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Attenuation of the prepulse inhibition of the acoustic startle response within and between sessions

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Abstract

Prepulse inhibition (PPI) and habituation of the acoustic startle response (ASR) are widely used biological markers in the study of psychiatric disorders and have been shown to be homologous across species. Previous studies in humans suggested that PPI is a stable and reliable measure between test sessions, but that PPI decreases within sessions. The purpose of this study was to explore the short- and long-term decrease in PPI as a potential confound in the measurement and interpretation of PPI. We investigated the progression of PPI and habituation of ASR in three test sessions spaced 4 weeks apart in a group of 20 healthy participants. Analysis revealed a significant decrease in the percent PPI within and between the test sessions. Nevertheless, PPI was reliable across three test sessions, indicating that the significant attenuation of PPI over time was a consistent phenomenon. These results suggest that PPI exhibits short- and long-term attenuation.

Keywords: Prepulse inhibition; Habituation; Acoustic startle response; Sensorimotor gating; Electromyography; Clinical studies; Stability; Reliability

1. Introduction

The startle reflex is a fast response to a sudden, intense stimulus such as a loud sound and consists of contraction of the skeletal and facial musculature. This reflex is usually classified as a defensive response. The acoustic startle response (ASR) of mammals is mediated by a simple three-synapse neuronal circuit located in the lower brainstem. Neurons of the caudal pontine reticular nucleus are key elements of this primary ASR pathway (Davis et al., 1982; Koch, 1999). The startle reflex shows several forms of behavioral plasticity, such as prepulse inhibition (PPI) and habituation. PPI refers to the reduction of ASR magnitude when a distinctive non-startling stimulus is presented 30–500 ms before the startling stimulus. PPI is used as an operational measure for sensorimotor gating that reflects the ability of an organism to properly inhibit sensory information (Graham, 1975; Hoffman and Ison, 1980). Habituation is a theoretical construct that refers to the reduction in magnitude of ASR after repeated presentation of the startling stimulus that is not due to muscle fatigue or blunting of sensory receptor responsiveness (Groves and Thompson, 1970; Siddle and Kroese, 1985).

PPI and habituation of the acoustic startle response are consistent phenomena across species and are widely used to measure sensorimotor gating and to investigate information processing (Braff et al., 1992; Geyer and Braff, 1987; Swerdlow et al., 1999). Several investigations have reported changes of habituation and/or PPI of ASR in neuropsychiatric disorders such as schizophrenia (Braff et al., 1992; Geyer and Braff, 1982; Parwani et al., 2000), schizotypal personality disorder (Cadenhead et al., 1993), obsessive-compulsive disorder (Swerdlow et al., 1993), and Huntington's disease (Swerdlow et al., 1995). Changes in PPI and habituation may provide trait markers for psychiatric disorders with altered neurotransmitter regulation (Cadenhead et al., 1999).

To enhance our knowledge of PPI deficits in patients with various neuropsychiatric disorders and to develop translational animal model studies, investigators have increasingly utilized psychopharmacological modulation of PPI in

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normal humans and animals (Braff et al., 2001). For a valid interpretation of pharmacological effects on a biological marker, such as in pre-post designs with a pharmacological treatment, the marker should be stable and reliable. Crossover designs are well established in studies with pharmacological modulation of PPI in rodents as well as healthy volunteers. However, clinical studies – especially with schizophrenic patients – utilizing longitudinal designs in combination with a control or a placebo group are missing so far.

Graham (1975) stated that PPI may reflect a strong and stable automatic process that serves to protect the processing of the weak prepulse from disruption by the intense startle stimulus. This view was supported by the findings that PPI is present on the first presentation of a prepulse-startle stimulus pairing, does not habituate, and occurs during sleep (Graham and Hackley, 1991). At first, these findings seemed to indicate that PPI might not be influenced by processes such as learning or habituation (Lipp et al., 1994). In the meantime, several studies have shown that the amount of PPI decreases over repeated trials within a startle session (Lipp et al., 1994; Blumenthal, 1996; Lipp and Krinitzky, 1998; Lipp and Siddle, 1998). Furthermore, it could be shown that selective attention influences the extent of PPI (Filion et al., 1993, 1994; Schell et al., 1995). These findings do not confirm the notion that PPI is a strong and stable automatic process (Lipp and Krinitzky, 1998).

Blumenthal (1997) remarked that a decrease of PPI within test sessions could be due to habituation of some aspect of the inhibitory processes initiated by the prepulse, or to habituation of the startle response itself. He found that the amount of PPI decreased across trials, but that the proportion of inhibition (percent PPI), measured as a difference between the average magnitude of blinks preceded by a prepulse and the average magnitude of those that were not, divided by the average magnitude of those that were not, remained constant across trials (Blumenthal, 1997). Previous habituation to the prepulse did not reduce subsequent PPI when prepulse trials were paired with startle stimuli (Blumenthal, 1997; Lipp and Krinitzky, 1998; Schell et al., 2000). In addition, the reduction in PPI across trials can be abolished after dishabituation of the startle reflex (Lipp and Krinitzky, 1998). These data supported the suggestion that the reduction of PPI seen across trials is not due to habituation of the prepulse but is related to startle reactivity in pulse-alone (control) trials, which is reduced by habituation.

Some studies have been performed to investigate the reliability and stability of PPI also between test sessions (Schwarzkopf et al., 1993; Abel et al., 1998; Cadenhead et al., 1999; Swerdlow et al., 2001). In contrast to previous studies, which found a decrement of PPI within sessions, none of these studies found significant changes in PPI between two or three test sessions, and all studies have shown high test-retest reliability of PPI. Only Abel et al. (1998) reported a slight decrease of percent PPI across sessions. Test retest reliability of PPI of somatosensoric elicited blink reflexes seems also to be very high (Flaten, 2002). However, the number of prepulse trials measuring PPI, as well as the sample sizes, in most of the previous studies was possibly not sufficient to investigate the long-term stability of PPI. The following listing of studies shows the number of trials of the single prepulse condition within a session which can be expected to exert the strongest effects on PPI: Schwarzkopf et al. (1993) used 24 trials in each of three sessions at 1-week intervals ($n = 11$), Abel et al. (1998) used eight trials in each of three sessions which were separated by a minimum of 2 h on 1 day ($n = 15$), and Cadenhead et al. (1999) used 12 trials in each of three sessions at 1-month intervals ($n = 10$). Swerdlow et al. (2001) used, however, a special study design to examine pre-testing of ASR measurement in humans to diminish variability across experimental groups ($n = 20$). They used 5 trials in a pre-testing session and 7–10 days later they used 25 trials (5 trials in 5 identical sessions with 15 min between each session).

Because of the different results between within- and between-session stability of PPI in previous studies, the aim of the present study was to investigate if there is a dissociation between short- and long-term stability of PPI. To accomplish our goal, we measured magnitude, habituation, and PPI of ASR three times during a span of 8 weeks using a startle sequence optimized for habituation effects consisting of 36 prepulse trials under a single condition (86 dB prepulse; SOA 140 ms) and 36 pulse-alone trials (116 dB) per session in 20 healthy volunteers.

2. Materials and methods

2.1. Participants

PPI and habituation of ASR were measured in 20 healthy participants (8 women, 12 men, all were of Caucasian ethnicity), who were recruited by advertisement in a local newspaper. Age ranged from 18 to 63 years (38.4 ± 12.2 (mean and standard deviation)), and the years of education ranged from 9 to 17 years (14.3 ± 2.5). Four of the participants were smokers (one woman, three men) and one woman was post menopausal. All participants were employed at time of experiment.

Exclusion criteria consisted of legitimate use of psychotropic medication and/or illicit drug use. An SCID-I interview was carried out according to DSM-IV procedures by a psychologist trained in the use of this instrument. None of the included participants had a personal or family history of any DSM-IV axis I psychiatric diagnosis. In addition, none of the participants had a history of migraine, epilepsy, or craniocerebral trauma.

The study was approved by the Ethics Committee of the Medical Faculty of the University of Bonn. After receiving a written and oral description of the aim of this study, all participants gave written informed-consent statements.