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Differences in Startle Reflex and Prepulse Inhibition in European-Americans and African-Americans

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Abstract

The acoustic startle reflex and its modulation by a prepulse are psychophysiological phenomena that are commonly studied to evaluate various aspects of information processing. Recent reports in human populations suggest that subjects from disparate racial backgrounds may have significant differences in the startle response. To determine if this pattern could be observed in our subject population, and whether it extended to prepulse inhibition (PPI), we evaluated baseline startle parameters and PPI in 53 African-Americans (AA) and 38 European-Americans (EA). In AA compared to EA, mean startle magnitude and probability of blink response were lower, with no difference in habituation. PPI was greater in AA than EA when groups were matched on baseline startle magnitude. These findings support the idea of racial differences in startle response. Implications for study design are highlighted, and possible environmental and genetic influences are considered.

Keywords

startle reflex; prepulse inhibition; race; European; African

The acoustic startle response is a reflexive contraction of the skeletal muscles in response to a sudden acoustic stimulus (Landis & Hunt, 1939). Modulations of this reflex have been widely studied to gain understanding about various aspects of information processing. Prepulse inhibition (PPI) is defined as the inhibition of the startle reflex that occurs when a nonstartling stimulus is presented approximately 30-500 ms before the startling stimulus (Graham, 1975; Hoffman & Searle, 1968). PPI is considered to be an operational measure of sensorimotor gating, the process of screening out excess or trivial stimuli in one’s environment (Braff & Geyer, 1990). Alterations in PPI have been most thoroughly characterized in psychiatric disorders, particularly schizophrenia (Braff & Light, 2005; Geyer, 2006). However, there has been relatively little examination of systematic variance in startle measures among different groups within the general population (Swerdlow, Filion, Geyer, & Braff, 1995), with the exception of gender (Jovanovic et al., 2004; Swerdlow, Hartman, & Auerbach, 1997).
As is the case with most physiological or behavioral measures, both environmental and genetic factors have been found to affect the expression of the startle reflex in humans. There is data to suggest that environmental influences such as social context, internal states, and pharmacological substances can alter the startle response (Anokhin, Golosheykin, & Heath, 2007; Braff, Geyer, & Swerdlow, 2001; Brown, Bradley, & Lang, 2006; Miller & Litz, 2004; Rissling, Dawson, Schell, & Nuechterlein, 2005). Furthermore, twin studies have found heritability of the startle response (Anokhin et al., 2007; Anokhin, Heath, Myers, Ralano, & Wood, 2003; Carlson, Katsanis, Iacono, & McGue, 1997), with genetic contributions to baseline startle estimated at 60-70%, and PPI at 50-60% (Anokhin et al., 2007; Anokhin et al., 2003). Considering the potential systematic environmental and genetic diversity that exists between racial groups, it is plausible that psychiatrically normal subjects from different racial backgrounds may express parametrically divergent startle responses.

Racial background, however, is a demographic variable that is often not reported in human startle research. Notably, a search of the U.S. National Library of Medicine database (MEDLINE) using the keywords “startle” and “race” reveals a mere 11 publications, only two of which compared startle responses between individuals with different racial backgrounds. The first, a study comparing Asian and Caucasian men, found lower baseline startle reflex in Asians, and no difference in PPI between Asian and Caucasian men when the analyses controlled for baseline startle magnitude (Swerdlow, Talledo, & Braff, 2005). The second study reported lower startle magnitudes in African-Americans (AA) compared to European-Americans (EA; Brown et al., 2006). Therefore, it seems that racial differences in startle measures may exist, at least with respect to baseline startle magnitude (Brown et al., 2006; Swerdlow et al., 2005). This effect needs to be examined more thoroughly in multiple populations, given that most research cohorts represent a diversity of racial and ethnic backgrounds, as do the patients diagnosed with mental disorders that are studied with acoustic startle paradigms. Moreover, the effect of racial differences on prepulse inhibition has not been adequately studied.

If consistent racial differences do exist in startle measures, this will have important practical applications in study design. Given the accumulating evidence that racial differences may exist in startle phenotypes, we performed a systematic analysis of the effects of racial background (AA vs. EA) on startle magnitude and PPI.

### Methods and Materials

#### Subjects

All subjects signed a consent form approved by the Emory Institutional Review Board and the Atlanta Veterans Affairs Medical Center Research and Development Committee as an indication of informed consent. These subjects were recruited from the Atlanta metropolitan area through listings at local universities and in community publications, and served as control subjects for a larger study on PPI in schizophrenia. Exclusion criteria were as follows: history of major mental illness (i.e.: schizophrenia spectrum disorder, bipolar disorder, or recurrent major depression, as assessed by SCID-NP; First, 2001), history of substance abuse or dependence, positive urine toxicology, history of head trauma resulting in sustained loss of consciousness (>5 minutes), history of any neurological illness, significant medical illness, or known hearing impairment. Subjects were excluded if audiometer testing of hearing threshold (using a Maico audiometer Model MA27) was greater than 40 dB(A) at 250, 500, 1000, 2000, 4000 or 8000 Hz in either ear. All female participants were tested during the first two weeks of their menstrual cycle (follicular phase), as studies have shown that women express reduced PPI during the luteal phase (Jovanovic et al., 2004; Swerdlow et al., 1997). Subjects were asked to identify their race, and the current analysis includes subjects self-identified as AA (a person having origins in...
any of the black racial groups of Africa) or EA (a person having origins in any of the original peoples of Europe). This study evaluated 53 normal AA and 38 normal EA; demographic information is presented in Table 1.

**Acoustic Startle Measurement**

Methodology for measuring the acoustic startle reflex was similar to that of Braff et al. (Braff, Grillon, & Geyer, 1992), and to that used previously in our laboratory (Jovanovic et al., 2004; Parwani et al., 2000). The eyeblink component of the acoustic startle response was measured via electromyography (EMG) of the right orbicularis oculi muscle. Two 5 mm silver/silver chloride electrodes filled with gel were positioned approximately 1 cm under the pupil and 1 cm below the lateral canthus and a ground electrode was placed behind the right ear over the mastoid, according to methods of Blumenthal and colleagues (Blumenthal et al., 2005). All resistances were less than 6 kilo-ohms. EMG activity was amplified and digitized using a computerized EMG startle response monitoring system (SR-LAB, San Diego Instruments). The EMG signal was filtered with low- and high-frequency cutoffs at 30 and 1000 Hz, respectively. The system was set to record 250 1-ms readings starting at the onset of the startle (pulse alone) stimulus. Digital signals were full-wave rectified and smoothed by an averaging routine that calculates a rolling average of 10 data points.

Subjects were seated in a chair in an audiology booth and asked to look straight ahead at a neutral picture and keep their eyes open during the test session. All acoustic stimuli were delivered binaurally through headphones (Maico,TDH-39-P). The startle session began with a 60-second acclimation period consisting of 70 dB white noise, which continued as the background noise throughout the session. The pulse alone stimulus was a 116 dB, 40 ms burst of white noise; the prepulse stimuli were 85 dB, 20 ms bursts of white noise presented 30, 60, and 120 ms prior to the startle stimulus. The session began with a habituation block of six pulse alone stimuli (HAB1). The main part of the session consisted of nine pulse alone trials and nine prepulse trials (prepulse plus pulse) at each of the three designated inter-stimulus intervals (30, 60, and 120 ms), for a total of 36 startle stimuli (BLOCK) presented in a pseudorandom order. Finally, a second habituation block of six pulse alone stimuli was presented at the end (HAB2) of the session. Inter-trial intervals were 10-25 sec (average 15 sec).

The baseline EMG value was calculated by taking the average of the minimum and maximum values recorded during the first 20 ms after the startle stimulus. Onset latency was defined as the time between the stimulus and a shift of 7.33 μV (6 machine units) from the baseline value. Peak latency was defined as the time between the stimulus and the point of maximal blink magnitude occurring no more than 150 ms after the stimulus. To be considered a valid blink response, the blink onset had to occur between 21 and 120 ms after the pulse alone stimulus. The minimum response criterion for a peak was set at 12.21 μV (10 machine units). Response amplitude was recorded as zero on trials in which the magnitude of the blink response was insufficient for scoring. Responses in which onset and peak latencies differed by more than 95 ms were considered to be artifacts (not generated by the stimulus) and were discarded. Trials were also discarded if baseline EMG activity during the first 20 ms of recording was greater than 36.6 μV (30 machine units). Less than 1% of all trials were discarded from the current study due to artifact or high baseline.

**Data Analysis**

Overall mean startle magnitude (including trials for which amplitude = 0) was calculated for the 21 pulse alone trials in the session, and habituation was calculated as the difference in the mean startle magnitude of the first and last six pulse alone trials (mean HAB1- mean HAB2). Data were investigated for normality with the Kolmogorov–Smirnov test (overall
mean startle: \( Z = 1.68, p = 0.007 \); habituation: \( Z = 1.44, p = 0.031 \); log transformations were employed to achieve a normal distribution of these two variables (log overall mean startle: \( Z = 1.00, p = 0.28 \); log habituation: \( Z = 0.57, p = 0.90 \)). Transformed data were subsequently used for parametric comparisons between groups. Overall mean startle magnitude and habituation were compared between races using one-way ANOVAs with gender, age and years of education as covariates. The probability of blinking on any given trial (i.e.: having startle amplitude > 0) was calculated for each subject across the 21 pulse alone trials, and was compared between races using a Mann-Whitney U test, as normality could not be achieved with standard transformations.

PPI \((100 - [100 \times \text{mean magnitude on prepulse trials/mean magnitude on BLOCK pulse alone trials}])\) was calculated for the 27 prepulse trials that comprised the BLOCK portion of the session. To control for observed group differences, groups were matched on pulse alone startle magnitude, resulting in two matched groups whose mean startle magnitude was not statistically different. PPI data for these matched subjects were normally distributed. To investigate racial differences in PPI, we employed a repeated-measures ANOVA with race as the main factor, trial type (30 ms, 60 ms and 120 ms prepulse) as the repeated measure, and gender, age and years of education as covariate factors. Alpha was set at 0.05 for all analyses.

**Results**

**Subject demographics**

Demographic information for all subjects in this study is listed in Table 1. There was no significant difference between the age of AA and EA \((t = 0.47, df = 89, p = 0.64)\), and a trend level difference existed for years of education \((t = -1.91, df = 89, p = 0.059)\). The two racial groups were made up of equal proportions of men and women \((\chi^2 = 0.026, df = 1, p = 0.87)\). A very small percentage of subjects were smokers at the time of testing \((7.7\%)\), and smoking status was not different across groups \((\chi^2 = 2.35, df = 1, p = 0.13)\). Removal of smokers from the dataset did not change the results. There was also no difference in the percentage of left-handed subjects between groups \((\chi^2 = 0.010, df = 1, p = 0.92)\).

**Startle measures**

ANOVA revealed a main effect of race on startle magnitude \((F(1,86) = 10.91, p = 0.001, \eta^2 = 0.11, \text{Figure } 1a)\), with AA having lower pulse alone startle levels than EA. There was also a main effect of age \((F(1,86) = 4.61, p = 0.035, \eta^2 = 0.051)\), with older subjects having lower startle magnitude, further confirming this well-established relationship \((Ellwanger, Geyer, & Braff, 2003)\). There was no significant main effect of gender \((F(1,86) = 0.76, p = 0.39, \eta^2 = 0.009)\) or years of education \((F(1,86) = 2.26, p = 0.14, \eta^2 = 0.026)\) on baseline startle.

Habituation was not different between races \((F(1,86) = 0.11, p = 0.75, \eta^2 = 0.001, \text{Figure } 1b)\). There was also no effect of gender \((F(1,86) = 0.047, p = 0.830, \eta^2 = 0.001)\), age \((F(1,86) = 0.93, p = 0.34, \eta^2 = 0.011)\) or years of education \((F(1,86) = 0.015, p = 0.90, \eta^2 < 0.001)\) on habituation of startle over the course of the session.

The probability of pulse alone stimuli eliciting a blink response was also significantly lower in AA compared to EA \((U = 549.00, p < 0.001; \text{Figure } 1c)\). To determine whether this reduced likelihood of blink response accounted for the racial effect on overall startle magnitude, we compared startle amplitude on only non-zero blinks between AA and EA. The effect of race on startle magnitude was reduced to a trend toward significance in this case \((F(1,86) = 3.15, p = 0.079, \eta^2 = 0.036)\); as expected, there was still a main effect of age \((F(1,86) = 4.83, p = 0.031, \eta^2 = 0.054)\). The reduction in significance and effect size after
removing blinks with amplitudes of zero provides evidence that the racial effect on startle magnitude is due in large part to the lower probability of blink response in AA compared to EA.

**Prepulse Inhibition**

To control for the lower baseline startle amplitudes found in AA compared to EA, groups were matched on pulse alone magnitude such that their mean startle magnitudes were comparable (AA: \( n = 30 \), mean pulse alone startle magnitude [SEM] = 110.35 [17.10]; EA: \( n = 36 \), mean pulse alone startle magnitude [SEM] = 111.88 [13.39]; \( t = -0.071, df = 64, p = 0.94 \); Figure 2). The matched groups also did not differ significantly on age, years of education, or distributions of gender, smoking status and handedness (Table 2). Probability of response was also not different between the matched racial groups (\( U = 443.00, p = 0.18 \)).

ANOVA on PPI in the matched groups revealed a main effect of race, \( (F(1,61) = 8.45, p = 0.005, \eta^2 = 0.12; \) Figure 3), with AA having consistently greater PPI than EA. There was no significant main effect of years of education on PPI \( (F(1,61) = 2.04, p = 0.16, \eta^2 = 0.032) \), and there were trends towards significance for age \( (F(1,61) = 3.89, p = 0.053, \eta^2 = 0.060) \) and gender \( (F(1,61) = 3.52, p = 0.065, \eta^2 = 0.055) \), with older subjects and male subjects tending to have greater PPI. The main effect of trial type on PPI was not significant \( (F(1.72, 105.19) = 1.17, p = 0.31, \eta^2 = 0.019, \) Huynh-Feldt correction), and there were no significant interactions between trial type and any of the variables entered into the model.

**Discussion**

This study has identified a number of differences in the startle reflex, as well as its modulation by prepulse, between normal AA and EA subjects. Compared with EA subjects, AA subjects exhibited reduced startle reflex magnitude and decreased probability of blink response. In addition, AA had greater PPI than EA across three prepulse intervals when groups were matched on baseline startle magnitude to control for observed differences in this variable. These findings support the idea that racial background can affect the startle response, as two recent reports have also described (Brown et al., 2006; Swerdlow et al., 2005).

Reduced startle magnitude in AA compared to EA has been noted previously, as part of a larger study on affective reactions to ingroup and outgroup pictures (Brown et al., 2006). Brown et al. also described a decreased probability of blink response in AA, similar to what we report here. This effect was largely responsible for the overall difference in startle magnitude in both studies, as this difference failed to remain significant when only trials with non-zero blink response amplitudes were compared. Thus, it appears that there is a subgroup of AA who are less likely than EA to blink in response to startle stimuli. It should be noted that methodological adjustments, such as lowering the minimum response criteria, may allow for detection of startle responses with very low amplitude. In the present study, the minimum response criteria for a blink was set at 10 machine units (as recommended by the manufacturer), and was chosen in an effort to remain consistent with many other researchers in this field. Thus, it is possible that AA may have been exhibiting blinks with amplitudes below our level of detection. However, even if very small amplitude blinks had been detected, their effect on mean startle magnitude would likely be negligible in comparison to the present data.

These results extend the investigation of acoustic startle differences between AA and EA. For example, Brown et al. (2006) suggested that the reduced probability of startle in AA compared to EA may be due to racial differences in threshold for startle (Brown et al., 2006). However, Brown and colleagues measured startle response to 95 dB white noise...
stimuli whereas the present study used 116 dB white noise stimuli and found a very similar effect. In addition, an analysis of baseline acoustic startle in other studies from our group reveals lower startle magnitude and decreased probability of startle in AA compared to EA at 108 dB as well (unpublished data). Therefore, while the mechanism underlying this finding remains unclear, the effect is nevertheless prevalent across a range of stimulus intensities, and has now been replicated in two separate labs. Interestingly, our findings are also consistent with those of a recent study showing that Asian men had lower startle magnitudes than Caucasian men in response to 118 dB stimuli (Swerdlow et al., 2005). It is not known whether AA differ from Asian subjects on baseline startle parameters; future research should systematically investigate startle differences, as well as the threshold at which blinks can be detected, across a number of ethnicities.

In addition to differences in baseline startle, this study identified greater overall PPI in AA compared to EA, the first such report to the authors’ knowledge. As PPI values are derived from a calculation that uses pulse alone startle magnitude as the denominator, we matched groups on this variable to control for the generally lower startle magnitude in AA, because this effect could have otherwise created a mathematical artifact giving AA the appearance of higher PPI. Our results suggest that, despite having reduced baseline startle magnitude, AA inhibit their startle reflexes more than EA in the presence of a prepulse, and therefore exhibit higher overall sensorimotor gating. This finding is in contrast to a previous report in which increased PPI in Asian men compared to EA men did not withstand matching of groups on baseline startle (Swerdlow et al., 2005).

It will be important to more fully understand normal population variance in startle and PPI, particularly because systematic differences among healthy controls could confound results of studies that compare these groups to other populations. For example, if a study were to compare PPI in a population of schizophrenia patients comprised mostly of EA to a control population comprised mostly of AA, there is a danger of incorrectly ascribing significant group differences to the disease state, and not to the underlying racial variations in PPI. Indeed, the nature of determining a “PPI deficit” is inherently dependent on the control group that is chosen. Stated differently, the identification of normal population variance in PPI illustrates that differences in sensorimotor gating are not always indicative of psychopathology. Thus, when conducting startle research in human populations, if it is not possible to obtain comparison groups in which race is equally represented, racial background should be investigated as a potential confound in all analyses of startle magnitude and its related measures.

The mechanisms underlying racial differences in startle and PPI are currently unclear. There are many potential bases for the differences we report, and the current study was not designed to determine which, if any, of these factors may be involved. Environmental influences such as social context (e.g., caste assignment), internal states (e.g., trait level anxiety), and pharmacological substances (e.g., cocaine) have been shown to affect the startle response (Anokhin et al., 2007; Braff et al., 2001; Brown et al., 2006; Miller & Litz, 2004; Rissling et al., 2005). We have attempted to control for pharmacological variability by ensuring that all subjects in the present study passed a urine screen for drugs of abuse (i.e.: amphetamines, benzodiazepines, cocaine, cannabinoids and opiates). However, common legal substances such as nicotine and caffeine can have also effects on startle and PPI (Braff et al., 2001). The rate of smokers in this sample was very low and not significantly different between groups. In addition, while caffeine intake was not measured here, this variable would not be expected to differ systematically between races.

Control of social and psychological environment is much more difficult, and it is possible that some of these factors may differ systematically between AA and EA. From a cultural
In summary, we present an analysis of the effect of racial background on startle measures and PPI. AA were found to express decreased baseline acoustic startle, reduced probability of startle, and increased PPI compared to EA. Despite the presently unknown basis of our findings, these results coupled with those of previous reports underscore the prevalence of divergent startle responses between racial and ethnic populations, and solidify the need to control for these differences in future investigations. Studies such as the one presented here...
represent a requisite first step in better understanding the heterogeneity of acoustic startle and PPI in normal populations. Ongoing research into the genetics of startle and its modulation may identify specific genes and resulting physiology that could contribute to these differences. Future research should also directly investigate possible environmental influences on racial differences in startle, such as outgroup effects and attentional or emotional states.

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References


Figure 1.
a: Overall mean pulse alone startle magnitude between races (across 21 trials). AA had uniformly lower startle magnitude than EA. * p = 0.001. b: Habituation (mean HAB1 - mean HAB2) across the startle session; there was no difference in habituation between AA and EA. c: Probability of exhibiting a blink response between races, calculated across the 21 pulse alone trials. AA showed a lower probability of blinking in response to pulse alone stimuli compared to EA. * p < 0.001. Error bars represent standard error of the mean; raw data is used for graphical representation.
Figure 2.
Distribution of overall mean startle magnitude for unmatched (all subjects) and matched groups. There is no difference in startle magnitude between races for the matched groups ($p = 0.94$). Raw data is used for graphical representation.
Figure 3.
PPI in both races after groups were matched on mean startle magnitude. AA had significantly greater PPI compared to EA across trial types. * p = 0.005. Error bars represent standard error of the mean; raw data is used for graphical representation.
## Table 1
Demographic information by race

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