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Reliability of the Flash Visual Evoked Potential P2: Double-Stimulation Study

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Abstract
The flash visual evoked potential P2 (FVEP-P2) has been identified as a potentially useful clinical, diagnostic tool for Alzheimer's dementia (AD) and mild cognitive impairment (MCIa) due to its association with cholinergic functioning in the brain. The FVEP-P2 is the second positive component of the VEP waveform elicited by a single strobe flash. Despite finding a selective delay in the latency of the FVEP-P2 in AD and MCIa groups, adequate levels of sensitivity and specificity have not been achieved due to natural group differences and inter-individual variability. In response, Fix and colleagues introduced a novel, double-stimulation paradigm that contained two strobe flashes (i.e., stimulations). The first stimulation served as a visual challenge while the second stimulation produced the recorded FVEP-P2 component. The results of that investigation indicated that the latency of the FVEP-P2 could be used to reliably discriminate between aMCI and healthy controls when the ISI of the double-stimulation condition was 100 ms or higher. Unfortunately, very little is known regarding the psychometric properties of the FVEP-P2 when produced by a double-stimulation condition. Consequently, we assessed the test–retest reliability of the FVEP-P2 latency produced by a single- and twelve double-stimulation conditions in a sample of young, healthy individuals (N = 20). Results indicated that while the FVEP-P2 latencies produced by the single- and double-stimulation paradigm were reliable, the intra-individual variability continued to be too high for the FVEP-P2 latency to be used clinically. Methods of reducing the intra-individual variability are discussed, including the use of monochromatic light.

Keywords Alzheimer's dementia · Mild cognitive impairment · MCI · Evoked potential · FVEP-P2 · Reliability

Introduction

Research on Alzheimer's dementia (AD) has become critical as the United States' "baby boomer" generation now approaches the age range associated with the onset of AD (Alzheimer's Association 2017). There were approximately 5.5 million diagnosed AD cases in 2017, and it has been estimated that by the year 2050 there will be 13.8 million adults aged 65 and older within the United States diagnosed with AD (Alzheimer's Association 2017). Along with the impact that this will have on the hospitals, families and caregivers, the US government is projected to have a four-fold increase in annual payments towards health care for AD from 2017 to 2050 (Alzheimer's Association 2017). Currently, other than necropsy, AD is diagnosed by exclusion criteria rather than the direct detection of the disease (Coburn et al. 2003; Fletcher et al. 2013). As a result, the AD diagnostic process has been described as inefficient and costly (Coburn et al. 2003; Fletcher et al. 2013).

In pursuit of a cost-effective and non-invasive diagnostic tool, researchers have examined a number of potential biomarkers, including the flash visual evoked potential P2 (FVEP-P2), which is an EEG biomarker (Laske et al. 2015). The FVEP-P2 is the second major positive component of the visual evoked potential waveform, and is produced by averaging electrical potentials recorded from the brain in response to a single strobe flash (Case et al. 2016; Contestabile et al. 1995; Odom et al. 2016; Schwartz and Shagass 1964; Subramanian et al. 2013). The FVEP-P2 has been of particular interest due to its association with the highly cholinergic visual association cortex (Case et al. 2016; Coburn et al. 2003, 2005; Fix et al. 2014). Deficits in cholinergic functioning are often the hallmark sign of beginning stages

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of AD and amnestic Mild Cognitive Impairment (aMCI; an early stage of AD), and may be identified using the FVEP-P2 latency (Fix et al. 2014). Indeed, research on visual processing in AD and aMCI patient groups have documented a selective delay of the FVEP-P2 latency (Fix et al. 2014; Moore 1997; Petersen 2004; Tartaglione et al. 2012). Unlike other dementias and neuropsychiatric disorders, the selective delay associated with the FVEP-P2 often increases progressively for those diagnosed with AD or aMCI and does not affect other components of the visual evoked potential, including the P1 or P100 that are produced by the sparsely cholinergic primary visual cortex (Ciuffini et al. 2014; Coburn et al. 2005; Fix et al. 2014).

Despite consistent reports of group differences between patients diagnosed with AD and age-matched, healthy controls, the within-group variation associated with the FVEP-P2 latency prevents it from being diagnostically useful (Ciuffini et al. 2014; Coburn et al. 2003, 2005; Fix et al. 2014). In an effort to minimize the within-group variability of the FVEP-P2 latency, the International Society for Clinical Electrophysiology of Vision (ISCEV) has adopted standards for the measurement of VEPs based on researched variables, such as luminance intensity, eyelids (i.e., open/closed), electrode recording site, and the physical properties of monochromatic light (Coburn et al. 2005; Subramanian et al. 2012, 2013). The results of these studies suggest that electrodes placed at O2, Oz, and PzP produced the most reliable FVEP-P2 component when the eyes are closed and the luminance associated with the strobe flash is low (Coburn et al. 2005; Odom et al. 2016; Subramanian et al. 2012, 2013). Unfortunately, these improvements have done little to reduce within-group variability, limiting the clinical usefulness of the FVEP-P2 latency in discriminating between aMCI and healthy controls (Fix et al. 2014).

In response, Fix et al. (2014) proposed using a novel double-stimulation paradigm (Cantello et al. 2011) where the first of the two strobe flashes would serve as a challenge to an already compromised cholinergic visual system (Cantello et al. 2011; Fix et al. 2014). Early research utilizing the double-flash stimulation paradigm (i.e. paired-pulse FVEPs, two-flash threshold, visual recovery cycle or visual refractory period research) had found that a double-flash presented at interstimulus intervals (ISIs) of 40–50 ms and shorter obscured the measurement of the cortical response to the second flash stimulus (Cantello et al. 2011; Fix et al. 2014). Reported refractory thresholds ranged from approximately 50–85 ms, at which point the FVEP produced additional VEP components corresponding to the second stimulus (Andreassi et al. 1971; Schwartz and Shagass 1964). However, research on the double-stimulation FVEP procedure was largely set aside after the early seventies, most likely due to technological and computational limitations (Cantello et al. 2011). As a result, issues identifying the components of the VEP elicited by the second stimulus, and discerning component waveform latencies despite individual differences of refractory period were left largely untouched until now (Andreassi et al. 1971; Buchsbaum 1970; Cantello et al. 2011; Schwartz and Shagass 1964).

Recent technological advances have given researchers the ability to revisit the double-flash stimulation and explore methods that would increase the paradigm's clinical utility (Cantello et al. 2011). Indeed, the results of the Fix et al. (2014) study demonstrated the possible clinical utility of the FVEP-P2 when a double-stimulation paradigm is used. Patients diagnosed with aMCI were much more likely to exhibit a selective delay in the latency of the FVEP-P2 under the single- and double-flash conditions (i.e., 100 ms ISI and 120 ms ISI) than controls. Despite these recent advances, however, very little is known about the psychometric properties of the FVEP-P2 when a double-stimulation paradigm is employed (Cantello et al. 2011).

Hence, the purpose of the current investigation was to assess the reliability of the FVEP-P2 (i.e., latency and amplitude) produced by the second of two strobe stimulations in a novel, double-stimulation paradigm. It was hypothesized that the test–retest reliabilities associated with the double-stimulation conditions (i.e., 100 ms ISI, 110 ms ISI, and 120 ms ISI) would be as large as those produced by the single-flash condition (Musselwhite and Jeffreys 1983; Skrandies and Raile 1989). It was further hypothesized that the within-group variability associated with the double-stimulation conditions would be lower than in the single-stimulation condition, and that a reduction in within-group variability might improve the diagnostic accuracy of the FVEP-P2 in the future. If diagnostic accuracy of the FVEP-P2 could be improved, it's possible that this biomarker could help add precision and earlier detection for AD diagnosis (Coburn et al. 2003).

Methods

Participants

Participants were recruited from a regional comprehensive university using a Participant Research Pool that allowed students from the university to sign up for participation in research for extra credit in selected courses. Participation in the study required that the student had no prior seizures or neurologic disorders that are known to be affected by light, no photosensitivity, and no history of loss of consciousness greater than 20 min. Before removing outlier data, 26 students ages 18–47 years ($M = 24.54$, $SD = 5.57$, males = 10, females = 16) participated in the study. Of those 26 participants, 24 self-reported having normal to corrected-normal vision. After performing Tukey's method of leveraging the

interquartile range to identify outliers, 22 students ages 18–47 years ($M = 24.41$, $SD = 6.01$, males = 7, females = 15) were included in the study analyses. Of those 22 participants, 20 self-reported having normal to corrected-normal vision. All participants provided informed consent.

Demographic Questionnaire

Demographic information was collected using a questionnaire comprised of items that assessed the age, sex, vision, and neurological history of participants.

Instrumentation

Instrumentation consisted of the Neuroscan Curry 7 software system, a SynAmpse RT DC amplifier, and a Stim2 program on a second computer that controlled the timing of the strobe flashes (5.5 lm s/ft^2, maximum energy 1.44 J) through a Grass Model PS 33 Plus photo stimulator that had a 13.7 cm diameter xenon strobe lamp. Synch pulses were sent to the Neuroscan Curry 7 system to incorporate triggers.

EEG acquisition

EEG data were collected using a CompuMedics Quik-Cap-EEG 64-channel electrode cap. EEG was sampled from two electrode-recording sites using a 64-channel Synamp DC amplifier at a sampling rate of 1,000 Hz, and a band pass of DC-400 Hz. The data were then band pass filtered 1–30 Hz using a zero phase shift digital filter. The two electrode-recording sites were Oz, and O2. Electrode recording sites were chosen based on the work of Coburn et al. (2005) and Odom et al. (2016), which indicate these as optimal sites for FVEP acquisition. All scalp electrodes were referenced to two electrodes placed on the left and right mastoid (M1 and M2), and a ground electrode was placed at Fz. Data were epoched and then averaged around each of the flash stimulus synch pulses (i.e., − 200 ms to + 500 ms). All impedances were kept below 15k ohms. Eye movement artifact was measured using two bipolar electrode pairs placed superior and inferior to the eye, and one set of electrodes placed lateral to each eye. Trials contaminated by artifact greater than ± 50 μv were rejected using an off-line artifact rejection algorithm. Eye movement artifact was corrected using the method described by Semlitsch et al. (1986).

Procedure

Upon arrival, participants were given an informed consent form and a demographics questionnaire to complete. Once both were signed and completed, participants were seated comfortably while electrodes (i.e., Oz and O2) were placed according to an expanded version of the international 10–20 system of electrode placement. Once the electrodes were placed, the participants were asked to leave any electronic equipment behind as they were escorted to the shielded room where the EEG data were collected. After impedances had been checked, the photo stimulator was placed 24.5 cm from the participant's closed eyes (Coburn et al. 2005). Participants were instructed to keep their eyes closed, and to remain still and relaxed for the duration of the study. The pre- and post-test periods were approximately 30-min long with a 10-min break in between. The post-test was given in order to assess 10-min test–retest reliability. Each testing session (i.e., pre and post) was comprised of 13 blocks, or conditions, presented in counterbalanced order. Of the 13 conditions, only one was a single-flash condition. The remaining 12 conditions were double-flash (10 ms ISI to 120 ms ISI in 10 ms increments). Each block was comprised of 100 flashes, with each flash being 10 μs in duration. Each flash or paired-flash in all blocks were randomly presented ($M = 1.5$ s, range = 1.25–1.75 s) to prevent habituation. During the 10-min break between the pre- and post-test, the participants were allowed to stand up and move as needed in the shielded room, and the light remained off within the room. Impedances were rechecked before beginning the post-test. All impedances were kept below 15k ohms. Afterwards, all participants were debriefed and thanked for their participation.

Data Analysis

An automated peak finding algorithm was used to determine the maximum positivity within the 100–300 ms latency window for both the single- and double-flash conditions (Fix et al. 2014). Data included in analyses were required to have a visible N1 deflection prior to a visible P2 peak in both the pre- and post-test single-flash trial conditions. A linear subtraction method was employed to eliminate the time-locked effects of the first flash in the double-flash condition. Maximum positivities were then identified and latencies were subsequently recorded.

Results

Pearson's test–retest reliability coefficients (r_{tt}) were calculated using the latencies and amplitudes obtained at pre- and post-test. This resulted in an r_{tt} for each of the 52 experimental conditions (2 electrode recording sites × 13 conditions × 2 waveform characteristics − latency and amplitude).

As can be seen in Table 1, the single-flash condition produced the most reliable FVEP-P2 waveform, regardless of electrode recording site. The test–retest reliabilities associated with the single-flash condition were not only *significantly different* from .00, they were also *not significantly*

Table 1 Test–retest reliabilities for the latency and amplitude of the FVEP-P2 when measured at electrode recording sites Oz and O2

Variable	Latency		Amplitude	
	r	ρ = .80[a]	*R*	ρ = .80
Oz				
Single	.77**	•	.86**	•
10	.27		.46*	
20	.31		.65**	•
30	.42		.61**	
40	.26		.51*	
50	.23		.72**	•
60	.35		.56**	
70	.40		.70**	•
80	.63**	•	.74**	•
90	.64**	•	.62**	•
100	.71**	•	.63**	•
110	.67**	•	.74**	•
120	.74**	•	.65**	•
O2				
Single	.72**	•	.89**	•
10	.29		.46*	
20	.48*		.66**	•
30	.38		.60**	
40	.20		.63**	•
50	.20		.63**	•
60	.01		.68**	•
70	.54**		.25	
80	.60**		.81**	•
90	.43*		.76**	•
100	.55**		.63**	•
110	.67**	•	.75**	•
120	.67**	•	.69**	•

ISI inter stimulus interval, *r* Pearson's correlation coefficient, *ρ* population correlation coefficient, *Oz* occipital midline electrode placement, *O2* occipital electrode placement just right of midline, • null hypothesis is true

*$p < .05$; **$p < .001$

[a]Fisher's *r*-to-z transformation and subsequent inferential tests

different from .80 ($p < .05$) using the Fisher's *r* to *z* transformation, suggesting that the single-flash FVEP-P2 is a highly reliable component of the FVEP wave form.

Similar to the single-flash condition, the 110 and 120 ms ISI double-flash conditions also produced FVEP-P2 waveforms that were reliable for both electrode recording sites. Again, the test–retest reliabilities were not only *significantly different* from .00, they were also *not significantly different* from .80 ($p < .05$), suggesting that the double-flash FVEP-P2 is also a highly reliable component of the FVEP waveform at ISI's over 100 ms. Interestingly, the 80, 90, and 100 ms ISI double-flash conditions also produced FVEP-P2 components that were reliable, but only when measured at electrode recording site Oz. Coburn et al. (2005) recommended electrode site O2 as the best site for reliable amplitude and latency measurements in single-flash paradigms, with Oz ranking as the third best site. However, in both our present study and in Fix et al. (2014) study, site Oz was recognized as the optimal site for recording the FVEP-P2 in a double-stimulation design.

As can be seen in Table 2, our FVEP-P2 single-flash condition average latency was 141 ms at Oz and 143 ms at O2, which is longer than the average 120 ms latency reported by the ISCEV standards (Odom et al. 2016). However, ISCEV standards also note that each laboratory may have its own standard norms based on equipment used, and that variation of this average is expected (Odom et al. 2016).

We also assessed the effect of the single- and double-stimulation conditions on within-group variability by calculating the coefficient of variation (CV) for both latency and amplitude. We found the double-stimulation paradigm had the unintended consequence of increasing the within-group variability (i.e., CV) of the FVEP-P2 latency across all ISI conditions (Fig. 1). Fortunately, the CV for the single-flash condition was comparable to the within-group variability reported by both Fix et al. (2014) and Coburn et al. (2005). The CV for Fix and Coburn were 0.11 and 0.13, respectively. The CV obtained from the single-flash condition in the present investigation equaled .08. We were unable to calculate Oz single-flash amplitude CV values across studies because amplitude values were not reported in the Fix et al. (2014) study.

Discussion

In the present investigation we examined the psychometric properties of the FVEP-P2 using a single- and double-stimulation paradigm. Coburn et al. (2005) demonstrated, among other things, that the latency of the FVEP-P2, while robust with respect to group differences, was unsuitable as a clinical diagnostic tool due to the overlap observed between the two latency distributions (Coburn et al. 2003). In response, Fix et al. (2014) examined the effects of a novel double-flash stimulation paradigm designed to increase the separation between clinical and control groups. Their findings indicated that the FVEP-P2 latency obtained from a double-flash paradigm (i.e., ISIs > 100 ms) could reliably separate clinical (i.e., aMCI) and control participants, especially when the electrode recording site was Oz (Fix et al. 2014). In essence, utilizing the double-flash stimulation paradigm produces additional delay of the FVEP-P2 component in aMCI patients as their visual cortex takes additional time to recover from the challenge of the first flash as a result of reduced cholinergic function (Fix et al. 2014).

Table 2 Mean latency and amplitude of the single- and double-stimulation FVEP-P2 at pre- and post-test

Variable	Oz latency		Oz amplitude		O2 latency		O2 amplitude	
	M	SD	M	SD	M	SD	M	SD
Pre-test								
Single	141.73	11.39	12.01	5.74	143.05	11.31	11.56	5.91
10	189.86	57.32	4.23	3.76	191.00	54.35	4.16	3.63
20	196.68	52.91	5.07	3.63	199.27	58.12	5.23	3.70
30	205.86	48.27	5.69	4.02	205.36	48.26	5.60	3.56
40	176.77	62.86	7.05	3.78	181.18	63.17	7.07	4.25
50	186.27	65.28	7.87	4.85	188.91	64.91	7.64	4.53
60	179.91	65.79	7.07	3.09	196.50	73.07	6.84	3.48
70	189.18	79.95	7.79	4.62	182.32	70.03	13.49	28.79
80	187.55	71.31	7.84	4.19	184.23	63.09	7.59	4.54
90	188.64	73.31	8.52	4.67	180.32	59.64	7.88	4.00
100	182.82	74.78	8.76	4.71	178.86	66.00	8.38	4.73
110	155.73	57.71	10.41	5.72	155.41	57.72	10.22	5.88
120	154.23	67.08	9.77	5.41	145.95	43.26	9.62	5.28
Post-test								
Single	143.77	15.79	11.66	5.48	148.68	25.92	11.01	5.69
10	186.59	61.04	4.29	2.30	179.14	60.52	4.10	2.26
20	201.95	58.83	5.05	3.24	211.86	58.22	4.72	3.05
30	185.77	59.47	5.12	2.98	188.05	61.60	5.01	3.06
40	185.91	52.81	6.47	3.27	184.45	52.70	6.23	3.35
50	216.14	62.41	6.33	3.93	215.95	62.63	6.16	3.67
60	202.00	64.95	6.85	2.86	196.82	61.13	6.60	2.87
70	182.55	56.68	7.78	4.77	179.45	52.83	7.43	4.74
80	202.50	74.04	8.61	5.25	204.64	72.00	8.38	5.22
90	197.68	84.29	7.55	4.24	183.95	69.34	7.31	4.19
100	176.59	78.26	7.53	3.96	168.45	62.87	7.36	3.99
110	167.32	69.25	8.59	4.16	167.05	68.86	8.39	4.31
120	159.82	63.58	8.81	4.85	161.18	63.26	8.61	4.96

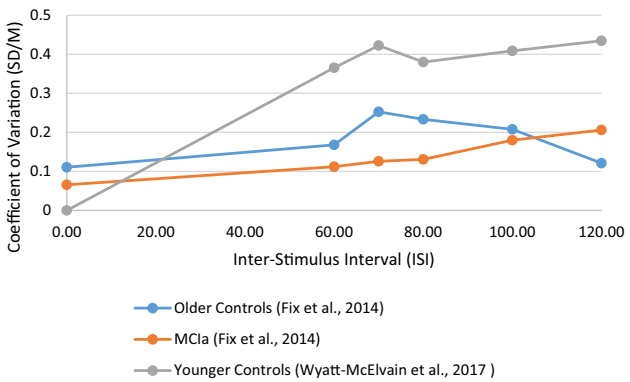

Fig. 1 Coefficient of variation for the latency and amplitude of the FVEP-P2 when measured at Oz and pre-test. (Color figure online)

This additional delay helps further separate healthy groups from clinical groups (Fix et al. 2014).

Our study, in an attempt to assess the reliability of the double-stimulation FVEP-P2 in a young and healthy adult population, confirmed that double-stimulation conditions with ISI's equal to or greater than 100 ms were reliable when recorded at electrode recording sites Oz and O2. We were also able to replicate the refractory effect reported by Fix et al. (2014). As can be seen in Table 2, FVEP-P2 the mean latency increased in the double-stimulation conditions until the refractory threshold was reached and then began to decline towards baseline (i.e., single-flash condition). Fix et al. reported the same refractory effect with older healthy controls. Test–retest reliabilities followed a similar trend with reliabilities increasing once the refractory threshold was reached. In other words, healthy adults, both young and old, displayed the ability to progressively recover to their baseline FVEP-P2 latency after crossing the refractory threshold.

Unlike Fix et al. (2014), however, the *variability* associated with the double-stimulation latencies were larger and failed to return to baseline (i.e., single-stimulation condition). In fact, the pattern of variability exhibited by the participants in the present investigation was much more similar

to the pattern of variability exhibited by aMCI patients when presented with a double-stimulation (Fix et al. 2014). While the increase in variability seen in the present investigation could represent individual differences in the response of the visual cholinergic system of young, healthy adults—a response not often seen in healthy, older individuals—the increase in variability seen in aMCI patients may have been due to pathological brain changes and declines in cholinergic functioning (Fix et al. 2014; Sannita 2006). A second, plausible explanation may be related to the use of different research methodologies. While Fix et al. (2014) used a semi-automated algorithm to identify the FVEP-P2, the present investigation employed an algorithm that was completely automated. While both methods utilized the same theoretical principles for identifying the characteristics of the second flash FVEP-P2, the latter employed a subtraction method and a peak finding procedure that would have reduced the effects of experimenter bias. With greater variability in the double-stimulation paradigm, it may be important to widen the range for automatic algorithms to detect the second FVEP-P2 as researchers could often visually identify a second P2 peak beyond the automated procedure's latency widow of 100–300 ms post second-flash stimulus.

Finally, despite finding adequate test–retest reliability for the FVEP-P2, the inter-individual variability remains far too high for the latency of the FVEP-P2 to be used diagnostically (Coburn et al. 2003; Fix et al. 2014). Since the goal of any diagnostic tool is sensitivity and specificity, the FVEP-P2 may be sensitive to group differences with a double-flash paradigm, but the individual variability needs to be reduced in order for this possible biomarker to gain specificity in identifying aMCI and AD diagnoses (Coburn et al. 2005). Recent research has begun to consider the impact of monochromatic flash stimuli on the inter-individual variability of the FVEP-P2 (Subramanian et al. 2012, 2013). The results of these investigations suggest that while the use of "colored" flash stimuli may increase the FVEP-P2 latency for healthy adults, the use of a monochromatic flash may also reduce both the intra- and inter-individual variability of the FVEP-P2 component (Subramanian et al. 2012, 2013). In these studies, the use of a blue flash reduced inter-individual variability of the FVEP-P2 below that of red or white light (Subramanian et al. 2012, 2013). Therefore, it is possible that utilizing monochromatic flash (i.e., blue light) may also reduce the inter-individual variability of the second P2 response. If the double-stimulation paradigm widens the group differences between healthy and clinical adults, and monochromatic stimulation reduces individual variability, perhaps the combination of the two procedures would provide a diagnostically useful tool that could pull apart group latency means and reduce variability to provide sensitivity and specificity. While the current study indicated that the double-stimulation paradigm is not yet suitable as a diagnostic tool, it did provide additional support for the FVEP-P2 double-stimulation refractory effect and the reliability of FVEP-P2 latency and amplitude measures at double-stimulation ISI's of 100 ms or greater. This study also provided additional insight concerning patterns of FVEP-P2 latency variability with the double-stimulation design, the importance of research methodologies used for identifying the second FVEP-P2 in a double-stimulation design, and a clear direction for future research that could further progress the utility of the FVEP-P2 as a future diagnostic tool.

Potential Limitation

Other researchers have noted that the click from the strobe discharge may be a potential confound to internal validity in the collection of VEP data. Current ISCEV standards have no recommendation for the control of sound in FVEP studies currently (Odom et al. 2016). Fix et al. (2014) and Coburn et al. (2005) both used 90db white noise to mask the sound of the click. Masking has been used in prior studies as an effort to prevent the possibility of auditory evoked potentials contaminating the VEP (Coburn et al. 2005). Although the potential for error exists because of this limitation, the estimation of the impact of this is marginal because our study replicated expected reliabilities and single-flash CV values from previous studies. Studies with white noise masking have not differed markedly from studies that do not use the white noise masking.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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