Hz deviant (red triangles) stimuli (Fz). (D) Recordings from F3 and Fz of AEPs elicited by 1500 Hz standard (black) and 500 Hz deviant (red) stimuli from Monkey 1. D-S, difference AEPs [AEPs elicited by the deviant stimuli (500 Hz) – those elicited by the standard stimuli (1500 Hz)]. (E). Topographical maps of AEPs at N1 latencies in Monkey 1.

4. Discussion

4.1. Comparison with previous methods in EEG recording from awake monkeys

As far as we know, eleven previous studies reported non-invasive EEG recording in monkeys. Of these, nine studies reported non-invasive EEG recordings without head holding in rhesus monkeys (Honing et al., 2012, 2018; Gindrat et al., 2015; Festante et al., 2018), spider monkeys (Cruz-Aguilar et al., 2015), and chimpanzee (Ueno et al., 2008, 2009; Fukushima et al., 2010; Hirata et al., 2013). In these studies, without head holding, the number of electrodes was limited, and it took a long time for training so that animals could learn suitable conditions for EEG recordings; approximately six months in chimpanzee (Ueno et al., 2008). Furthermore, anesthesia was required to place electrodes on the head (Cruz-Aguilar et al., 2015; Gindrat et al., 2015). Thus, non-invasive EEG recordings without head holding has several difficulties, which is not suitable for pharmacological studies requiring a relatively large number of animals. Therefore, head holding is recommended even for awake monkeys. The remaining two studies reported non-invasive EEG recording with head holding. In one study, to prevent head movements, a head post was implanted into the skull of monkeys as in neurophysiological studies for single unit recording (Gil-da-Costa et al., 2013). In another study, head movements were restricted by polystyrene blocks placed on both sides of the head on a monkey chair and horizontal bars placed above the nose and supraorbital ridge (Itoh et al., 2015).

In the present study, the monkey head was non-invasively fixed, and monkeys could easily adapt to the experimental situation. The head-holding allowed precise placement of electrodes on the head, and precise calibration of auditory stimuli at the positions of the ears as well as presentation of identical auditory stimuli throughout experiments. Furthermore, high-impedance active electrodes used in this study also contribute to EEG recording with low noise baseline levels; in case of AEPs, 100 times are enough to record clear AEP waves (Supplementary Figure S2A). In addition, placement of the holder (face mask and acrylic plate) on the monkey chair took only 2–3 min after a monkey was seated on the monkey chair. These characteristics of the present system are useful for pre-clinical translational studies requiring experiments with relatively large number of animals in a short term.

4.2. Application to auditory sensory gating

Auditory sensory gating was quantified using the present non-invasive EEG recording system in monkeys, in which paired clicks were presented in a short interval. In human studies, reduction of AEPs was observed in positive potentials around 50 ms latency (P50) and negative potentials around 100 ms latency (N100) (Jin et al., 1997; Brockhaus-Dumke et al., 2008). In the present study, latencies of positive and negative peaks were around 20–24 and 50–80 ms, respectively, which was almost half of those in human P50 and N100. These findings are consistent with previous studies in which latencies of somatosensory evoked potentials in monkeys were almost half of human data (Hayashi et al., 1995; Allison et al., 1989). The shorter latencies in monkeys might be ascribed to smaller brain sizes in monkeys. However, a previous study using cynomolgus monkeys reported AEP latencies comparable to human data (positive potentials around 10–60 ms and negative potentials around 60–150 ms) (Huang et al., 2016). The longer latencies in this study might be ascribed to anesthetics used during the experiment.

In the present study, reduction of P1 was more evident in the frontal cortex. It has been proposed that the frontal cortex is involved in reduction of human P50 (Weisser et al., 2001), consistent with the present study. Furthermore, AEP reduction was lowered in patients in schizophrenia (Jin et al., 1997; Brockhaus-Dumke et al., 2008), in which frontal functional deficits are reported (Mubarik and Tohid, 2016). These findings indicate that the present non-invasive EEG recording system allows to assess auditory sensory gating in awake intact monkeys, where auditory sensory gating could be used as neurophysiological biomarkers for schizophrenic symptoms and drug development (Javitt, 2007; Smucny et al., 2015). Thus, the system should be useful for preclinical researches in drug development for schizophrenia.

4.3. Application to MMN

Although large EEG changes above the threshold associated with eye blinks and saccades were removed and extensive eye movements were not observed by occasional visual inspection through the mesh holes in the present study, it should be noted that eye movements were not monitored in the present study. Therefore, it is possible that the present results of the MMN analysis might be ascribed to small artifacts associated with saccades in response to the deviant stimuli. However, it is unlikely because of two reasons. First, MMN latencies were around 50 ms after the stimulus onset in the present study, while saccade latencies to auditory stimuli ranged from 250 to 350 ms, which were longer than those to visual stimuli (200–300) in humans (Zambarbieri et al., 1982). Since saccade latencies to visual stimuli (200–300 ms) were comparable between humans and monkeys (Zambarbieri et al., 1982; Tian et al., 2016), it is presumed that saccade latencies to auditory stimuli in monkeys might be comparable to those in humans (i.e., 250–350 ms), or at least longer than those to visual stimuli in monkeys (200–300 ms). The findings suggest that the MMNs with 50 ms latencies in the present study might not be susceptible to saccade artifacts. Second, the present study used diotic auditory stimulation (same sound in both ears), which reduced sound-induced eye movements (Braga et al., 2016). Furthermore, mean incidence of large EEG changes in the anterior part of the channels (F3, Fz, F4, C3, Cz, and C4) (rejection times for noise cancelation per epoch) were comparable between the standard and deviant stimuli (standard: 0.040 ± 0.0030 times/epoch; deviant: 0.052 ± 0.0077 times/epoch) in the present study, suggesting that incidence of events with large EEG changes including saccades and eye blinks were comparable between the standard and deviant stimuli. All of the findings suggest that MMNs were not ascribed to EEG artifacts in response to the deviant stimuli. However, a hole for the eye region can be made in the face masks of the present system, which can be applied to eye-tracking to remove EEG artifacts. Future studies should consider to monitor eye movements.

In the present study using the odd ball paradigm with two different frequency tones (330 kHz; 349 kHz), MMN was observed at negative potential around 50 ms (N1) in Cz and Fz in two subjects, consistent with previous monkey studies with large MMN amplitudes at Cz and Fz (Honing et al., 2012; Gil-da-Costa et al., 2013). In AEP recording from monkeys (*Macaca fascicularis, Macaca mulatta*), N1 latency recorded from scalp electrodes was around 50 ms (Itoh et al., 2015; Honing et al., 2018), consistent with the present study. In another neurophysiological study with cynomolgus monkeys, two different loudness click tones (85 dB and 65 dB) were presented in a similar oddball paradigm. This study recorded AEPs from epidural electrodes, and reported that MMN was observed around N40/N70 complex (which corresponds to N1 component in the present study) (average peak latency of the MMNs across 3 monkeys, 81.9 ms) (Javitt et al., 1992). Although peak latencies of N40/N70 complex were different among the 3 monkeys in the study by Javitt et al. (1992), they reported that both amplitudes of N40 and N70 in one monkey (monkey 1) were larger in the oddball condition in the frontal electrodes, consistent with the present study. In a study using a head post-fixation, two different loudness 1500 kHz tones (60 and 80 dB) were presented, and MMN was observed at negative potential around 48–120 ms (N1) in two rhesus macaques (Gil-da-Costa et al., 2013). The waveforms recorded from epidural intra-cerebral electrodes (Javitt et al., 1992; Fishman and Steinschneider, 2012) and those from scalp electrodes with head post-fixation (Gil-da-Costa et al., 2013) were very similar to those recorded from scalp electrodes in the present study. However, peak latencies of MMNs were not identical across the studies including the present study. In humans, MMN latencies were highly

variable depending on magnitudes of stimulus changes, stimulus complexity, stimulus presentation rate, number of standard stimuli preceding a deviant stimulus, IQ of subjects, etc. (Alain et al., 1994; Matuoka et al., 2006; Näätänen et al., 2007; De Pascalis and Varriale, 2012). In addition, there were individual differences in MMN latencies even within the same species in monkeys (Honing et al., 2018). These findings suggest that the differences in MMN latencies across the studies might be ascribed to the difference in stimulus presentation procedures as well as individual differences across the studies. Although further studies are required to investigate latencies of MMNs, MMN was observed in N1 or waves after N1 in all studies including the present study. These findings suggest that AEPs recorded using the non-invasive head holding in the present study are comparable to those in the previous studies with the different recording methods.

Previous studies suggest that there are at least two generators of auditory MMN; the frontal and superior temporal cortices (Jemel et al., 2002; Opitz et al., 2002; Doeller et al., 2003; Tse et al., 2013). A recent study reported that MMN reflects stimulus-specific adaptation rather than deviance detection in the auditory cortex in monkeys, and other brain areas such as the frontal cortex might be involved in deviance detection (Fishman and Steinschneider, 2012). Consistently, a direct cortical recording from common marmosets indicated that electrodes in the frontal areas showed different patterns of negativity from those around the lateral sulcus (near the temporal lobe) (Komatsu et al., 2015). Since the frontal cortex was more sensitive to small deviance while the auditory cortex was more sensitive to large deviance (Opitz et al., 2002; Doeller et al., 2003), we used the standard and deviant stimuli with small pitch difference in the present study. The present study indicated relatively stronger MMN component in the frontal area although generators of the MMN were not analyzed. However, the present findings suggesting a frontal involvement in deviant detector is not conclusive. Further studies with intra-cerebral recording are required to locate brain areas involved in true deviant detector. However, since MMN is reduced in various types of schizophrenic patients and sensitive to N-methyl--d-aspartate (NMDA) antagonists (Nagai et al., 2013; Todd et al., 2013), the present EEG recording system for intact awake non-human primates could contribute to preclinical pharmacological studies.

4.4. Conclusions

Since anesthetics could affect AEPs in auditory sensory gating and oddball paradigms (Simpson et al., 2002; Hentschke et al., 2017), it is important to record AEPs from awake animals. In EEG recording from awake monkeys, stable head holding is important to avoid movement-related artifacts. In the present study, a novel non-invasive EEG recording system for awake monkeys was developed so that top, side and rear of the head can be open for attachment of EEG electrodes during head fixation. Monkeys could easily adapt to the system. Furthermore, this system is especially useful to AEP (EEG) recording since both sides of the head including the ears are open for auditory stimulation. In this system, AEPs such as auditory sensory gating and MMN were reliably recorded. Furthermore, this system can be applied to other paradigms such as that for auditory steady-state responses (ASSRs), deficits of which have been reported in schizophrenia and bipolar disorder (Tada et al., 2014; Mulert et al., 2011; Tsuchimoto et al., 2011; Oda et al., 2012). Although the eye region was covered by a mesh plate in the present study, a hole in the eye region in the face masks can be made, which allows to monitor eye movements by various methods (see above). Furthermore, a hole around the mouth region of the facial mask allows to deliver liquid reward to a monkey through a small tube. These modifications in the face masks would allow to apply this system to record neural activity including EEGs during performance of a task in which monkeys respond to visual or auditory stimuli by pressing a button to acquire liquid reward.

Thus, useful biomarkers of psychiatric disorders such as AEP components of auditory sensory gating and MMN can be analyzed using this present system, suggesting that this present system should be useful in preclinical translational studies to develop new therapeutic agents for psychiatric disorders. In addition, the features of the system recommend it for various types of neuroscientific researches.

Declarations

Author contribution statement

Tomoya Nakamura: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Trong Ha Dinh, Etsuro Hori: Performed the experiments; Wrote the paper.

Makoto Asai, Hiroshi Nishimaru, Sokichi Honda, Hiroshi Yamada, Mitsuyuki Matsumoto: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper

Jumpei Matsumoto, Yusaku Takamura: Analyzed and interpreted the data; Wrote the paper.

Takuma Mihara: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hisao Nishijo: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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