Test–retest reliability of brain oscillations in a prepulse inhibition and facilitation paradigm: effects of gender in healthy humans

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There is a growing interest in assessing the reliability of electroencephalographic (EEG) measures in clinical and research settings. Prepulse inhibition (PPI: representing attentional modulation) and facilitation (PPF: reflecting selective attention) paradigms have been used to study inhibitory function and selective attention, respectively. However, to date, little has been known with regards to the stability of brain oscillatory activity during PPI and PPF. We investigated the stability of event-related EEG oscillations during PPI and PPF in healthy humans over two monthly sessions. Power spectral densities were analysed at traditional frequency bands (delta, alpha, beta sub-bands, and gamma). We assessed test–retest reliability by calculating intraclass correlation coefficients (ICCs, absolute agreement definition) and examined potential effects of gender. The results showed good-to-excellent reproducibility of EEG power (both in PPI and PPF) over all frequency bands (ICCs>0.75), except for delta (ICCs<0.75), with alpha exhibiting the highest repeatability performance. In addition, females showed reduced reliability compared to males in both PPI and PPF, possibly attributed to menstrual cycle phase across our female participants. Overall, our findings suggest that brain oscillatory activity can be test–retest reliable, while gender needs to be controlled with caution. Finally, event-related EEG oscillations during both PPI and PPF could provide a complementary tool to study psychopathology in clinical practice. *NeuroReport* XXX: 000–000 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Humans and other animals reflectively react to sudden stimulation induced by an intense auditory stimulus, called *the acoustic startle reflex* [1]. This reflex is reduced if a prepulse tone immediately precedes the startle [*prepulse inhibition* (PPI) [1]]. PPI has been associated with various cognitive functions, such as attention, working memory and executive function [2]. In contrast to PPI, the startle response can be enhanced if the startle follows the prepulse after a longer time interval (>500 ms) [*prepulse facilitation* (PPF) [3]. In PPF, the prepulse guides the individual's attention towards an upcoming stimulus, thus leading to an augmented startle response [4]. While PPI reflects automatic sensorimotor gating [1], PPF represents sensory enhancement and selective attention to incoming information thus increasing the response to the startle [5].

Importantly, reduced PPI has been found in various psychiatric disorders, such as schizophrenia and obsessive-compulsive spectrum disorder (OCD), attributed to dysfunctions in corticostriatopallidothalamic circuitry [6]. In this framework, our team [7] recorded the electroencephalographic (EEG) oscillations associated with PPI and PPF in patients with body dysmorphic disorder (BDD), which is considered as an OCD [8], vs healthy controls. Results showed that BDD exhibited increased low-theta power and reduced low-beta power during PPI and PPF [7]. Because the OCD symptomatology involves the malfunctioning of the frontal-striatal-thalamic operational connectivity [9], and theta oscillations reflect this functional connectivity [10], the obtained results could be potentially an indicative of disrupted thalamocortical activation. On the other hand, because beta oscillations are mostly associated with endogenous, top-down-controlled processing during attentional orienting [11], the observed reduced low-beta power was considered an indicative of impaired top-down processing during attention orienting.

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Previous physiological research has demonstrated the stability of the PPI and PPF measures over time in healthy adults [12–14]. For example, Braff *et al.* [12] recorded the blink reflex in response to auditory PPI, and found significant reliability of that measure 10 days later. This was also shown in a three-session study with 1-week intervals recording eye blink activity [14]. Similarly [14], Cadenhead *et al.* [15] reported high intraclass correlations for PPI and PPF across three sessions with 1-month intervals. High stability of the PPI was also confirmed across three 1-day sessions [16]. However, little is known yet as to the stability of event-related EEG oscillations to PPI and PPF.

Therefore, our study is the first (to our knowledge) to investigate the stability of event-related EEG oscillations during PPI and PPF in healthy adults. In contrast to previous studies measuring the blink reflex, we investigated the test–retest reliability of brain oscillatory activity. Specifically, we analysed power at traditional frequency bands (delta, alpha, beta sub-bands, and gamma), and tested the reliability of brain responses between test and retest (1-month interval) using intraclass correlations.

Previous EEG studies [16,17] found that PPI is associated with inhibition of auditory-evoked alpha oscillations at central and temporal regions, as well as inhibition of gamma at frontal, central, and temporal regions [17]. Burgess and Gruzelier [18] showed suppressed auditory-evoked theta at frontal, central, and parietal areas during PPI. The aforementioned studies suggest that prepulses affect both blink reflexes and brain oscillatory activity. Here, we hypothesized that brain activity in response to PPI and PPF would be substantially stable between test and retest. Furthermore, we expected at least good reliability across all frequency bands. Finally, females show lower PPI than males attributed to hormonal state [19]. Therefore, we expected that females would show lower test–retest reliability in event-related EEG oscillations during PPI and PPF due to variability in menstrual cycle phase.

Methods

Participants

Fifty neurologically healthy adults (27 females) aged between 19 and 40 years old (26.1 ± 5.3) participated in the experiment. Education level was balanced across participants (16.3 ± 1.4 years). The study was approved by the Ethics committee of Eginition Hospital, Athens, Greece. All subjects gave their consent prior to the experiment.

Procedure

Two identical sessions were conducted with a minimum one-month gap between them. Each participant heard 51 pairs of tones through headphones. In each trial, subjects were presented with a prepulse tone (60 dB) followed by a startle tone (140 dB). Each trial recording had a duration of 4 s, time-locked to startle onset (−2 to +2 s). The time interval between the two tones varied between 0 and 500 ms (PPI; 26 trials) and 500–2000 ms (PPF; 25 trials). Both tones had a duration 40 ms and a frequency of 2 kHz. Trials were randomized across participants.

Electroencephalographic recording and preprocessing

The EEG signals were recorded from 30 Ag–AgCl electrodes according to the 10–20 International System placements. Horizontal (placed above the right eye) and vertical (placed at the outer canthi of the left eye) electro-oculogram electrodes were also recorded. Electrode impedance was kept constantly below 5 kΩ.

First, datasets were downsampled to 250 Hz. The data were then high-pass filtered at 1 Hz and notch filtered at 45–55 Hz. Channels with consistently poor signal quality, as observed by visual inspection and by studying the topographical maps of their power spectra, were removed and reconstructed by interpolation from neighbouring channels. Data were then re-referenced to common average. Subsequently, independent component analysis was run to correct for eye blink-related artefacts. Rejection criteria of noisy components involved simultaneous consideration of their time-course, topography, spectra, and correlation with EOGs. Finally, continuous data were epoched from −2 to 2 s around startle onset. Preprocessing was implemented using EEGLAB.

Electroencephalographic analysis

Power spectral density

The power spectral density (PSD) was calculated using Welch's method by dividing the data into 2-s (poststartle) windows with an overlap of 50%. We computed power from 1 to 45 Hz in steps of 0.5 Hz. The power values at each electrode for each condition and session were summed (band energy calculation) over the following bands: delta (1–4 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz), beta1 (13–16 Hz), beta2 (16.5–20 Hz), beta3 (20.5–28 Hz), and gamma (30–40 Hz). The power values of each frequency band were normalized relative to the sum power of all frequencies.

Intraclass correlation analysis

Intraclass correlation coefficients (ICCs) derived from a two-way mixed model with an absolute agreement definition [18] were calculated to quantify test–retest reliability of the EEG spectral measures, separately for PPI and PPF. ICC is a conservative statistic to evaluate agreement in measurements over time. The traditional classification of ICC values was used: <0.50 (poor), 0.50–0.75 (moderate), 0.75–0.90 (good), and >0.90 (excellent reliability).

To assess whole-scalp differences, a 2 *(condition: PPI vs PPF)* × 7 *(frequency band)* repeated-measures ANOVA was conducted with electrode-specific ICCs as the dependent variable (ICC of each electrode calculated over subjects).

The corresponding *P* values of ICCs were adjusted to the conservative alpha level of 0.00167 (0.05/30; number of electrodes).

The ICC analysis was performed twice: (1) we assessed stability across all subjects and conditions and (2) we compared ICC in males vs females, separately in PPI and PPF. Independent samples *t* tests confirmed no significant differences in age [$t(48)=1.51$, $P=0.14$] or educational level [$t(48)=0.90$, $P=0.37$] between groups. To assess the whole-scalp differences between groups, a 2 *(group: male vs female)* × 7 *(frequency band)* mixed ANOVA was conducted on electrode-specific ICCs. A threshold of 0.0024 (dividing 0.05/21; total number of comparisons) was used for between-bands comparisons, whereas 0.0071 (=0.05/7) was set for between-groups comparisons.

Results

Electroencephalographic reliability across participants

Intraclass correlation coefficient per electrode

Scalp-maps show the topographical distribution of ICCs for PPI and PPF (Fig. 1a). For more detailed information see Table 1. As a general observation, PPI and PPF demonstrated similar patterns of reliability. Delta band exhibited bad-to-moderate reliability under both conditions. Theta band showed excellent ICCs at CPz, Cz, and CP3 electrodes (max. ICC = 0.93 at CPz) in PPF, whereas good levels of reliability were observed at several central sites in PPI. Alpha band demonstrated enhanced ICC levels compared to all other bands in both PPI and PPF, whereas beta1 was mostly reliable in PPF (max. ICC = 0.93 at Pz). Beta2, beta3, and gamma bands showed equally good ICCs over several sites (max. ICCs at Fp2).

Whole-scalp intraclass correlation coefficient

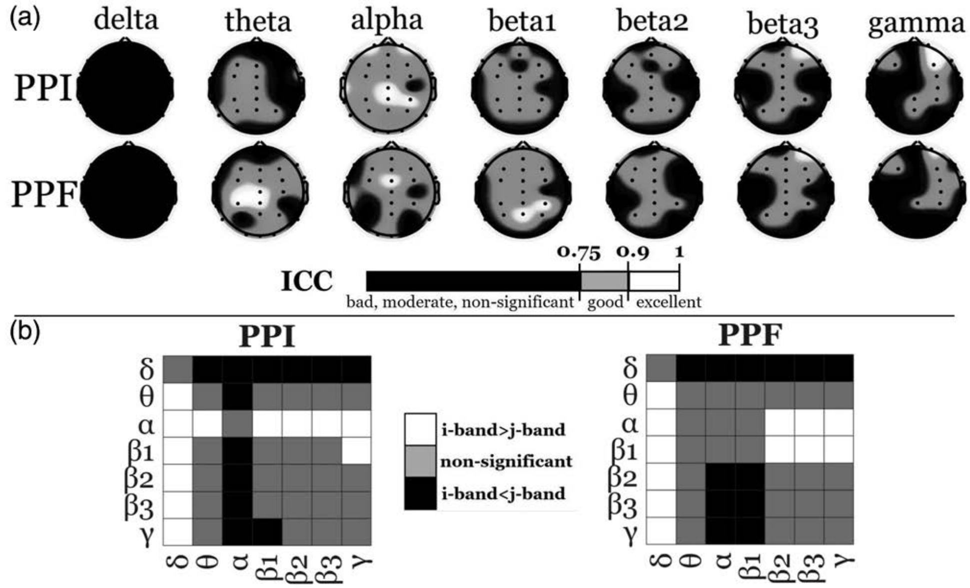
Whole-scalp reliability was assessed by comparing the mean ICCs over all electrodes across bands and conditions. A Condition × Band repeated-measures ANOVA was conducted on electrode-specific ICCs. There was a significant interaction between Condition and Band [$F(6,174)=8.48$, $P<0.001$, $\eta^2=0.226$, Greenhouse–Geisser corrected]. Condition-specific tests were performed to contrast the ICCs between bands and the results are illustrated as heatmaps (Fig. 1b). There were no significant differences between conditions.

Gender-specific reliability testing

Intraclass correlation coefficient per electrode

Identical reliability calculations were also conducted separately for males and females (Table 2). In particular, delta band revealed poor ICCs. Considering the number of reliable channels, females exhibited lower reliability than males over all bands in PPI. In PPF, females also showed reduced ICC in beta2 and beta3. Males showed good-to-excellent ICCs at many electrodes over theta,

Fig. 1



(a) Scalp map representations of intraclass correlations (ICC) between test and test sessions during prepulse inhibition (PPI; top) and prepulse facilitation (PPF; bottom), separately for each frequency band. Black signifies non-significant ICCs ($P>0.00167$) or bad-to-moderate ICCs (<0.75); grey signifies significant ($P<0.00167$) and good ICCs ($0.75<\text{ICC}<0.9$); and white signifies significant ($P<0.00167$) and excellent ICCs (>0.9). (b) Heatmaps of the pairwise comparisons of ICCs between frequency bands, separately for prepulse inhibition (PPI; left) and prepulse facilitation (PPF; right). White {i,j} boxes indicate significantly higher ICC in i-band than j-band, whereas black boxes indicate significantly lower ICC in i-band than j-band. Grey boxes indicate nonsignificant differences between bands. Statistical significance was assessed using Bonferroni corrected *P* values.

Table 1 **Descriptive results of intraclass correlation analysis**

	Number of good-to-excellent electrodes[a]		Most reliable electrode (ICC)[b]		Mean ICC over all electrodes	
Frequency band	PPI	PPF	PPI	PPF	PPI	PPF
Delta	0	0	P4 (0.49)	Cz (0.55)	0.22	0.25
Theta	11	19	CPz (0.88)	CPz (0.93)	0.66	0.73
Alpha	29	22	CP4 (0.93)	FCz (0.90)	0.83	0.76
Beta1	15	18	CP4 (0.88)	Pz (0.93)	0.67	0.71
Beta2	13	12	F7 (0.83)	Fp2 (0.82)	0.65	0.64
Beta3	14	14	Fp2 (0.94)	Fp2 (0.93)	0.63	0.62
Gamma	10	9	Fp2 (0.92)	Fp2 (0.93)	0.55	0.56

ICC, intraclass correlation coefficient; PPF, prepulse facilitation; PPI, prepulse inhibition.
[a] Number of electrodes with good-to-excellent reliability.
[b] Band-specific electrode with the maximum ICC.

Table 2 **Descriptive results of the intraclass correlation analysis comparing males vs females**

		Number of good-to-excellent channels[a]		Most reliable electrode (ICC)[b]		Mean ICC over all electrodes	
	Gender	PPI	PPF	PPI	PPF	PPI	PPF
Delta	M	1	0	P4 (0.79)	Cz (0.69)	0.33	0.27
	F	0	0	FC4 (0.57)	FC3 (0.64)	0.10	0.24
Theta	M	17	18	CPz (0.95)	CP3 (0.94)	0.72	0.72
	F	9	19	FT8 (0.86)	CPz (0.96)	0.58	0.73
Alpha	M	27	22	CP4 (0.96)	T6 (0.89)	0.85	0.73
	F	23	21	Cz (0.94)	Cz (0.98)	0.77	0.76
Beta1	M	20	23	CP4 (0.96)	Pz (0.97)	0.74	0.77
	F	5	9	FC4 (0.81)	CPz (0.82)	0.49	0.53
Beta2	M	20	20	P3 (0.94)	CP3 (0.88)	0.73	0.72
	F	9	8	Fp2 (0.87)	CPz (0.84)	0.56	0.55
Beta3	M	18	19	Pz (0.94)	Cz (0.91)	0.71	0.69
	F	8	7	Fp2 (0.96)	Fp2 (0.95)	0.53	0.54
Gamma	M	11	11	CP4 (0.84)	CP4 (0.93)	0.58	0.59
	F	7	7	Fp2 (0.93)	Fp2 (0.95)	0.49	0.50

F, female; ICC, intraclass correlation coefficient; M, male; PPF, prepulse facilitation; PPI, prepulse inhibition.
[a] Number of electrodes with good-to-excellent reliability.
[b] Band-specific electrode with the maximum ICC.

alpha, beta1, beta2, and beta3 bands in both PPI and PPF, while females showed stable measures over theta and alpha bands in PPF only.

Whole-scalp intraclass correlation coefficient

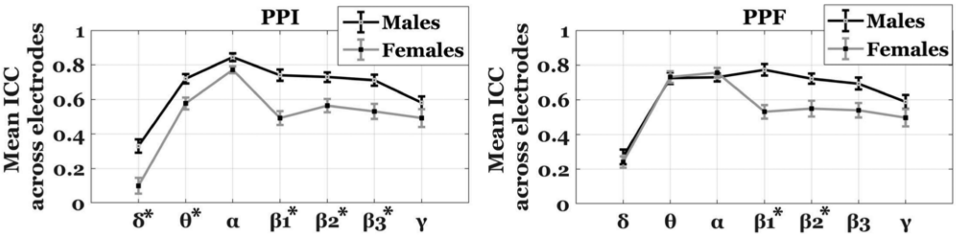
We juxtaposed the whole-scalp reliability between the groups. To that end, we compared the mean ICCs over all electrodes in each frequency band with a Band × Group mixed ANOVA. The Band × Group effect was significant in both PPI [$F(6,348)=2.65$, $P=0.047$, $\eta^2=0.044$] and PPF [$F(6,348)=5.63$; $P=0.001$, $\eta^2=0.088$]. The results of follow-up unpaired *t*-tests between groups for each band are notated with '*' in Fig. 2. Group differences were predominantly revealed in PPI with females exhibiting reduced levels of whole-scalp reliability in the delta, theta, and beta bands. On the contrary, PPF showed more balanced group reliabilities, except for beta1 and beta2 bands where females showed lower ICCs than males.

Discussion

Our main goal was to investigate the stability of event-related EEG oscillations during PPI and PPF, as well as to examine differences between males and females. Our study was the first, to our knowledge, to investigate test–retest reliability of brain oscillatory activity in PPI and PPF. In line with previous physiological studies showing that responses to PPI and PPF constitute a stable measure over time [15], we found that EEG oscillations show high ICC over two monthly sessions in healthy adults, suggesting that brain oscillatory activity to PPI and PPF might constitute a stable neurophysiological measure. Women showed lower stability of that measure compared to men, potentially attributed to variability in the menstrual cycle phase.

First of all, we observed widespread good-to-excellent reliability in both PPI and PPF conditions, in all frequency bands above the delta band. The alpha band was the most reliable band in PPI. In PPF, beta1 was also more reliable compared to frequency bands higher than beta1. On the other hand, the delta band was the least reliable frequency band with zero reliable electrodes. Similarly, in a study on spatiotemporal reliability of EEG power during eyes open and motor execution [18], good-to-excellent reliability was demonstrated for alpha, but poor reliability for the delta band. Our results revealed that electrodes at frontoparietal areas were the most reliable.

Fig. 2



Lineplots illustrate the mean (over electrodes) ICCs in all frequency bands for males (black) and females (grey) in PPI (left) and PPF (right). Error bars represent ±1 standard error mean (SEM). * indicate significant differences between groups (Bonferroni corrected). ICC, intraclass correlation coefficient; PPF, prepulse facilitation; PPI, prepulse inhibition.

This frontoparietal network is believed to initiate and adjust task control within the attention operation [20]. The importance of the frontoparietal network in top-down regulation of attention has been previously shown in anatomical and lesion studies [21–24]. Specifically, using an autoradiographic technique, Petrides and Pandya [24] demonstrated various projections of posterior parietal regions to the frontal cortex in the rhesus monkey. In a combined PET and EEG study investigating sustained attention during a vigilance task, Paus *et al.* [22] identified an auditory attention network extending from the right parietal to the dorsolateral frontal cortex. Corroborating evidence for the role of frontoparietal network in attention provide the results of a lesion study [21], which found impaired selective attention in patients with unilateral frontal cortical lesions in a reaction time task.

With regards to the effect of gender, we found that females showed substantially reduced reliability of their EEG measurements compared to males. In PPI, males were more reliable than females in the delta, theta, and beta bands, whereas in PPF, males were more reliable in beta1 and beta2 only. This is in line with previous research demonstrating sex differences in acoustic startle response paradigms, such as PPI (for a review see [19]). The predominant explanation of this lies onto menstrual cycle effects [19]. Specifically, women exhibit lower PPI in the luteal phase of the menstrual cycle, where hormonal levels are elevated [25]. Therefore, it could be that the stability of the EEG measurements was impaired due to the variability of the menstrual cycle phase across our female participants.

Our experimental design is not without limitations. First, it is possible that there is individual variability with regards to the stability of the EEG oscillations. The absence of a control condition where participants would be presented with single tones comprises another limitation of our study, which could be investigated in the future. Furthermore, we acknowledge that information on menstrual cycle phase of our female participants would help us understand better how menstrual cycle affects stability measures. Finally, it would be interesting to examine how test–retest reliability of brain oscillatory activity is modulated in psychiatric disorders, as PPI and PPF are known to vary with psychopathology [4].

Conclusion

We conclude that event-related EEG oscillations in response to PPI and PPF might constitute a reliable measure over time. Special attention needs to be given to the gender, as our findings provided evidence for potential effects of hormonal state on the stability of that measure. Finally, the test-retest reliability of brain oscillatory activity to PPI and PPF could provide a complementary measure for research on healthy humans, as well as a corroborative tool in clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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