Anxiety and prepulse inhibition of acoustic startle in a normative sample: The importance of signal-to-noise ratio

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A R T I C L E   I N F O

Article history:
Received 12 July 2008
Received in revised form 26 September 2008
Accepted 3 November 2008
Available online 13 December 2008

Keywords:
Startle
Anxiety
Prepulse inhibition
Personality disorders
Signal-to-noise ratio
PPI
Blink
EMG

A B S T R A C T

Previous studies have used prepulse inhibition of the startle response (PPI) to investigate the anxiety spectrum, primarily in patient samples, with mixed results. The inconsistency in findings may be due, in part, to the use of non-optimal signal-to-noise ratios (SnRs: the difference between background noise intensity and prepulse intensity) in some studies. We proposed that, as SnR approaches +15 dB, anxiety spectrum variables will be negatively correlated with PPI, even in a normative sample. Thus, we used the MCMI-III to measure levels of trait anxiety, posttraumatic stress disorder (PTSD), and the three Cluster C personality disorders in a sample of 53 undergraduate females, and then correlated their scores with their PPI levels at SnRs of +5, +10, and +15 dB. All of the anxiety constructs except obsessive-compulsive personality disorder (OCPD) were correlated with PPI, but only in the +15 dB condition. Although OCPD symptomatology was not correlated with PPI, it was negatively correlated with PTSD and may have been indicative of adaptive functioning in this normative sample. The present study demonstrates that PPI is a sensitive index of anxiety symptomatology even in the normative range, and that a SnR near +15 dB may be necessary to reliably detect associations between PPI and these psychological variables.

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1. Introduction

The acoustic startle reflex is a defensive reaction that occurs in response to a sufficiently sudden and intense sound (Blumenthal et al., 2005). Although this response can involve a full-body reaction, it is most often quantified as electromyographic (EMG) activity of the orbicularis oculi, the muscle that controls eyeblinking, because the blink component is the most sensitive and is the most resistant to habituation. Prepulse inhibition (PPI) of the acoustic startle response occurs when a stimulus (i.e., the prepulse) is presented 30–500 ms before the startle-eliciting stimulus, and causes a decreased startle response relative to non-prepulse trials (Blumenthal, 1999). PPI traditionally has been theorized to be a psychophysiological index of information processing (e.g., Graham, 1975) and sensorimotor gating (Swerdlow, Braff, & Geyer, 2000), such that less PPI is associated with poorer information processing, and with impairments in sensorimotor gating that are characteristic of schizophrenia spectrum disorders. PPI is due to an inhibitory projection from the tegmentum to the startle center in the brainstem (Swerdlow et al., 2000), and variations in PPI can be used to index variations in functioning of a variety of brain areas. Specifically, frontal lobe deficits may cause less activation of the midbrain inhibitory center responsible for PPI, and therefore a reduction in PPI in this condition.

Although most of the PPI research in clinical populations has focused on the schizophrenia spectrum, with findings of decreased PPI across most of the spectrum (e.g., Cadenhead, Swerdlow, Shafer, Diaz, & Braff, 2000; Duncan et al., 2006; Swerdlow, Filion, Geyer, & Braff, 1995), over the past decade there has been an increasing focus on the anxiety spectrum. Findings indicate decreased PPI in post-traumatic stress disorder (PTSD; Grollon, Morgan, Southwick, Davis, & Charney, 1996; Grollon, Morgan, Davis, & Southwick, 1998; Ornitz & Pynoos, 1989), obsessive-compulsive disorder (OCD; Hoenig, Hochrein, Quednow, Maier, & Wagner, 2005; Swerdlow, Benbow, Zisook, & Geyer, 1993), and panic disorder (Ludewig, Ludewig, Geyer, Hell, & Vollenweider, 2002; Ludewig et al., 2005), and in college students with high trait anxiety (Duley, Hillman, Coombes, & Janelle, 2007). Five other studies, however, did not find any association between anxiety spectrum constructs and PPI (Butler et al., 1990; Grollon, Dierker, & Merikangas, 1997; Larsen, Norton, Walker, & Stein, 2002; Lipschitz et al., 2005; Morgan, Grollon, Lubin, & Southwick, 1997).

Although many of the anxiety spectrum PPI studies that yielded null findings had small sample sizes and, therefore, may not have possessed sufficient power to detect PPI differences, many of these null findings also may be explained, in part, by other methodological issues, such as non-optimal signal-to-noise ratio (SnR). The SnR of a PPI study is the difference between the background noise intensity...
and prepulse intensity (because sound intensity is usually measured in decibels, which are on a logarithmic scale, taking the difference between two intensities yields a ratio). Many PPI labs traditionally have used background noise levels around 70 dB in order to mask variable ambient noise; however, Wynn et al. (2004) posited that if background noise was not used, it may be more difficult to detect associations between PPI and psychological variables. Blumenthal, Noto, Fox, and Franklin (2006) supported this position by finding that PPI decreased as background noise increased above 50 dB, and concluded that when background noise is not used, the prepulse may be so salient that PPI deficits do not appear in clinical populations. It should be noted, however, that ambient noise levels may sometimes approach 70 dB, and these ambient sounds may act like prepulses in some cases, or may mask prepulses in other cases. Based on this and other research (e.g., Franklin, Moretti, & Blumenthal, 2007; Swerdlow, Blumenthal, Sutherland, Weber, & Talledo, 2007), we propose that the optimal SnR may be +15 dB because the effects of masking at SnRs below this level may be obscured by sensory masking effects, and the effects of prepulses at SnRs above this level may be obscured by ceiling effects of prepulse salience.

Supporting this hypothesis, most of the anxiety spectrum PPI studies that have used SnRs between +10 dB and +16 dB have detected significantly decreased PPI in anxiety groups (Duley et al., 2007; Hoenig et al., 2005; Ludewig et al., 2002, 2005), with two exceptions: Butler et al. (1990), which used a SnR of +15 dB, but may have possessed limited power because of a small sample size and a combat veteran control group, and Swerdlow et al. (1993), which found that a SnR of +4 dB, but not +16 dB, was associated with decreased PPI in 11 OCD patients. Nevertheless, Hoenig et al. (2005) conducted a study similar to that of Swerdlow et al. (1993), with SnRs between +2 and +16 dB, but with a sample of 34 OCD patients, and found that only the +16 dB condition was associated with decreased PPI. The results of anxiety spectrum PPI studies that either used lower SnRs (<+10 dB), or did not report background noise intensities, have been mixed, with some finding PPI deficits (Grillon et al., 1996; Grillon et al., 1998; Ornitz & Pynoos, 1989; Swerdlow et al., 1993), and others finding no significant effects (Grillon et al., 1997; Larsen et al., 2002; Lipschitz et al., 2005; Morgan et al., 1997). Grillon et al. (1996, 1998) and Ornitz and Pynoos (1989) did not report background noise intensity but still detected PPI deficits; thus, it may be that the ambient background noise levels in these studies produced SnRs close to +15 dB, as was the case in Duley et al. (2007), which reported an ambient background noise of approximately 60 dB and a prepulse intensity of 70 dB. In any case, a systematic investigation of the effects of different SnRs on PPI in relation to various anxiety spectrum constructs may help to explain the aforementioned discrepancies of PPI findings in the anxiety spectrum.

As mentioned above, the anxiety spectrum is often associated with decreased PPI; nonetheless, it remains unknown if this association is specific to certain disorders (i.e. PTSD, OCD, panic disorder) or if this association applies more generally to the anxiety spectrum as a whole, including Axis II anxiety spectrum disorders (i.e. the Cluster C personality disorders: APD, DPD, and OCPD) theoretically belongs to the same spectrum, we hypothesized that each of these constructs should be negatively correlated with PPI. A second purpose of the present study was to examine the hypothesis that the associations between PPI and psychological variables should be most evident at SnRs that approach +15 dB (Franklin, Bowker, & Blumenthal, 2007; Swerdlow et al., 2007). Accordingly, we posited that, as the SnR approaches +15 dB (in this study, the 85 dB prepulse intensity condition), the associations between anxiety spectrum constructs and PPI would become stronger. The findings of the present study should help to elucidate the relationship between PPI, SnR, and the anxiety spectrum, and would provide strong support for the position that many of the null findings of PPI in the anxiety spectrum may be explained, in part, by the use of non-optimal SnRs. In addition, the findings of this study should demonstrate that PPI is generally sensitive to elevations in anxiety, even in a subclinical normative sample.

2. Methods

2.1. Participants

Female participants (N = 53) ranging from 18 to 22 years of age were randomly selected from a group of Wake Forest University introductory psychology students earning credit for a research participation option. As this study was part of a larger project necessitating a predominantly female sample, only females participated in this study. Participants signed an informed consent form and all procedures were approved by the Institutional Review Board of Wake Forest University. In the first portion of the experiment, participants completed the third version of the Millon Multiaxial Clinical Inventory (MCMI-III: Millon, Davis, & Millon, 1996). One to six weeks later, they completed the startle portion of the experiment. None of the participants in the startle portion indicated that they had any illness or psychiatric diagnosis, used any psychoactive medication, or used any tobacco products within four hours prior to the experiment.

2.2. Stimuli

Startle stimuli were 100 dB(A) broadband noises (20 Hz to 20 kHz), with a 50 ms duration and a rise/fall time of <1 ms. Pre- pulses were 75, 80, and 85 dB(A) broadband noises, each with a 40 ms duration and a rise/fall time of 5 ms. The stimulus onset asynchrony (prepulse to startle stimulus) for each trial was 120 ms. Background noise was a continuous 70 dB(A) broadband noise present during the entire testing session. Intertrial intervals varied randomly from 14 to 23 s. All stimuli were generated by Coulbourn S-series noise generators, gated through Coulbourn rise/fall gates, amplified by Coulbourn audio mixer amplifiers, and presented to the participants through Telephonic TDH-39 headphones. Stimulus intensities were calibrated with steady-state signals presented through the headphones and measured with a Quest sound level meter with a fitted earpiece.

2.3. Response measures

Eyeblink EMG responses were measured from the orbicularis oculi muscle with In Vivo Metric surface recording electrodes
(Ag/AgCl, 11 mm outer diameter, 4 mm inner diameter contact surface) placed below the left eye. EMG activity of this muscle was amplified with a Biopac EMG amplifier and sampled (1000 Hz) by a Biopac MP150 workstation which stored four versions of the EMG input: raw unfiltered EMG, filtered EMG in a pass-band of 28–500 Hz, a rectification of the filtered EMG signal, and a rectified and smoothed (five sample boxcar filter) derivation of the filtered signal. The data reported in this paper are based on the smoothed EMG signal.

2.4. Self-report measures

To measure anxiety spectrum constructs, we used the MCMI-III (Millon et al., 1996), which was designed to be in accord with the DSM-IV (APA, 1994), though it includes some scales for personality disorders found in the DSM-III-TR (APA, 1987; Strack, 1999). The MCMI-III consists of 175 true/false items, which compose 10 clinical syndrome scales and 14 personality disorder scales. These 24 scales have shown good reliability and validity (Davis, Wenger, & Guzman, 1997; Millon et al., 1996). In this study, we used the Anxiety, PTSD, APD, DPD, and OCPD scales. We utilized the MCMI-III because of its comprehensiveness and specificity to DSM-IV constructs. The MCMI-III has been used widely in a variety of research and clinical settings, but is expressly not for diagnostic use in a normative population because its norms are based on a psychiatric sample (Millon et al., 1996; Strack, 2005). In the present study we were not concerned with diagnoses or clinically significant levels of disorders; rather, we were interested in variations on these scales in a normative sample, and in how scores on these scales vary with PPI of acoustic startle. The MCMI-III has been used in several studies with normative populations that were also primarily concerned with the covariance of MCMI-III scores with other constructs, rather than diagnoses (e.g. McCann et al., 2001; Stredny, Archer, & Mason, 2006).

2.5. Procedure

In the first portion of the study, participants, in groups of 15–20, were given 1 h to complete the MCMI-III. The MCMI-III contains a validity scale and no participants reached the cut-off for ‘invalidity’ as recommended by Millon et al. (1996). In the startle portion of the experiment, participants were seated individually in a sound-attenuated room, where they read and signed an informed consent form and filled out a brief medical history questionnaire. The skin on the left temple and below the left eye was cleaned with a cotton swab dipped in rubbing alcohol. Surface recording electrodes fitted with Synapce conducting paste were then placed on the cleaned areas; one electrode was attached to the skin overlaying the orbicularis oculi muscle directly below the pupil, but below the lower eyelid, and another electrode was placed approximately 15 mm (center to center) lateral to and slightly higher than the other electrode. The ground electrode was placed on the skin overlaying the left temple. Headphones were then comfortably placed on the participant (see Franklin et al., 2007).

Background noise was then turned on (and remained on throughout the session) and participants were given 5 min to acclimate to it before any other stimuli were presented. Three habituation trials of a 100 dB(A) startle stimulus were then presented (these trials are not included in the analyses). Then the session of 32 trials, each containing a startle stimulus, was presented. Each session was composed of 8 blocks, with each block containing a random order of a control trial (no prepulse), and 75, 80, and 85 dB(A) prepulse trials. This resulted in 8 trials for each of the 4 stimulus conditions. Block order was counterbalanced across participants. After the session, participants were debriefed, given credit, and allowed to leave.

2.6. Data analysis

Blink response amplitude was calculated for each stimulus condition (see Blumenthal et al., 2005). Response amplitude was the average of the difference between peak and onset voltage of the smoothed EMG, within a window of 20–150 ms after stimulus onset, for all trials on which a response was detected (3.7% of trials were deleted due to movement artifacts or unstable baselines). Because 8 participants failed to respond on any trials in one of the stimulus conditions, the results are based on data from 45 participants.

PPI was calculated as the proportion of the difference from control (1 prepulse condition–control condition)/control condition for response amplitude, as recommended by Blumenthal, Elden, and Flaten (2004). The resulting data were multiplied by −1 so that negative correlations with anxiety measures would signify a decrease in PPI. The effect of prepulse intensity was evaluated with repeated measures analysis of variance (ANOVA); Greenhouse–Geisser degrees of freedom were used to test for significance, but uncorrected degrees of freedom are reported.

The scores on the MCMI-III scales were calculated and intercorrelated. Scores on the anxiety scales were then correlated with PPI levels. All correlations were one-tailed Pearson correlations, and all alpha levels were .05.

3. Results

Correlational analyses revealed that all anxiety spectrum constructs were significantly positively intercorrelated (p < .05; see Table 1), with the exception of intercorrelations with OCPD, which was only significantly associated with PTSD and, moreover, this association was negative (p < .05; see Table 1). Correlational analyses also revealed that all anxiety spectrum constructs, with the exception of OCPD, were significantly negatively associated with PPI in the 85 dB prepulse condition (p < .05), and that there were no significant associations in the 75 or 80 dB conditions (p > .05; see Table 2). In contrast, there was a nonsignificant trend for a positive correlation between OCPD and PPI in the 80 and 85 dB conditions (p < .1). Additionally, similar to previous studies (Blumenthal et al., 2006; Franklin et al., 2007), a repeated measures ANOVA showed that there was a significant main effect of prepulse intensity on PPI of startle response amplitude, F(2,88) = 35.52,
p < .001, ϵ = .765, with PPI increasing as prepulse intensity (and SnR) increased.

4. Discussion

In the present study, we examined the association between PPI, SnR, and various anxiety spectrum constructs in a normative sample. Our hypotheses were mostly confirmed as all anxiety spectrum constructs were significantly positively intercorrelated, with the exception of OCPD, and all anxiety spectrum constructs were significantly negatively correlated with PPI, again with the exception of OCPD. Additionally, there was support for the hypothesis that the association between anxiety constructs and PPI strengthens as SnR approaches +15 dB, as all constructs, with the exception of OCPD, were significantly negatively correlated with PPI in the 85 dB prepulse condition, but not in the 75 or 80 dB prepulse conditions.

Although our findings regarding OCPD were contrary to predictions, they are in accord with reports that moderately elevated levels of three MCMI-III scales – the OCPD, histrionic (HPD), and narcissistic personality disorder (NPD) scales – may indicate healthy functioning, rather than psychopathology, in a normative population (Strack, 2005). As such, in the present study, the OCPD scale may have primarily indexed the tendency to be responsible and conscientious which, in our normative college sample, is likely to be highly represented and indicative of normal functioning. Supporting this possibility, OCPD was not correlated with any of the other anxiety spectrum variables, with the exception of PTSD, with which it was significantly negatively correlated. As a result, we posit that in our college sample, OCPD was indicative of healthy functioning, rather than increased anxiety. Further supporting this interpretation, we recently reported that the other two MCMI-III scales that may be indicative of healthy functioning in normative populations, HPD and NPD, were significantly positively associated with PPI (Franklin et al., 2007).

The present study provides support for the contention that the anxiety spectrum is generally associated with decreased PPI. These results replicate findings of decreased PPI in college students high on the anxiety spectrum, which is generally associated with decreased PPI. These findings support the hypothesis that the association between anxiety spectrum and PPI strengthens as SnR approaches +15 dB. Correspondingly, the present study indicates that OCPD was not correlated with decreased PPI, as our measure of OCPD may have actually indexed healthy functioning (Strack, 2005). As clinically significant levels of OCPD are likely to be more associated with anxiety, an investigation of clinically significant OCPD may be associated with decreased PPI. In addition, the larger context within which this study was conducted necessitated a female-only sample and, although there is no theoretical reason to believe that results for males should be different, these associations have yet to be empirically investigated in males.

Second, because this study was largely exploratory, we used a simple correlational design that prevented us from inferring the directionality of the PPI – anxiety spectrum relationships. Nonetheless, studies that separate groups based on anxiety levels use essentially the same correlational design, with the only difference being that such studies have categorical independent variables (i.e. group membership), whereas the present study had continuous independent variables (i.e. scores on constructs). Consequently, one might argue that the design of the present study is as strong as, if not stronger than, categorical designs (see MacCallum, Zhang, Preacher, & Rucker, 2002); nevertheless, experimental designs where anxiety is experimentally induced (e.g. Grillon & Davis, 1997) may provide greater insight into the relationship between PPI and the anxiety spectrum. Finally, in order to collect information on a large number of constructs within a short amount of time, the present study utilized a self-report measure, which is subject to self-report bias. Although we obtained promising results using this method with the MCMI-III, future studies may benefit from using other more specific questionnaires (e.g. a more comprehensive PTSD measure), structured clinical interviews, and observational methods to index anxiety spectrum constructs.

In sum, this study provides support for the argument that PPI is a sensitive measure of anxiety by demonstrating that PPI is negatively correlated with various anxiety spectrum constructs in a normative sample. This point is highlighted by the fact that the present study did not select participants based on their anxiety scores, but rather simply correlated PPI with anxiety scores that fell across the subclinical dimensions of each construct. Although the present study used a somewhat larger sample size than has typically been utilized in PPI-anxiety research, we maintain that the power of the present study to detect associations between PPI and anxiety constructs was largely due to the utilization of a SnR of +15 dB. Correspondingly, the present study indicates that a SnR of +15 dB allows for the most powerful examination of associations between PPI and psychological variables, and that these relationships exist at levels of symptomatology below clinically significant levels.

Acknowledgements

This project was supported in part by the Social, Behavioral, and Economic Sciences Research Fund of Wake Forest University (awarded to JCF).

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